APPLICATION OF CHIRAL BORATES IN ASYMMETRIC CATALYSIS AND CHIRAL RESOLUTION

By

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ABSTRACT

APPLICATION OF CHIRAL BORATES IN ASYMMETRIC CATALYSIS AND CHIRAL RESOLUTION

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A highly diastereoselective and enantioselective epoxidation of aldehydes with diazoacetamides has been developed with *meso*borate ester catalyst of VANOL. A wide range of aromatic and aliphatic aldehydes could be employed in this method to afford the *cis*-3,4-epoxy amides with good to excellent ee (67 to >99% ee) in good to excellent yield (47 to 99%). The synthetic application was demonstrated by the synthesis of the side-chain of taxol (6 steps, 63% overall yield). Based on the non-linear effect studies, the *meso*borate catalyst was proposed to consist of two VANOL ligands in contrast to one for boroxinate catalyst, which was also effective for the same reaction. The mode of activation for aldehydes was proposed to be via a Lewis acid catalysis mechanism, supported by NMR studies. The *meso*borate catalysts were found to be also effective in hetero-Diels-Alder reaction of aldehydes with Danishefsky's diene, aziridination reaction of imines and ethyl diazoacetate and three-component Passerini reaction of aldehydes.

A simple and efficient chiral resolution of VANOL/BINOL/VAPOL and their derivatives via the *spiro*borate formation with quinine/quinidine has been developed. This method can be applied to 18 different ligands, including 9 new ligands such as 5,5'-, 3,3'- and 7,7'-substituted VANOLs. Optically pure ligands could be obtained in up to 47% yield (50% maximum). These ligands are thought to be useful in optimization and mechanistic investigation of various asymmetric reactions.

This thesis is dedicated to my mother Lihua Chen and my father Dechun Yin who always supported me, whatever path I chose to take.

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I would like to thank a handful of people who have had a profound impact on the path I have taken. First, I thank Mr Xu, my high school chemistry teacher, for being an inspirational instructor with patient and great organizational skills. Dr Hao Sun, my undergraduate mentor at Nanjing University, I owe most of what I know about column chromatography, hard effort in the lab, and value of clean, organized bench to you. Finally, I have to thank Professor William Reusch, for creating the Virtuall Textbook of

Organic Chemistry, which I came across when I took organic chemistry course in my sophomore year. It was this book that make me appreciate the mechanism, and enjoy the logic and reasoning in organic chemistry. And that was my first encounter with Michigan State University.

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Athletics in MSU

One of the reasons that there isn't another institute I would rather finish a PhD than Michigan State University is the sport here. I have been really fortunate to witness the golden era of Spartan sports during my time. I would like to give a special shout-out to Coach Dantonio and Coach Izzo not only for building two successful sport teams I really

enjoy watching and cheering for, but also for being two classy and well-respected individuals.

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It is so amazing to have you by my side. Thank you for your crucial support through the journey. Without you, I would be 99% less happy during my time here. I am happy that things have led us to exactly where we are now, and I look forward to our next chapter in life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

CHAPTER ONE

VANOL *MESO*BORATE CATALYSIS — ASYMMETRIC EPOXIDATION OF ALDEHYDES AND DIAZOACETAMIDES

"Everything should be made as simple as possible, but no simpler."
– Albert Einstein

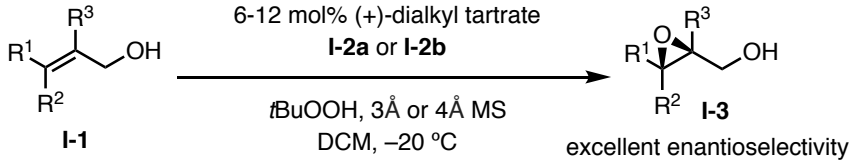
1.1 Asymmetric epoxidation

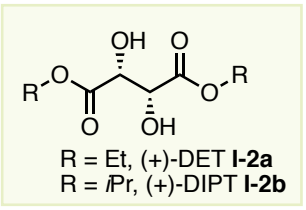
Chiral epoxides are important building blocks and widely used in asymmetric synthesis of complex molecules because of the versatility in their ring opening by nucleophiles. Asymmetric epoxidation has been extensively studied for over 30 years. Most of the efforts have been focused on asymmetric alkene epoxidation, of which three successful examples are shown in (*Scheme 1.1*). The Sharpless epoxidation[1-2] is one of the most widely used methods in asymmetric oxidation and earned him a share of the 2001 Noble Price in chemistry. The reaction is limited to allylic alcohols but proceeds in high enantioselectivity with virtually any substitution pattern on the alkenes. Katsuki[3] and Jacobsen[4] pioneered the asymmetric epoxidation of unfunctionalized olefins catalyzed by Mn(salen) catalyst. The Jacobsen-Katsuki epoxidation can be applied to mono-, di-, tri-, and tetrasubstituted aryl olefins. However, *trans*-alkenes and *cis*-dialkyl alkenes are generally poor substrates (slow and low ee) for Mn(salen) and related systems[5]. Another efficient asymmetric epoxidation with a wide scope substrates was pioneered by Shi[6-7]. The reaction is mediated by dioxiranes, which are generated in situ from fructose-derived ketone catalysts **I-8** and Oxone as an oxidant. By carefully tuning the ketone catalysts,

this methodology displays a broad generality for alkene with different substitution patterns. The major drawbacks include difficult set up (slow addition of Oxone, careful control of pH to ensure consistent result) and the unequal accessibility of the enantiomeric catalyst.

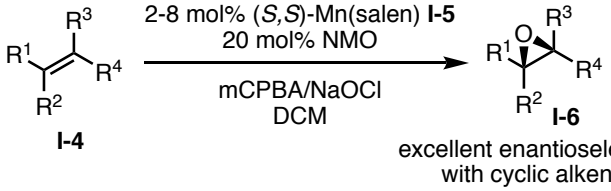
Scheme 1.1 Catalytic Asymmetric Alkene Epoxidation

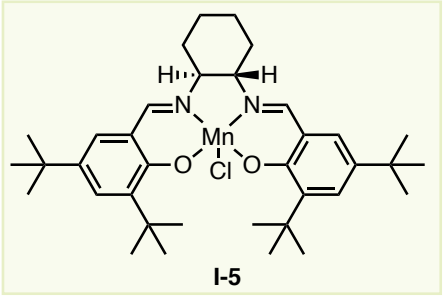
Sharpless Epoxidation[2] (1980)



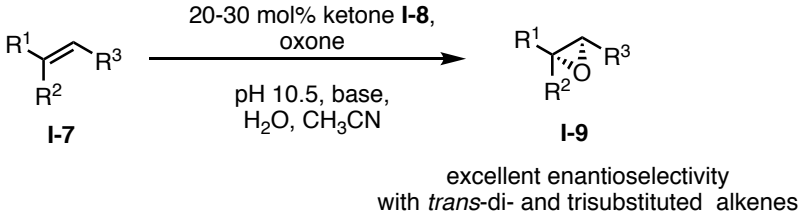


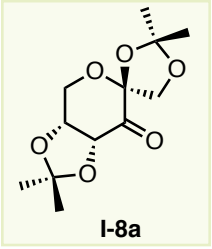
Jacobsen Epoxidation[4] (1990)





Shi Epoxidation[7] (1996)

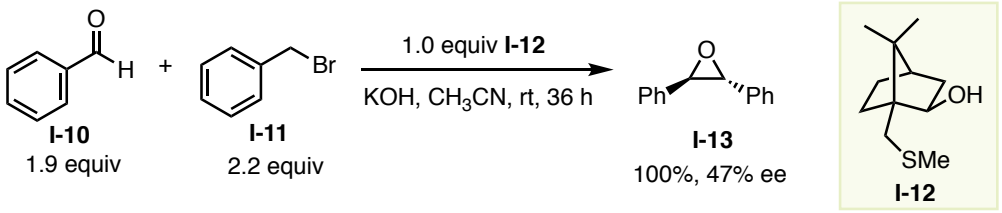




A complementary approach to chiral epoxides from alkenes is the addition of either an ylide, a Darzens reagent or a carbene to an aldehyde (*Scheme 1.2-4*). The enantioselective Corey-Chaykovsky reaction was developed by many groups since its first report[8] by Furukawa et al in 1989 (a, *Scheme 1.2*).

Scheme 1.2 Asymmetric Corey-Chaykovsky Reaction

a) Furukawa et al.[8]



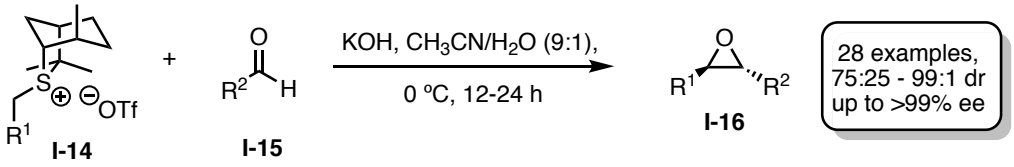
I-10
1.9 equiv

I-11
2.2 equiv

I-13
100%, 47% ee

I-12

b) Aggarwal, McGarrigle, et al.[9]



I-14

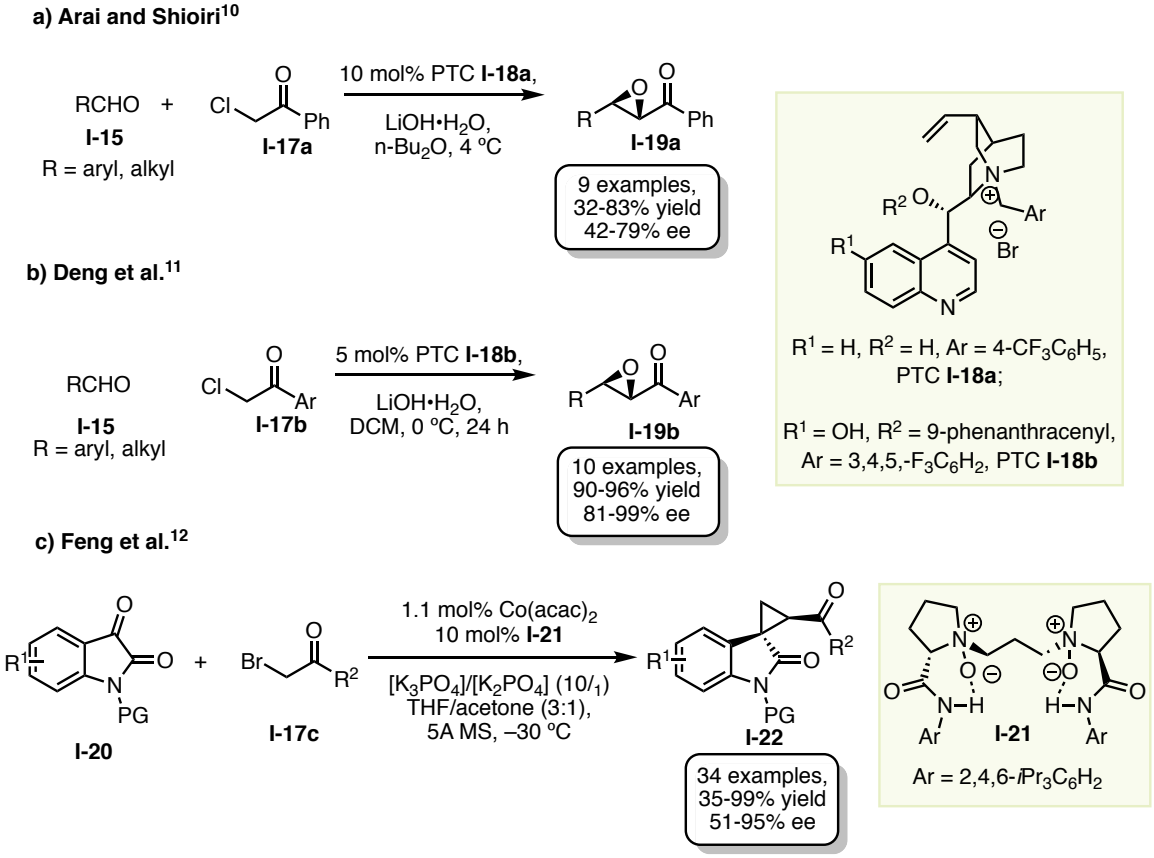
I-15

I-16

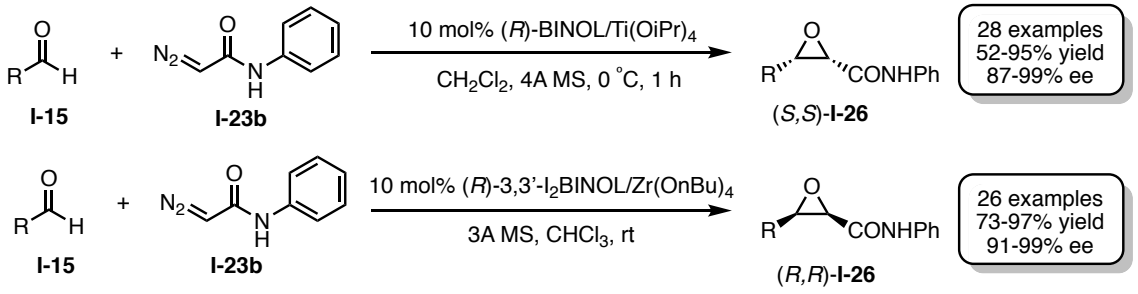
R^1 = aryl, alkenyl; R^2 = aryl, alkenyl, alkyl

The lack of synthetic applications of this methodology in the literature can be attributed to 1) limited substrate scope with excellent (>90%) ees; 2) stoichiometric amount of chiral sulfide is used to ensure high yield and enantioselectivity. Aggarwal and coworkers demonstrated[9] a practical process using a cheap sulfide to prepare chiral *trans*-epoxides in moderate to good yields and up to >99% ees (b, *Scheme 1.2*). The first catalytic asymmetric Darzens reaction was reported[10] by Arai and Shioiri in 1998 (a, *Scheme 1.3*). The desired product was afforded using 10 mol% phase transfer catalyst (PTC) **I-18a** in moderate to high yield with up to 79% ee. In 2011, Deng and coworkers reported[11] a synthetically useful procedure using their modified PTC **I-18b**, with a phenanthracenyl group in the 9-position and a hydroxyl group in the 6'-position (b, *Scheme 1.3*). The reaction gave excellent yield with good to excellent enantioselectivity. Feng et al reported[12] a Co-catalyzed Darzens reaction of isatins with phenacyl bromides (c, *Scheme 1.3*). A wide range of optically active products were obtained in moderate to good yields and enantioselectivities.

Scheme 1.3 Asymmetric Darzens Reaction

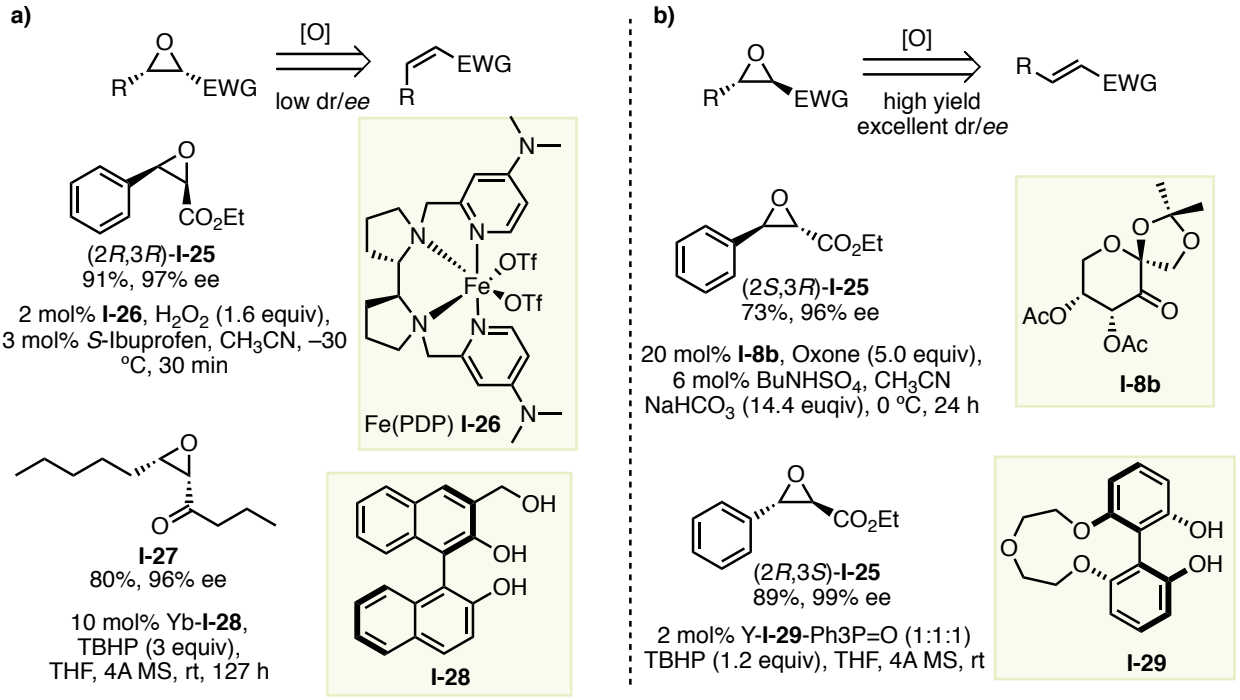


Scheme 1.4 Asymmetric Epoxidation of Aldehydes with Diazoacetamides



In 2009, Gong and co-workers reported[13] a breakthrough, where they reacted aldehydes with diazoacetamides **I-23b** catalyzed by a Ti/BINOL complex to prepare epoxides with excellent yields and ees. They later reported[14] excellent results could also be obtained with a Zr/3,3'-I_2BINOL system (*Scheme 1.4*).

Scheme 1.5 Asymmetric Epoxidation of Electron-Deficient Alkenes



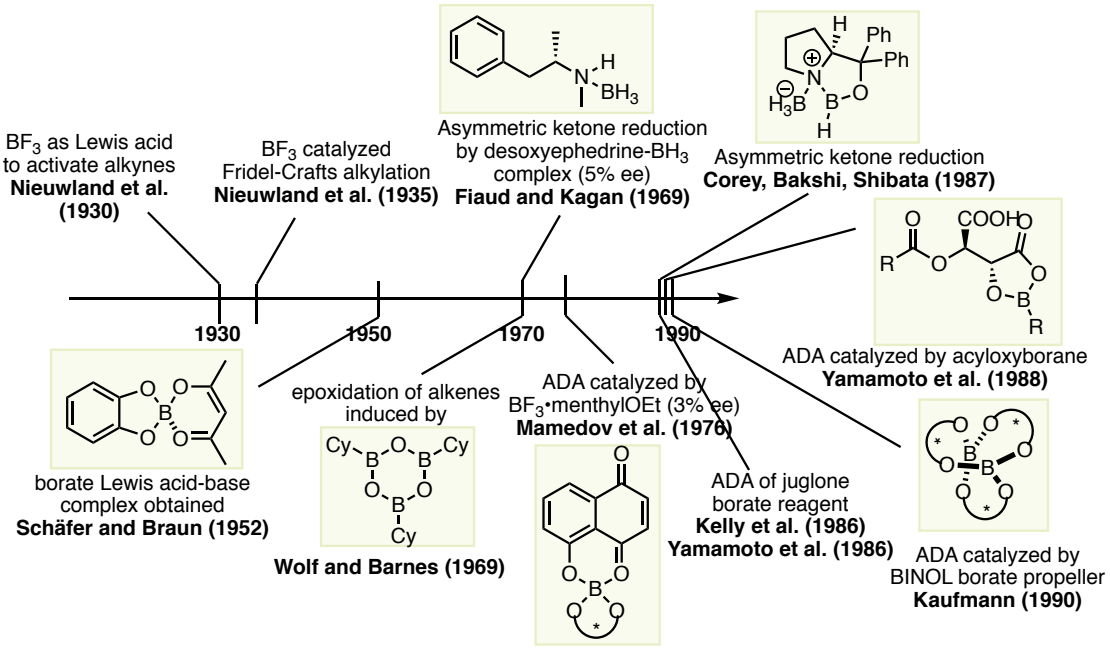
One of the key aspects of this transformation is that *cis*-epoxide products are difficult to synthesize from the *cis*-α,β-unsaturated carbonyl compounds. In contrast to *trans*-epoxides, which can be obtained by epoxidation of *trans*-α,β-unsaturated carbonyl compounds with excellent ees using a variety of methodologies[15], such as Shi epoxidation[16] and the nucleophilic epoxidation method developed[17] by Shibasaki (b, *Scheme 1.5*). The *cis*-substrates under the same conditions usually gave mixture of *cis*- and *trans*-epoxides with moderate ees. Only two catalytic systems provide the *cis*-epoxides from electron-deficient *cis*-alkene with both high diastereo- and enantioselectivities (a, *Scheme 1.5*). Costas reported[18] a highly enantioselective Fe(PDP)[19] catalyst **I-26** for asymmetric epoxidation with H_2O_2. Excellent ee could be obtained by the use of a catalytic amount of a carboxylic acid additive. They also obtained[20] **I-25** with slightly higher enantioselectivity (98% ee) but in lower yield (77%)

using Mn(PDP) catalyst. However, the substrate scope of their methodologies was limited to aryl alkenes. Shibasaki reported[21] asymmetric epoxidation of *cis*-enones catalyzed by Yb-**I-28**, the reaction with alkyl olefins gave rise to *cis*-epoxides with excellent drs and ees. Only a 2:1 dr was achieved with aryl alkenes.

1.2 Boron catalysts in asymmetric catalysis

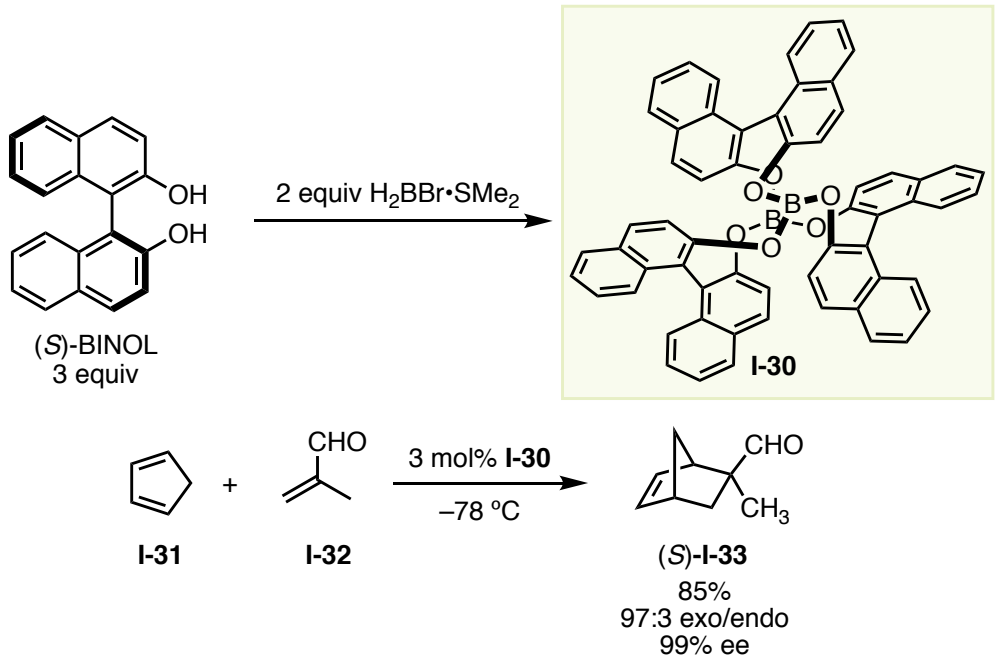
It is well known[22] that boron compounds are Lewis acids because there is an unfilled p-orbital on boron (*Scheme 1.6*). Applications of BF_3 as a catalyst in a number of organic reactions has been well documented[23-26] by Nieuwland dating back to the early 1930. In 1933, Meerwein found[27] that BF_3 reacts with water to give a stable complex which can act as a Brønsted acid. The ability of borate esters to form Lewis acid-base complex also has been documented[28] in 1952 by Schäfer and Braun. It was not until 1969 that the capability of using borate esters to catalyze a reaction was reported. Wolf and Barnes described[29] the epoxidation of olefins with tetralin hydroperoxide induced by 1 equiv of tricyclohexylboroxine. Since the early 1970, a large number of research groups have been interested in developing asymmetric catalysts for the Diels-Alder reaction and for ketone reductions. There has been remarkable progress in the area of asymmetric catalysis employing chiral boron Lewis acids.

Scheme 1.6 Historical perspective of boron catalysts in organic chemistry before 1990



Mamedov and coworkers reported[30] the first example of an asymmetric Diels-Alder reaction (ADA) with BF_3•menthylOEt as chiral catalyst in 1976. Although the enantioselectivity of this method is far from satisfactory (3.3% ee), it laid the foundation for the significant discovery[31] in 1979 by Koga and coworkers where they achieved up to 72% ee with (menthyloxy)aluminum dichloride. Borate complexes of naphthoquinone (juglone) and 3,3'-Ph_2BINOL was prepared by Kelly and coworkers[32]. These complexes promote the ADA reaction with various dienes in high yields and excellent enantioselectivities. The BINOL ligand could be recovered quantitatively. Yamamoto reported[33] a similar reaction using tartrate derivatives as the ligand. The first ADA induced by catalytic amounts of borates was reported[34] by Kaufmann and Boese in 1990. They unexpectedly discovered a propeller compound **I-30** by reacting BINOL with H_2BBr•Me_2S. This catalyst gave excellent results for the ADA reaction of cyclopentadiene **I-31** and methacrolein **I-32** (*Scheme 1.7*).

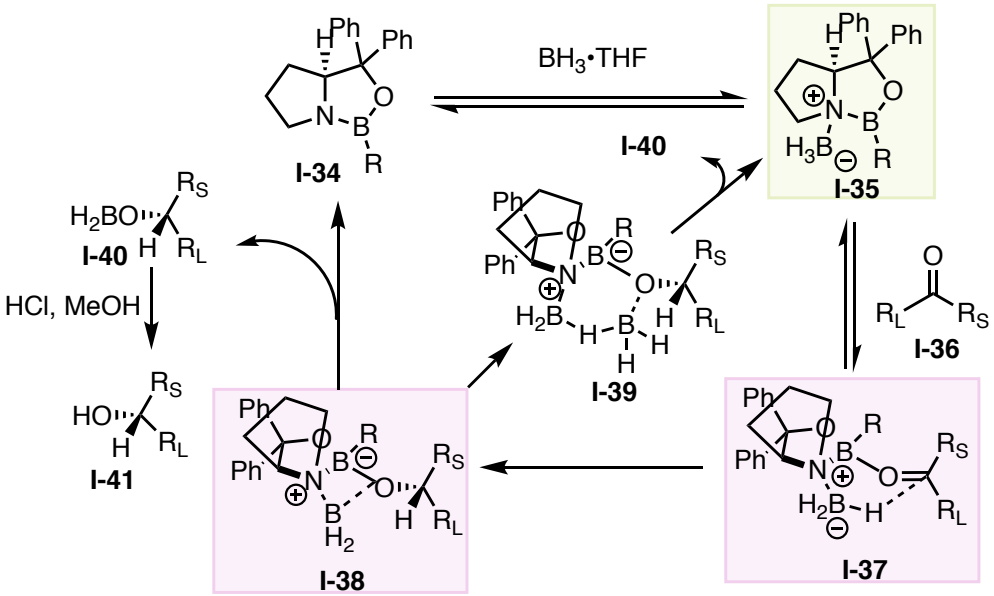
Scheme 1.7 Kaufmann's propeller catalyzed ADA reaction



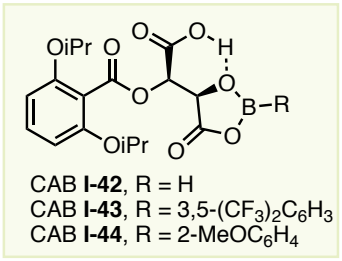
The asymmetric reduction of ketones employing chiral borane reagents was first reported[35] by Fiaud and Kagan in 1969 with poor asymmetric induction (less than 5% ee). A major improvement[36] in the evolution of chiral borane reagents was made by Itsuno and coworkers in 1981. Propiophenone can be reduced with up to 60% ee using the borane complex of an α,β-amino alcohol. Intrigued by the work of Itsuno and others, Corey's group began detailed mechanism studies of this reaction and their efforts led to the discovery[37] of a highly enantioselective catalytic reduction of ketones by an isolable and structurally defined oxazaborolidine catalyst (CBS reduction). The catalytic cycle including the six-membered transition state **I-37** were proposed[38] and is shown in *Scheme 1.8*. The coordination of borane to the nitrogen atom of oxazaborolidine **I-34** not only activates the reducing power, but also strongly enhances the Lewis acidity of the endocyclic boron atom. This was one of the earliest examples of Lewis acid assisted

Lewis acid catalysis (LLA), the concept Yamamoto came up with[39] in 1998. The high enantioselectivity can be explained by favorable coordination of the less sterically hindered lone pair of the carbonyl and face-selective hydride transfer via a six-membered transition state. The catalyst turnover may be achieved by two pathways: 1) the alkoxide coordinated to the endocyclic boron reacts with the exocyclic boron through a 4-membered ring transition state **I-38** to generate borinate **I-40** and oxazaborolidine **I-34**; or 2) reacts with another BH_3 molecule via a 6-membered ring transition state **I-39** to produce borinate **I-40** and complex **I-35**. Applying a similar strategy, Brown and coworkers reported[40] the asymmetric addition of organozinc reagents to aldehydes using an oxazaborolidine catalyst to produce chiral alcohols with 52-95% ees.

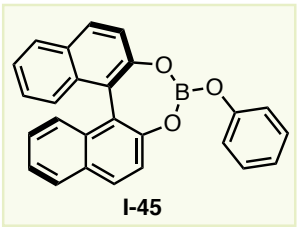
Scheme 1.8 Proposed mechanism for the CBS reduction



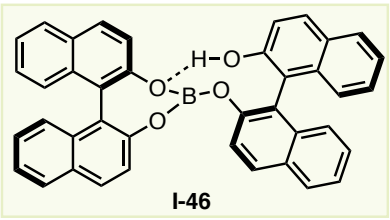
Scheme 1.9 Borate catalysts by Yamamoto



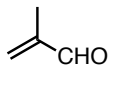
CAB **I-42**, R = H
CAB **I-43**, R = 3,5-$(CF_3)_2C_6H_3$
CAB **I-44**, R = 2-$MeOC_6H_4$



I-45



I-46

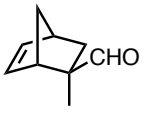


I-32

+

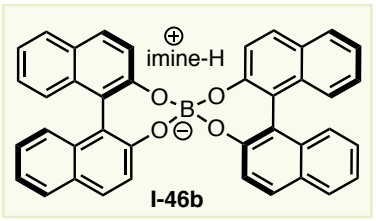
4 equiv
I-31

catalyst
–78 °C

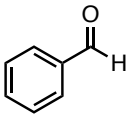


I-33 (1)

catalyst	
10 mol% CAB **I-43**	85%, 89:11 exo/endo, 96% ee (*R*)
10 mol% BLA **I-47**	>99%, >99:1 exo/endo, 99% ee (*R*)
10 mol% **I-48**	97:3 exo/endo, 65% ee (*S*)
5 mol% BLA **I-49**	96%, >99:1 exo/endo, 99% ee (*S*)
5 mol% BLA **I-50**	>95%, 94:6 exo/endo, 86% ee (*R*)

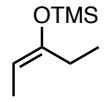


I-46b



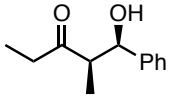
I-51a

+

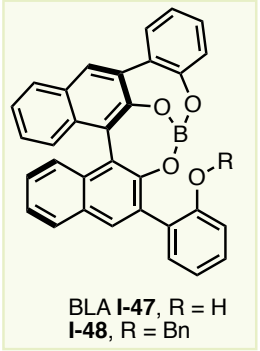


I-52

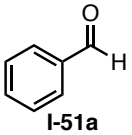
20 mol% CAB **I-42**
EtCN, –78 °C, 2 h



I-53
96%, 94:6 syn/anti
96% ee (2)

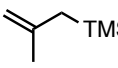


BLA **I-47**, R = H
I-48, R = Bn



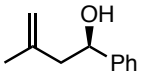
I-51a

+

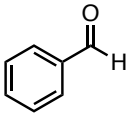


I-54

20 mol% CAB **I-43**
EtCN, –88 °C, 4.5 h

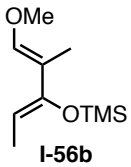


I-55
94%, 91% ee (3)



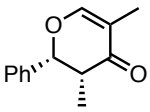
I-51a

+

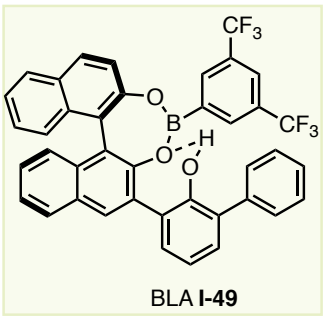


I-56b

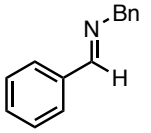
20 mol% CAB **I-44**
EtCN, –78 °C



I-57
86%, 97% ee (4)

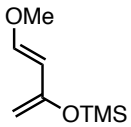


BLA **I-49**



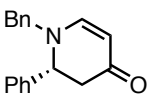
I-58a

+



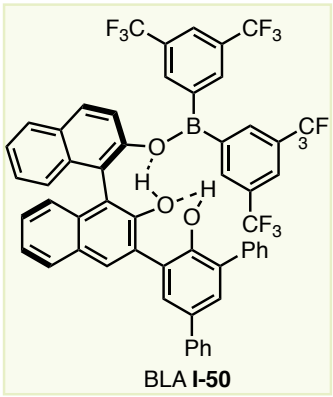
I-56a

1 equiv catalyst
DCM, 4A MS
–78 °C, 12 h

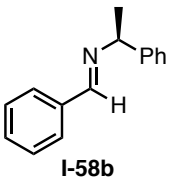


I-59 (5)

catalyst	
BLA **I-45**	75%, 82% ee
BLA **I-46**	78%, 86% ee

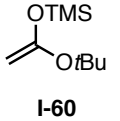


BLA **I-50**



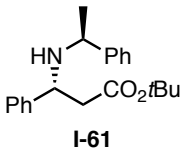
I-58b

+



I-60

1 equiv catalyst
DCM, 4A MS
–78 °C, 12 h



I-61 (6)

catalyst	
BLA **I-45**	59%, 92% ee
BLA **I-46**	65%, >99% ee

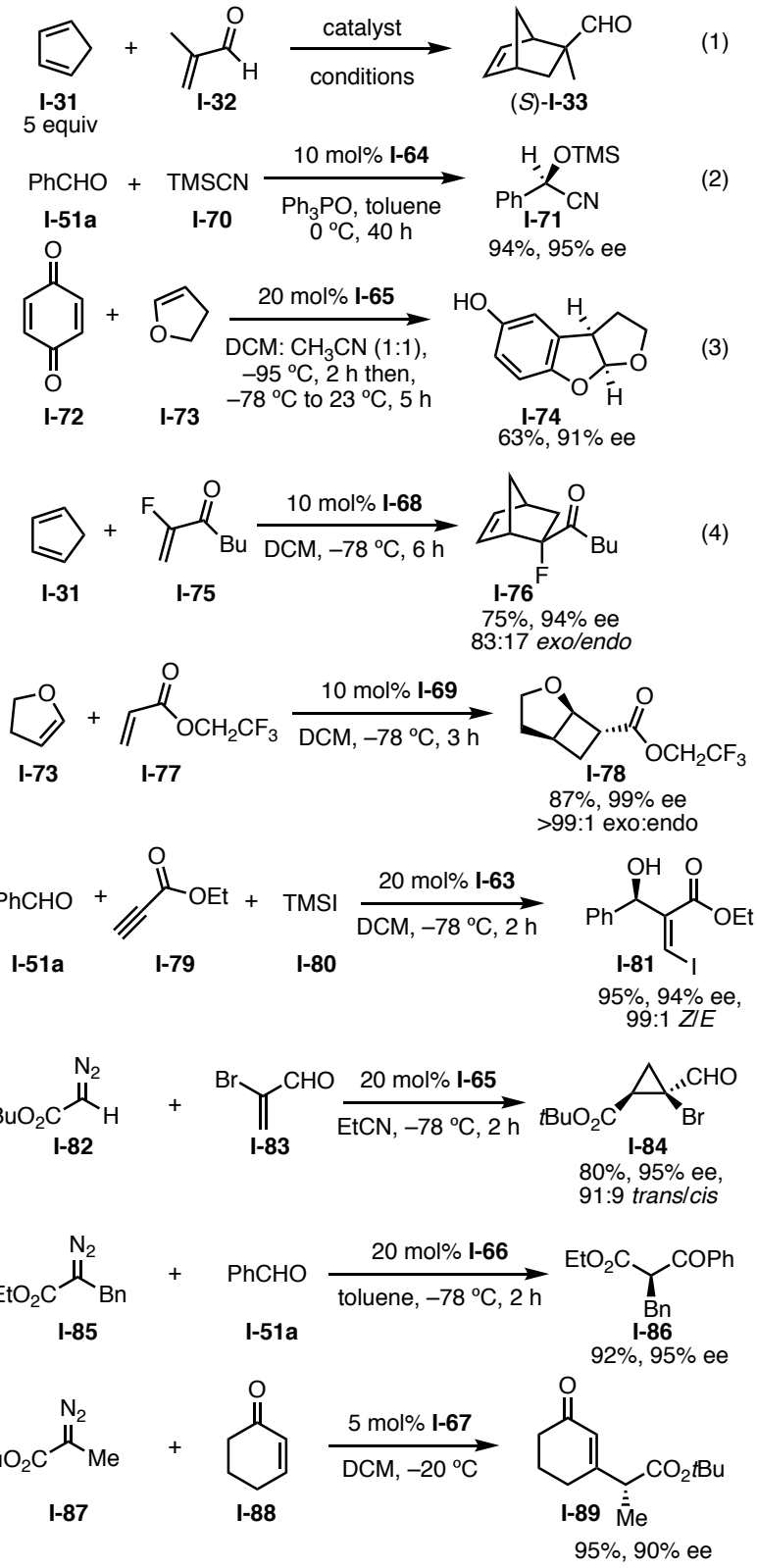
Yamamoto's group was the major player in the field of asymmetric borate catalysis. In 1988, they reported[41] the ADA reaction of acrylic acid and cyclopentadiene catalyzed by 10 mol% of a chiral acyloxyborane (CAB) catalyst **I-43** derived from tartaric acid (eq 1, *Scheme 1.9*). They later successfully applied CAB **I-42** to **I-44** to the ADA reaction of α, β-unsaturated aldehydes with dienes[42-43], the aldol reactions of silyl ketene acetals with aldehydes (eq 2, *Scheme 1.9*)[44], the allylation of aldehydes (eq 3, *Scheme 1.9*)[45] and the asymmetric hetero Diels-Alder reaction (AHDA) of aldehydes with Danishefsky diene **I-56b** (eq 4, *Scheme 1.9*)[46]. The activation of CAB was later proposed[47] to be a Brønsted acid assisted chiral Lewis acid catalysis (BLA). In 1992, another boron catalyst **I-45** was prepared[48] from optically pure BINOL and triphenyl borate in a 1:1 ratio. The proposed mixed borate **I-45** was not isolated or spectroscopically characterized. It was employed as a stoichiometric chiral Lewis acid for AHDA of imines **I-58a** with Danishefsky diene **I-56a** (eq 5, *Scheme 1.9*)[48-50] and aldol reactions of aldimines **I-58b** (eq 6, *Scheme 1.9*)[51-52]. By changing the ratio of BINOL and $B(OMe)_3$ to 2:1, the borate **I-46** was generated and the structure of its complex with an imine was determined by X-ray diffraction[53]. The complex **I-46** can promote the same reaction with higher efficiency in general (eq 5 and 6, *Scheme 1.9*). The structure of **I-45** was called into question by other researchers[54] due to the fact that many attempts to prepare it gave Kaufmann's propeller **I-30** instead of the mixed borate **I-45**. Moreover, involvement of **I-46** was indicated by a nonlinear effects study[55] on the AHDA catalyzed by a presumed catalyst with the structure **I-45**. The mode of activation of the imine by the catalyst was misinterpreted[56] as a BLA catalyst **I-46** in Yamamoto's paper: the X-ray structure clearly suggested it to be a Brønsted acid catalyst.

Therefore, this would be one of the earliest examples[57] of asymmetric counteranion-directed catalysis (ACDC), a concept first described[58] in 2006 by List. The concept and designed of BLA was first introduced in the report[59] of ADA of α,β-enals and dienes by Yamamoto and coworkers in 1994. Excellent enantioselectivity and exo/endo selectivity were obtained in the presence of 10 mol% catalyst **I-47**. The control catalyst **I-48** lacking the 4th hydroxyl group gave the opposite ee of the desired product **I-33** with low selectivity. This result provided strong evidence for the combined acid catalysis[47]. They subsequently introduced[60-61] new BLA catalysts **I-49** and **I-50** generated from a boronic acid and a chiral triol. These catalysts provide excellent enantio- and exo/endo selectivity for ADA reaction (eq 1, *Scheme 1.9*) and gave better results for intramolecular ADA than the CAB catalyst **I-42**. In 2007 and 2008, Nakagawa and coworkers reported[62-63] the enantioselective Pictet-Spengler reaction promoted by 2 equivalents of BLA **I-46**. High yields (39-94%) and moderate enantioselectivities (15-91%) were achieved for 6 examples.

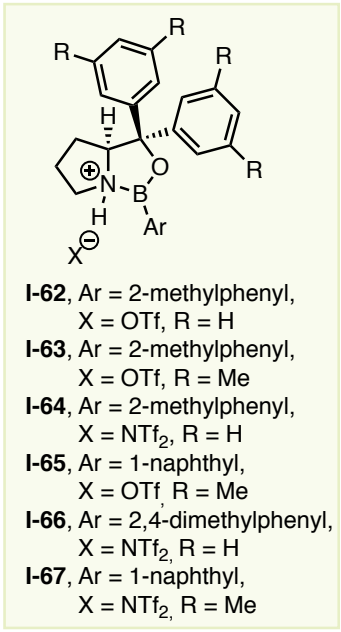
The activation mode of the acid activated chiral oxazaborolidine was revisited[64] by Corey and coworkers, who reported the highly enantioselective ADA reaction of α,β-enals catalyzed by **I-62** and **I-63** (eq 1, *Scheme 1.10*). The same type of catalyst was subsequently employed in the ADA reaction of other α,β-unsaturated carbonyl compounds[65-68], enantioselective cyanosilylation of aldehydes[69] and ketones[70] (eq 2, *Scheme 1.10*), and asymmetric [3+2] cycloaddition of 1,4-benzoquinones **I-72** and 2,3-dihydrofuran **I-73**[71] (eq 3, *Scheme 1.10*). The ADA reactions catalyzed by chiral oxazaborolidine **I-62**-**64** were applied in multiple total synthesis[72-75]. Yamamoto and

coworkers extended their concept of LLA catalysis to oxazaborolidine catalyst **I-68** by employing Lewis acid $SnCl_4$ instead of Brønsted acid as an activator. They successfully applied this moisture-tolerant **I-68** in the ADA reaction of dienes with α,β-unsaturated carbonyl compounds (eq 1, *Scheme 1.10*)[76] and α-halo-α,β-unsaturated ketones (eq 4, *Scheme 1.10*)[77]. Corey and coworkers also demonstrated that oxazaborolidine **I-69** activated by Lewis acid $AlBr_3$ were effective in catalyzing the ADA reactions (eq 1, *Scheme 1.10*)[78-79] and [2+2] cycloadditon reaction of trifluoroehtyl acrylate **I-77** to enol ethers (eq 5, *Scheme 1.10*)[80]. Ryu and coworkers reported[81-82] an asymmetric three-component coupling reaction catalyzed by oxazaborolidine catalyst **I-63**. The chiral β-iodo Morita-Baylis-Hillman product **I-81** can be prepared in up to 99% yield and excellent asymmetric induction (62-94% ee) (eq 6, *Scheme 1.10*). Subsequently they reported a variety of enantioselective reactions involving diazoesters catalyzed by acid activated oxazaborolidine catalyst **I-65**-**67**[83-85]. Cyclopropanation of substituted acroleins afforded the chiral *trans*-cyclopropane **I-84** in excellent yield and ee (eq 7, *Scheme 1.10*). Interestingly, a similar reaction in DCM catalyzed by **I-66** gave 1,3-dipolar adducts with high to excellent ees (not shown)[86]. An asymmetric Roskamp reaction[87-90] of diazo compounds with aldehydes catalyzed by **I-66** produced chiral β-keto carbonyl compounds in high yields and excellent enantioselectivities (eq 8, *Scheme 1.10*). When they switched solvent from toluene to propionitrile, the same insertion intermediate underwent 1,2-aryl migration instead of 1,2-hydride migration to yield the formal aryl-CHO bond insertion product (not shown)[91]. A highly enantioselective formal C_{sp2}-H insertion of diazo esters to cyclic enones has been developed[92] (eq 9, *Scheme 1.10*).

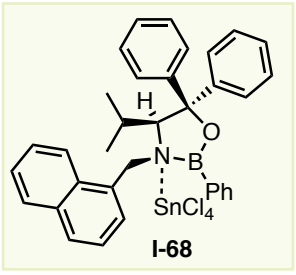
Scheme 1.10 Activated oxazaborolidine catalysts



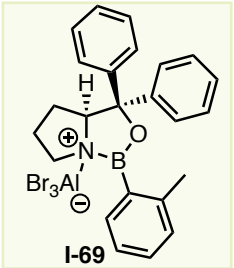
catalyst/condition for eq 1	(*S*)-**I-33**
6 mol% **I-63** –95 °C, 1 h	97%, 96% ee 91:9 *exo/endo*
1 mol% **I-68** DCM, –78 °C, 2 h	99%, 95% ee 68:32 *exo/endo*
4 mol% **I-69** –78 °C, 2 h	99%, 93% ee 92:8 *exo/endo*



I-62, Ar = 2-methylphenyl,
X = OTf, R = H
I-63, Ar = 2-methylphenyl,
X = OTf, R = Me
I-64, Ar = 2-methylphenyl,
X = NTf_2, R = H
I-65, Ar = 1-naphthyl,
X = OTf, R = Me
I-66, Ar = 2,4-dimethylphenyl,
X = NTf_2, R = H
I-67, Ar = 1-naphthyl,
X = NTf_2, R = Me



I-68



I-69

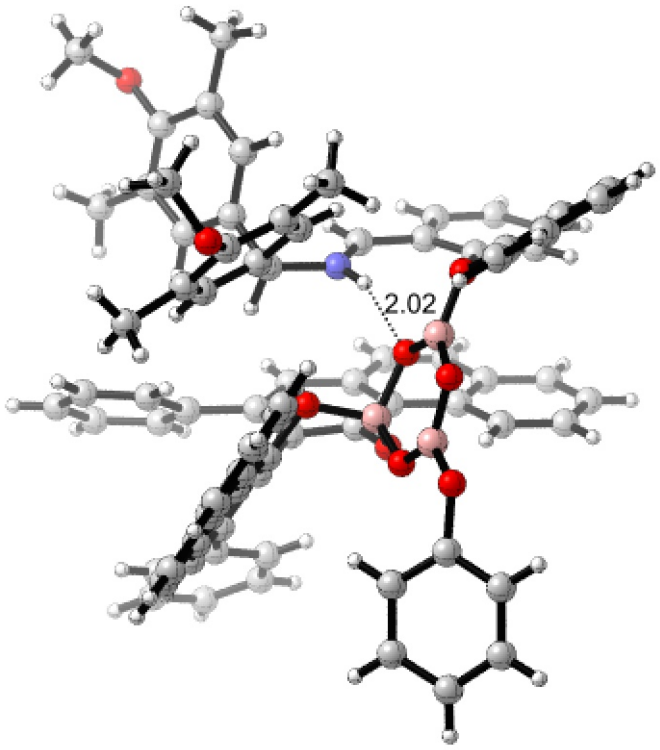


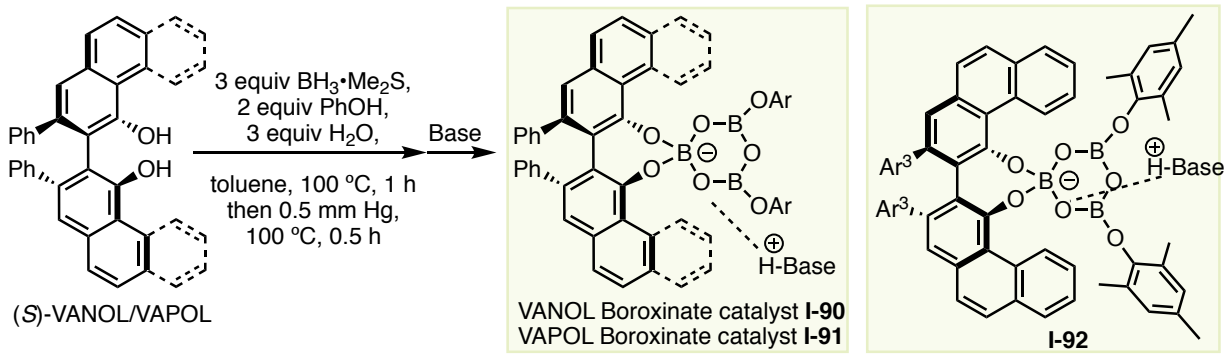
Figure 1.1 X-ray Structure of boroxinate-imine complex

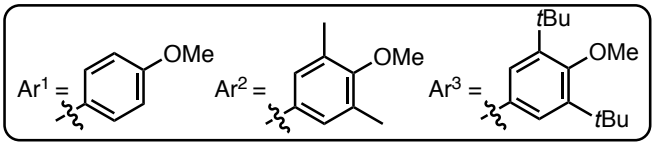
Another important boron catalyst in asymmetric catalysis has been contributed by the Wulff group (*Scheme 1.11*). In 1999, Wulff and Antilla reported[93] the asymmetric aziridination (AA) reaction of imines with ethyl diazoacetate **I-94** (EDA) catalyzed by a VAPOL-boron species. The catalyst was generated by reacting 1 equiv of VAPOL with 3 equiv BH_3•THF and was thought to be functioning as a Lewis acid catalyst. Understanding of the nature of the catalyst increased along with the evolution[94-95] of the preparation method for the catalyst. Nonlinear studies[95] with the ligands revealed a linear relationship between the ee of the ligands and product, suggesting that one molecule of the ligand most likely was involved in the active catalyst. Mechanistic investigations[96-97] by ^{11}B and ^{1}H NMR, together with crystal structures of the precatalyst-iminium complex (*Figure 1.1*) provide strong evidence that the reaction of imines is catalyzed by a Brønsted acid

mechanism. Natural abundance ^{13}C KIE studies[98] showing unity for the iminium carbon in contrast to a large KIE for the α-carbon of the EDA suggested that aziridine formation is a two-step process with the ring closure step to be the first irreversible step. This aziridination of imines was extensively studied by Wulff and coworkers (eq 1, *Scheme 1.11*). Benzhydryl imines **I-93a** prepared from aromatic and aliphatic aldehydes can be aziridinated with EDA in high yield and excellent asymmetric induction. By introducing electron-donating groups into the phenyl group of the benzhydryl imine[99-101] (DAM **I-93b**, MEDAM **I-93c**, BUDAM **I-93d**), both the yields and stereoselectivities of the *cis*-aziridines were generally improved. In terms of the scope of the diazo compounds, diazomethyl ketones bearing alkene, alkyne, ester, amide, acetal and bromo group, prepared either from diazo transfer reaction of methyl ketone with 4-dodecylbenzenesulfonyl azides[102], or by reacting acid chlorides with $TMSCHN_2$[103], were compatible with the reaction condition, giving *cis*-aziridines with high yields and excellent ees. Trisubstituted aziridines can also be obtained[104] with good yields (30-85%) and excellent ees (83-98%) by employing α-alkyl-diazo-*N*-acyloxazolidinone with the more reactive *N*-Boc aryl imines. More recently, a multi-component AA of aldehydes with amines and EDA was developed[105-106]. This method enables the preparation of unbranched aliphatic substituted aziridines since their imines were difficult to obtained in high purity. A systematic study[107] of structure-activity relationship on the VANOL ligand for the *cis*-aziridination identified the optimal VANOL ligand as 7,7'-*t*Bu_2VANOL. The synthetic utility of *cis*-aziridination has been illustrated by the synthesis of (–)-Chloroamphenicol[108], BIRT-377[109] and most recently, two stereoisomers of sphinganine[110] via a multicomponent AA. By simply changing the ethyl

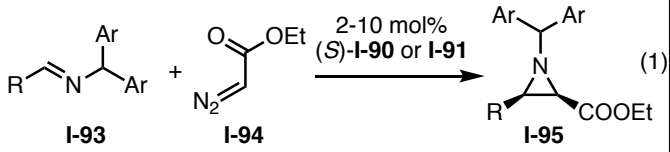
diazo acetate (EDA) to diazoacetamide **I-23b**, *trans*-aziridines could be prepared[111] in good (7:1 to 36:1) *trans*/*cis* ratios and excellent (82-99%) ees (eq 2, *Scheme 1.11*). The reason for the reversal in diastereoselectivity has been identified[112] by DFT calculation to be associated with a H-bonding between the amidic hydrogen and an oxygen atom of the boroxinate catalyst. The synthetic application of the *trans* AA was demonstrated in the syntheses of all four stereoisomers of sphinganine[110]. Hetero ADA of imines **I-93a** with Danishefsky diene **I-56a** was developed[113] by Wulff and coworkers (eq 3, *Scheme 1.11*). Interestingly, it was found that an excess of triphenylborate could help with the turnover with sub-stoichiometric amount of chiral boron catalyst. The catalyst was proposed to be a Lewis acid in the original report but now it is thought that a boroxinate is involved[56, 114]. In 2011, Wulff and Ren reported[114] the aza-Cope rearrangement of imines **I-98** catalyzed by a boroxinate catalyst in the presence of benzoic acid (eq 4, *Scheme 1.11*). Chiral homoallylic amines **I-99** could be prepared with excellent optically purities (80-96%) via a simple process. The usefulness of this method has also been demonstrated[115] in the total synthesis of (+)-sedridine and (+)-allosedridine. Wulff and coworkers reported[116] that the asymmetric catalytic three-component Ugi reaction could be possible by using a boroxinate catalyst (eq 5, *Scheme 1.11*). The optimal catalyst **I-92** was identified by screening 13 ligands, 12 amines and 47 alcohols or phenols.

Scheme 1.11 Boroxinate catalysts by Wulff





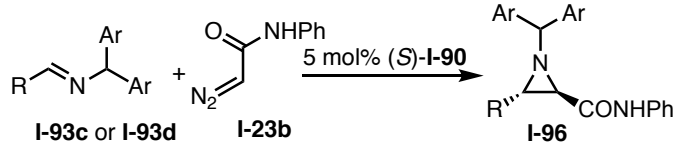
***cis*-Aziridination**
Base = imine **I-93a**-**I-93d**



(1)

R = aryl, 1°-, 2°-, 3°-alkyl;
I-93a, Ar = Ph, 15 examples, 54-91%, 90-98% ee
I-93b, Ar = Ar^1, 10 examples, 14-95%, 52-98% ee
I-93c, Ar = Ar^2, 10 examples, 67-98%, 90-99% ee
I-93d, Ar = Ar^3, 11 examples, 57-99%, 78-99% ee
R = alkynyl,
I-93d, 6 examples, 24-86%, 53-97% ee

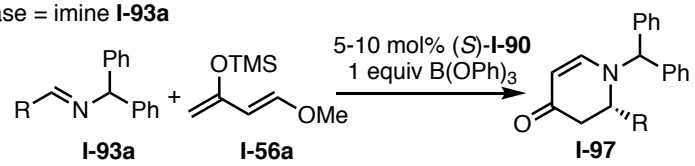
***trans*-Aziridination**
Base = imine **I-93c** or **I-93d**



(2)

R = aryl, 1°-, 2°-, 3°-alkyl;
Ar = Ar^1, Ar^2,
13 examples,
64-90%, 82-99% ee

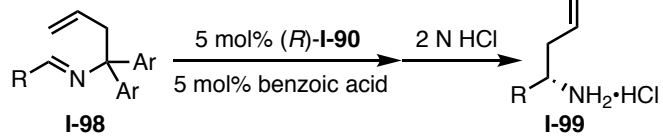
Heteroatom Diels-Alder
Base = imine **I-93a**



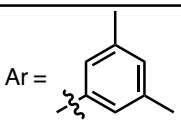
(3)

R = aryl, 2°-alkyl,
10 examples,
45-85%, 73-93% ee

aza-Cope rearrangement
Base = imine **I-98**

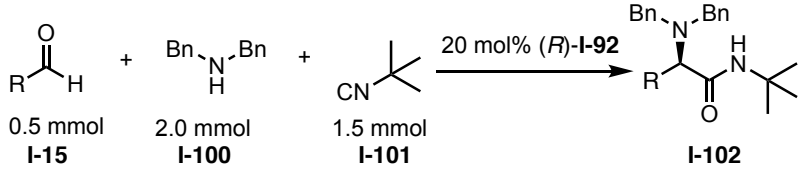


(4)



R = aryl, 1°-, 2°-, 3°-alkyl;
18 examples,
57-99%, 80-96% ee

Three-Component Asymmetric Catalytic Ugi Reaction
Base = iminium generated from **I-15** and **I-100**

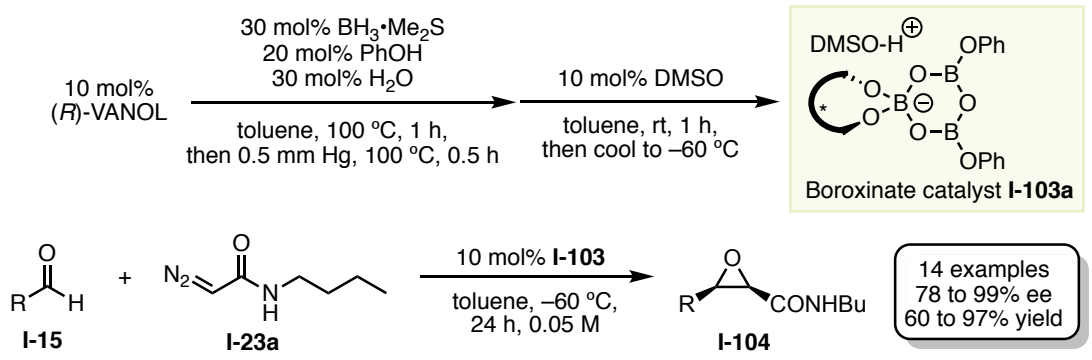


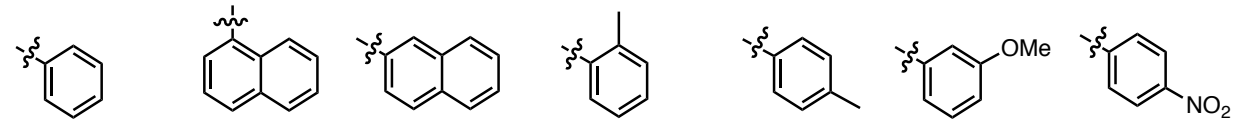
(5)

R = aryl
16 examples,
51-87%, 56-90% ee

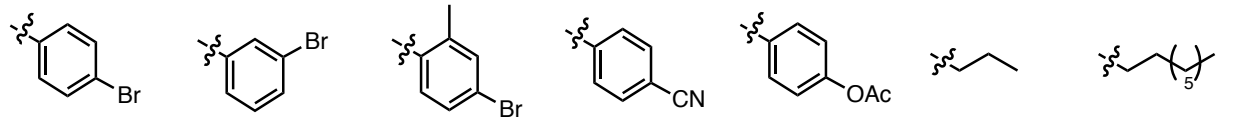
While developing the *trans*-aziridination of imines with diazoacetamides with boroxinate catalyst, Desai and Wulff found[117] that *cis*-epoxides could be formed from aldehydes and diazoacetamides, although in low yields. Gupta and Wulff went on to further develop this reactions[118] and found that the *cis*-epoxide can be obtained in 62% yield by reacting benzaldehyde and phenyl diazoacetamide in the presence of 20 mol% $B(OPh)_3$. And gratifyingly, chiral *cis*-epoxides could be obtained in the presence of 10 mol% of boroxinate catalyst albeit with rather low yields and asymmetric inductions. Gupta also found that DMSO was the optimal base for generation of the boroxinate catalyst (an aldehyde is not basic enough to induce boroxinate formation). After further optimization by screening different diazoacetamides, concentration, solvent and temperature, the optimal condition for boroxinate-catalyzed epoxidation was established by Gupta (*Table 1.1*). Excellent yields and ees were observed for aromatic aldehydes with substitutions in the *m*- or *p*-positions. *o*-Substituted aromatic aldehydes and aliphatic aldehydes only gave moderate to good results. The goal of further studies would focus on improving asymmetric inductions for these substrates. The strategy of optimization would be similar to that used for Ugi reaction development which led to the first highly enantioselective Ugi reaction[116].

Table 1.1 Scope of boroxinate catalyzed asymmetric epoxidation[118]





88%, 99% ee | 97%, 92% ee | 92%, 98% ee | 60%, 80% ee | 80%, 99% ee | 80%, 90% ee | 70%, 92% ee

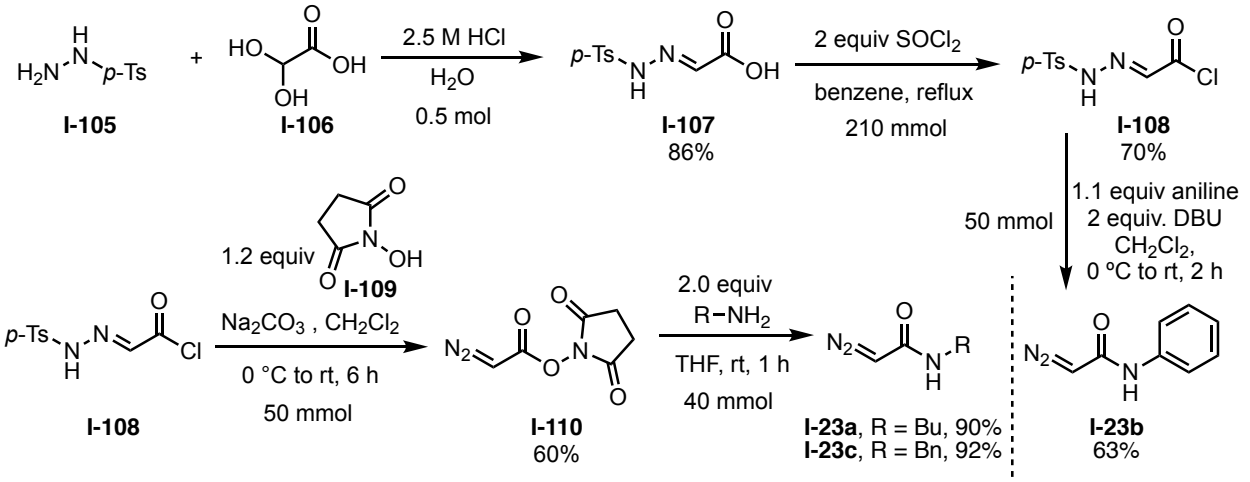


88%, 99% ee | 88%, 96% ee | 70%, 80% ee | 84%, 96% ee | 82%, 97% ee | 65%, 78% ee | 84%, 90% ee

1.3 Optimization and KIE study of epoxidation catalyzed by VANOL-boroxinate

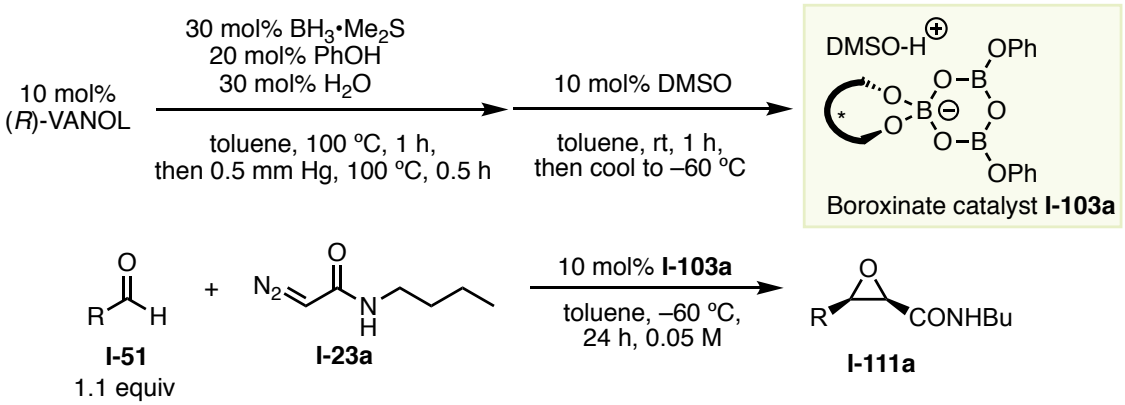
We started the investigation by preparing the diazo acetamide by a modified procedure from literature[119] (*Scheme 1.12*). Succinimidyl diazoacetate **I-110** could be obtained in good yield from gram scale preparation and is stable in crystalline form at room temperature under nitrogen for months. The *N*-alkyl diazoacetamide **I-23a** and **I-23c** can be prepared in excellent yield in a single step under mild conditions from **I-110**. However, the reaction of **I-110** with aniline is quite slow. Therefore, the preparation of the *N*-aryl diazoacetamide **I-23b** was achieved by reaction of **I-108** with aniline and then elimination of the tosyl group in the presence of DBU.

Scheme 1.12 Syntheses of diazoacetamide **I-23**



With the diazoacetamides in hand, attention was next turned to testing the epoxidation of benzaldehyde with *N*-butyl diazoacetamide **I-23a** following the procedures by Gupta (*Table 1.2*). It was found that the results of reactive aromatic aldehydes could be reproduced (entry 1 and 2, *Table 1.2*). The results from reactions with less reactive substrates were rather hit and miss (entry 3-5, *Table 1.2*). It was also noticed that the yields and asymmetric inductions of the reaction were very sensitive to temperature (entry 4 vs 6, *Table 1.2*). When the addition of aldehydes was carried out as a solution at –60 ºC instead of neat at rt, the reduced temperature fluctuations improved the ees of the epoxides. To increase the reproducibility, we made a few modifications to the procedure: 1) increased the scale of the reaction from 0.2 to 0.5 mmol; 2) the aldehydes were cooled to the reaction temperature before addition.

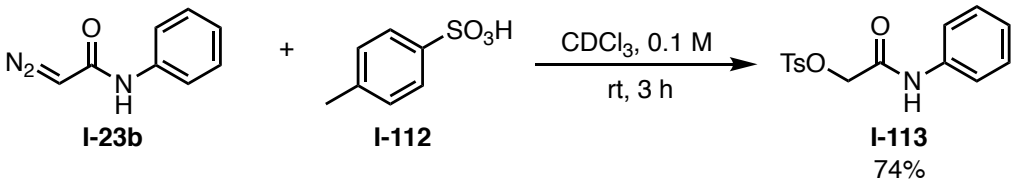
Table 1.2 Boroxinate catalyzed asymmetric epoxidation



entry	aldehyde	R	%conversion[c] (**I-23a**)	%yield[d] (**I-111a**)	%ee[e] (**I-111a**)
1[a]	**I-51a**	Ph	> 99	88	> 99
2[a]	**I-51b**	4-MeC_6H_4	> 99	81	99
3[a]	**I-51c**	2-MeC_6H_4	84	53	79
4[b]	**I-51d**	cyclohexyl	93	54	67
5[b]	**I-51e**	nonyl	ND	81	79
6[bf]	**I-51d**	cyclohexyl	93	55	84

[a]The reaction was carried out on a 0.2 mmol scale. [b]The reaction was carried out on a 0.5 mmol scale. [c]Determined by ^1H NMR analysis of crude product using Ph_3CH as an internal standard. [d]Isolated yield after chromatography on silica gel. [e]As judged by chiral HPLC. [f]Aldehyde was added as a toluene solution precooled to –60°C.

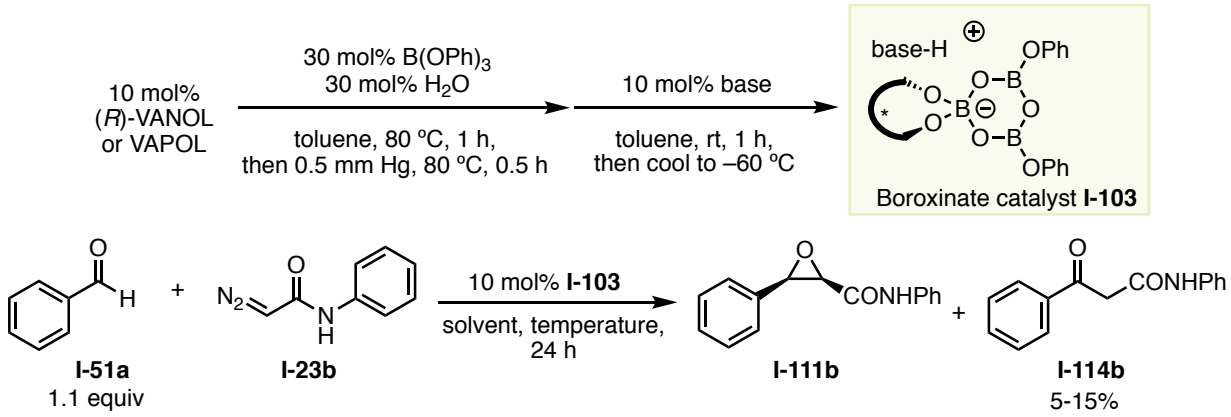
Scheme 1.13 Protonation/nucleophilic addition to **I-23b**



In order to have a good comparison, it was decided to use *N*-phenyl diazoacetamide **I-23b** as the substrate for ^{13}C KIE study because the same substrate has been employed in the KIE studies for *trans*-[120] and alkynyl *cis*-aziridination[121]. Epoxidation of benzaldehyde **I-51a** with **I-23b** was chosen as the model epoxidation and further optimized (*Table 1.3*). The reaction is very sluggish at room temperature giving low yield and racemic product (entry 1 and 2, *Table 1.3*). Presumably this was due to the side

reaction between diazoacetamide with boroxinate catalysts or ligands at room temperature[106]. Indeed, treatment of diazoacetamide **I-23b** with 1 equiv TsOH at room temperature gave rise to **I-113** in 74% yield (*Scheme 1.13*). The same reaction at –60 ºC only gave 25% of the O-H insertion product. In terms of ligands, VANOL is superior to VAPOL, which gave almost racemic epoxide at –40 ºC either with or without DMSO (entry 4 & 6 vs 3 & 5, *Table 1.3*). The enantioselectivity of epoxidation was improved in the presence of weak basic additives (entry 4,7,8 vs 6, *Table 1.3*). Whereas, stronger amine base shut down the reaction completely (entry 9 & 10, *Table 1.3*). Among the bases we screened, DMSO gave best result in terms of yield. Surprisingly the reaction gave comparable result with aniline given that there is the significant pKa difference between protonated aniline and aldehyde (pKa = 4.6 vs pKa = –7). Unlike *N*-butyl diazoacetamide **I-23a**, switching the solvent from chloroform to toluene resulted in lower conversion and lower ee (entry 11 & 12 vs 4 & 14, *Table 1.3*). This might be explained by the huge solubility difference of these two diazoacetamides in toluene. Enantioselectivity was indicated to be dependent on concentration. Lowering the concentration resulted in higher ee but gave a slower reaction (entry 13 & 15 vs 12 & 14, *Table 1.3*). Further experiments using different addition techniques indicated that the local warming effect seems to play a role (entry 17 & 18 vs 14, *Table 1.3*). A higher yield and enantioselectivity was observed when boron source was changed from triphenylborate to borane dimethyl sulfide complex (entry 16 vs 14, *Table 1.3*). It is worth noting that in the epoxidation reaction catalyzed by boroxinate, the major side product we observed in 5-15% NMR yield is the Roskamp product β-ketoamide **I-114b**.

Table 1.3 Optimization of asymmetric epoxidation using *N*-phenyl diazoacetamide **I-107b**



I-51a
1.1 equiv

I-23b

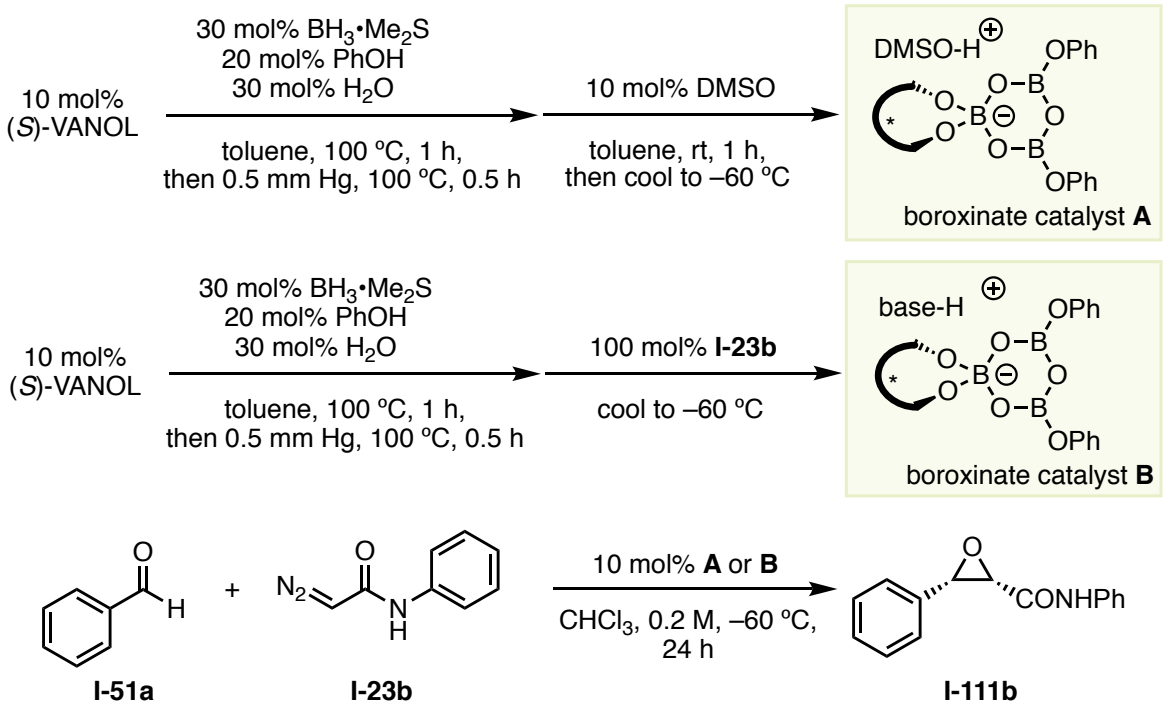
I-111b

I-114b
5-15%

entry[a]	ligand	base	solvent	conc. [M]	temperature [° C]	%conversion[d] (**I-23b**)	%yield[e] (**I-111b**)	cis/trans[d] (**I-111b**)	%ee[f] (**I-111b**)
1	VAPOL	DMSO	$CHCl_3$	0.5	25	99	26	8.8:1	7
2	VANOL	DMSO	$CHCl_3$	0.5	25	99	25	11:1	0
3	VAPOL	DMSO	$CHCl_3$	0.5	–40	99	47	25:1	–5
4	VANOL	DMSO	$CHCl_3$	0.5	–40	99	64	49:1	62
5	VAPOL	none	$CHCl_3$	0.5	–40	99	48	26:1	5
6	VANOL	none	$CHCl_3$	0.5	–40	99	53	35:1	36
7	VANOL	$PhNH_2$	$CHCl_3$	0.5	–40	98	51	> 50:1	64
8	VANOL	acetanilide	$CHCl_3$	0.5	–40	99	51	24:1	51
9	VANOL	DMAP	$CHCl_3$	0.5	–40	ND	< 1	—	—
10	VANOL	Et_3N	$CHCl_3$	0.5	–40	ND	< 1	—	—
11	VANOL	DMSO	toluene	0.5	–40	99	60	26:1	41
12	VANOL	DMSO	toluene	0.5	–60	99	44	29:1	51
13	VANOL	DMSO	toluene	0.05	–60	ND	29	32:1	82
14	VANOL	DMSO	$CHCl_3$	0.5	–60	95	60	> 50:1	61
15	VANOL	DMSO	$CHCl_3$	0.05	–60	87	53	> 50:1	92
16[b]	VANOL	DMSO	$CHCl_3$	0.5	–60	99	70	> 50:1	67
17[c]	VANOL	DMSO	$CHCl_3$	0.5	–60	99	69	> 50:1	70
18[d]	VANOL	DMSO	$CHCl_3$	0.4	–60	99	58	> 50:1	76

[a]General procedure: Reaction was performed in a Schlenk flask. Benzaldehyde was added using a syringe at rt. [b]BH_3•Me_2S and PhOH were used instead of $B(OPh)_3$. [c]Benzaldehyde was precooled and added using canula. [d]Reaction was performed in a RBF; catalyst was precooled and added using syringe. [d]Determined by ^1H NMR analysis of crude product using Ph_3CH as an internal standard. [d]Isolated yield after chromatography on silica gel. [e]As judged by chiral HPLC. [f]Aldehyde was added as a precooled toluene solution.

Table 1.4 KIE samples preparation



Set	Catalyst	**I-51a** [mmol]	**I-23b** [mmol]	%yield[a] (**I-111b**)	%ee[b] (**I-111b**)
1	**A**	2	10	57	91
	A	10	2	37	82
2	**A**	2.4	12	80	90
	A	12	2.4	67	93
3	**B**	2.4	12	65	60
	B	12	2.4	45	58
4	**B**	2.4	12	65	61
	B	12	2.4	60	58

[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC.

Entry 16 in *Table 1.3* was chosen as the condition for KIE sample preparation with 0.2 M as the concentration to ensure 100% conversion of the limiting reagent. Under the optimized reaction conditions, 4 sets of modified procedures[122] to measure KIE were performed (*Table 1.4*). Two sets were with DMSO as an additive while the other two were without DMSO to explore the possibility of a different mechanism. In each set of

experiments, there were two reactions: reaction #1 with 0.2 equivalent aldehyde and 1.0 equiv of diazoacetamide and the reverse stoichiometry for reaction #2. One reactant is excess and reacts with low conversion in reaction #1, while it is the limiting reagent in reaction #2, where the product serves as the 100%-reaction standard. Interestingly, in 4 sets of experiments, those with excess diazoacetamide gave higher yields than those with excess aldehyde. In agreement with the optimization studies, the samples obtained from the reactions with DMSO were determined to have higher ees (entry 1&2 vs 3&4, *Table 1.4*).

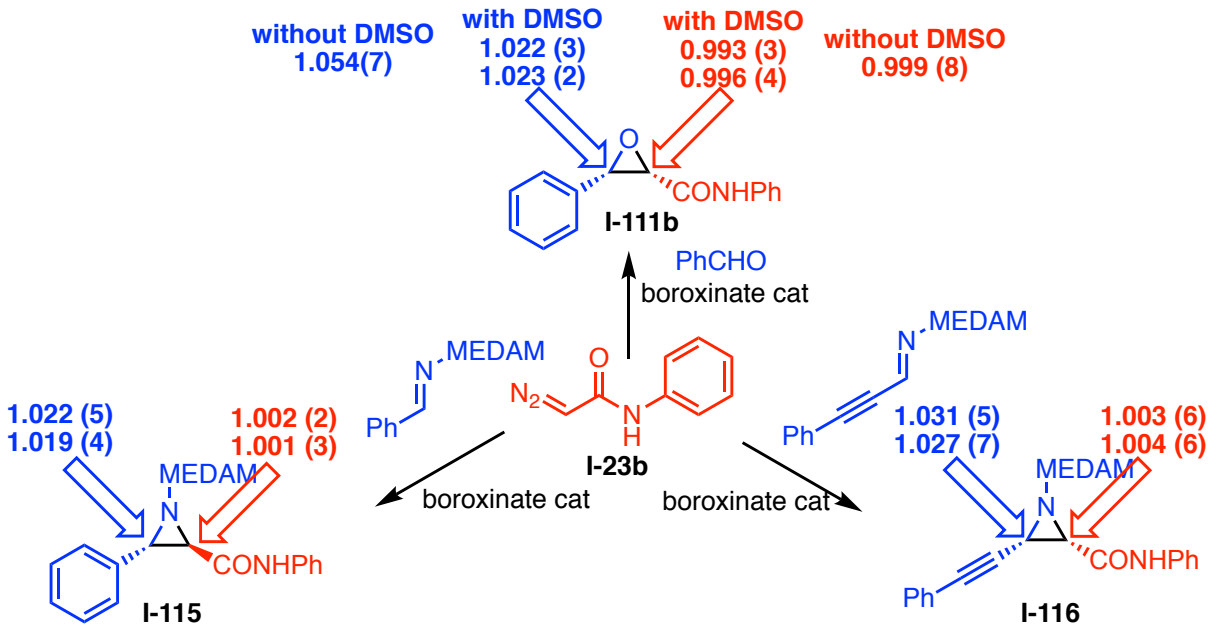


Figure 1.2 Experimental ^{13}C KIE for the reaction of *N*-phenyl diazoacetamide **I-107b**

The ^{13}C KIEs for both substrates in this reaction were determined by the methodology[123] for high-precision determination of small KIEs at natural abundance developed by Singleton and coworkers. The data was collected and processed by Dr. Mathew Vetticatt. The KIE values obtained from three independent experiments are shown in *Figure 1.2*, together with the KIE data[124] of *trans*-aziridination and alkynyl *cis*-

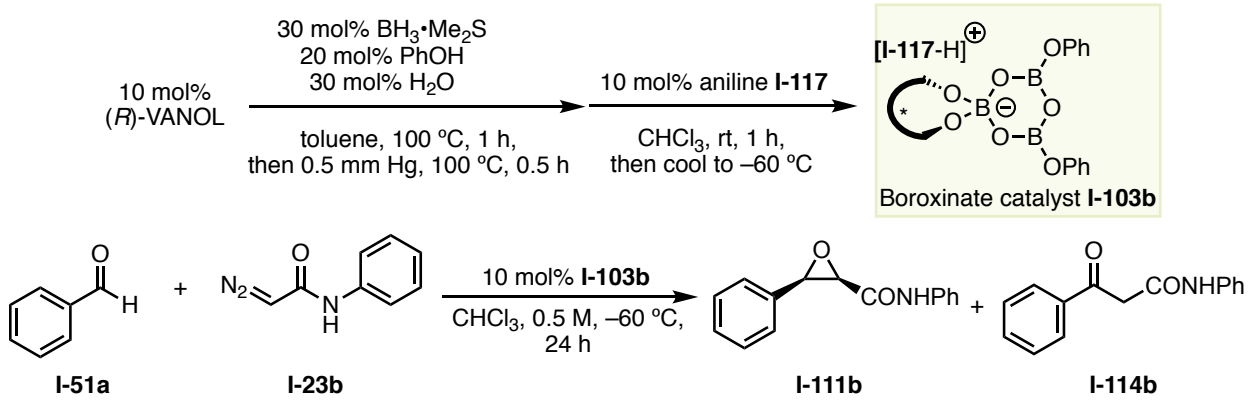
aziridination. In contrast to the KIE results from *cis*-aziridination[98] where a large ^{13}C KIE of ~5% was observed for the α-carbon of EDA, moderate ^{13}C KIEs (2-3%) were observed for the α-carbon of the imine or of the aldehyde for the three reactions with *N*-phenyl diazoacetamide **I-107b**. This suggest that the first irreversible step would be the addition of the diazoacetamide to imine/aldehyde carbons to form the diazonium ion intermediate. The disparity of KIE between epoxidation reactions with and without DMSO indicated the mechanism is different for two conditions.

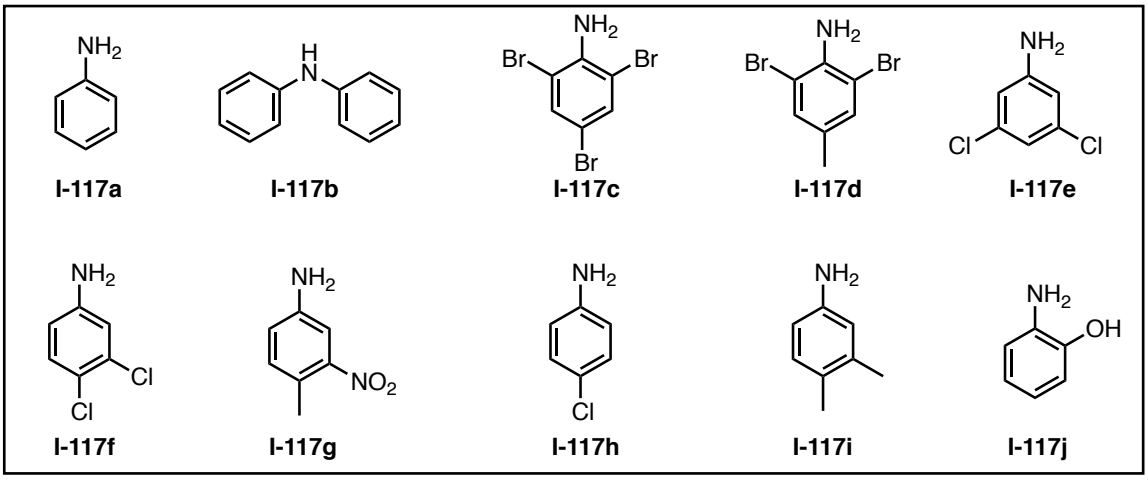
1.4 Screening of aniline as base additive

During the optimization of the epoxidation reaction, it was found that addition of aniline gave comparable result to DMSO. Examining variations of aniline might be worthwhile for further optimization and a mechanistic study. A variety of aniline derivatives **I-117a**–**j** was tested under the optimized condition (*Table 1.5*).

The weakest base in the bunch, diphenylamine **I-117b**, gave a result that is close to DMSO and better than aniline. Interestingly, the highest ee was observed when 2-aminophenol **I-117j** was used, a base that is slightly stronger than aniline. All the other anilines with either an electron donating group (**I-117i**) or withdrawing groups (**I-117c**-**e**, **I-117f-h**) gave slightly worse results than aniline. Another observation is that when the reaction is more enantioselective, the yield of the side product **I-114b** was subdued. However, the real role of 2-aminophenol is not clear. Because not only can **I-117j** function as a base, but it also can switch with the phenol in the boroxinate and become incorporate into the catalyst.

Table 1.5 Epoxidation catalyzed by boroxinate with various anilines as base additive





entry	base	%conversion[a] (**I-23b**)	%yield[a] (**I-114**)	%yield[b] (**I-111b**)	cis/trans[b] (**I-111b**)	%ee[c] (**I-111b**)
1	none	95	9	56	37:1	70
2	DMSO	99	6	59	> 50:1	79
3	**I-117a**	92	9	47	> 50:1	76
4	**I-117b**	96	5	65	> 50:1	81
5	**I-117c**	99	9	48	45:1	70
6	**I-117d**	97	7	64	45:1	73
7	**I-117e**	94	16	28	18:1	71
8	**I-117f**	95	16	33	29:1	75
9	**I-117g**	93	14	42	40:1	74
10	**I-117h**	95	10	42	> 50:1	71
11	**I-117i**	ND	6	44	> 50:1	72
12	**I-117j**	99	5	55	28:1	87

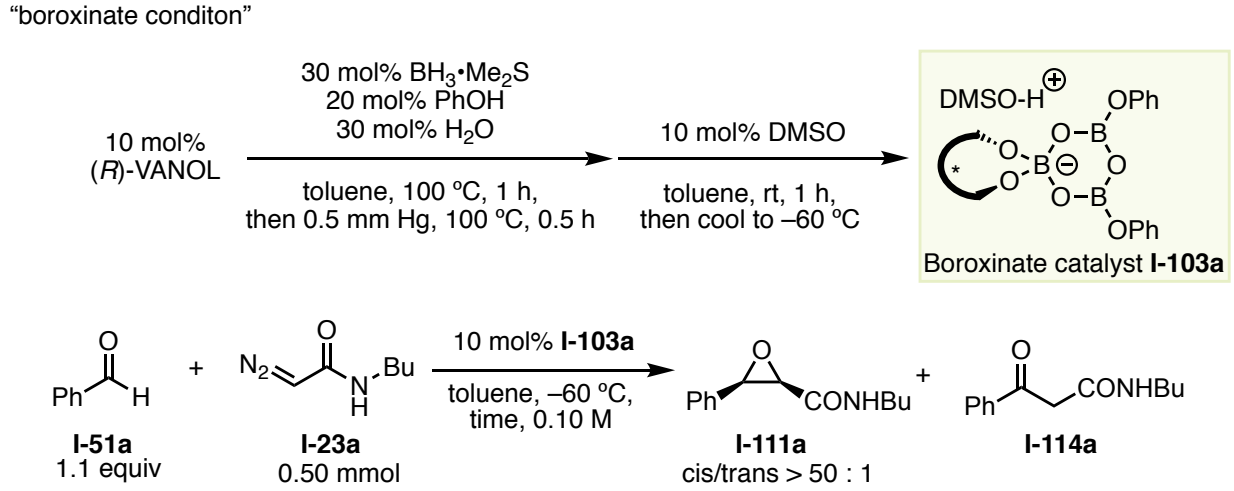
[a]Determined by ^{1}H NMR analysis of crude product using Ph_3CH as an internal standard. [b]Isolated yield after chromatography on silica gel. [c]As judged by chiral HPLC.

1.5 Discovery of VANOL *meso*-borate catalyst

We attempted to optimize the boroxinate catalyst by varying the phenol/alcohol component. We start off the screening by setting up a control experiment without the phenol, where a negative result was expected. Surprisingly, the reaction gave an equally great yield and excellent ee (entry 3 vs 1, *Table 1.6*). For the reaction without DMSO, the control (without phenol) experiment gave higher yield than the experiment with phenol with a comparable ee (entry 4 vs 2, *Table 1.6*). In the absence of phenol, it is still possible that a boroxinate forms from water molecule to give a catalyst where the phenols are replaced by hydroxides. Therefore, both phenol and water were left out of the recipe for the precatalyst. It was shocking to find that the results are as good as, if not better than, those from original conditions (entry 5 & 6 vs 1 & 2, *Table 1.6*). The boroxinate catalyst **I-103a** can't be the catalytic species under these new conditions. After reviewing the types of chiral borate catalysts known in the literature, it was suspected that the active catalyst might be a *meso*borate BLA[53] or a propeller borate[34]. The stoichiometry of BH_3•Me_2S was readjusted to such that the VANOL/borane ratio was 2:1 based on a *meso*borate structure. We were delighted to obtain the *cis*-epoxide **I-111a** in 98.6% yield and >99% ee after 5 hours (entry 7, *Table 1.6*). The reaction that was catalyzed by a precatalyst generated with a ligand/boron ratio of 2:1 proceeded faster and gave higher enantioselectivity at –40 ºC (entry 8 vs 9, *Table 1.6*). A control experiment showed that the boron is essential for the catalytic reaction (entry 10, *Table 1.6*). Modifications such as decreasing the catalyst loading, and precatalyst formation by heating DMSO with

VANOL and borane, have negative effects on the yield of the reaction (entry 11 & 12, *Table 1.6*).

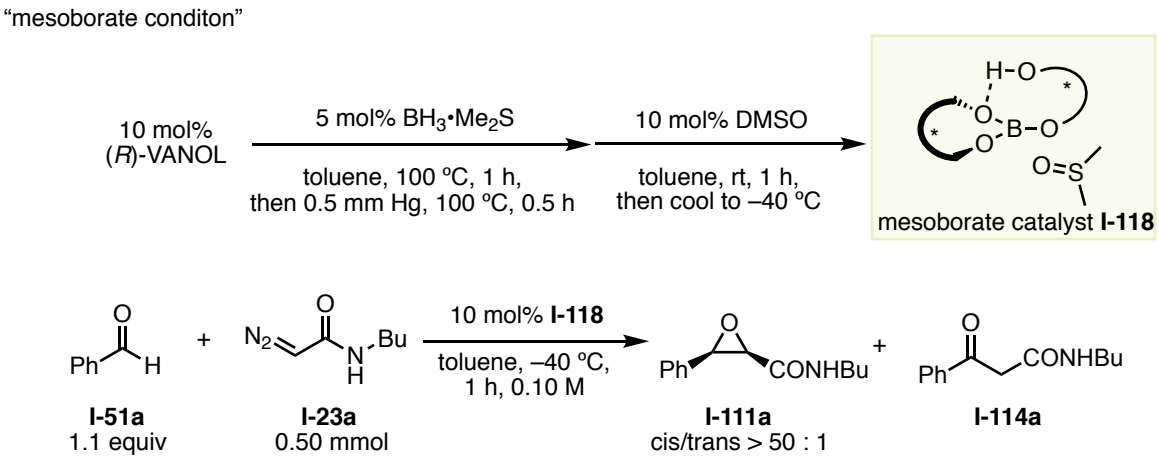
Table 1.6 Evolution of catalyst



entry	variation from "boroxinate conditon"	time (h)	%yield[a] (**I-111a**)	%ee[b] (**I-111a**)	%yield[c] (**I-114a**)
1	none	24	88	99	< 1
2	w/o DMSO	24	79	90	5
3	w/o phenol	24	92	99	< 1
4	w/o phenol and DMSO	24	90	89	< 1
5	w/o phenol and H_2O	8	92	99	< 1
6	w/o phenol, H_2O and DMSO	24	90	96	< 1
7	entry 4, 5 mol% BH_3•Me_2S	5	99	99	< 1
8	**entry 7, –40 °C**	**1**	**97**	**99**	**< 1**
9	–40 °C	24	90	98	< 1
10	entry 7, w/o BH_3•Me_2S	24	0	—	—
11	entry 7, half the catalyst loading	24	69	—	18
12	entry 7, heating with DMSO	24	36	—	18

[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC. [c]Determined by ^1H NMR analysis of crude product using Ph_3CH as an internal standard.

Table 1.7 Optimization of condition for epoxidation catalyzed by *meso*borate **I-118**



entry	variation from "boroxinate conditon"	%yield[a] (**I-111a**)	%ee[b] (**I-111a**)	%yield[c] (**I-114a**)
1	none	97	99	< 1
2	4 Å MS, –60 ºC	99	99	< 1
3	w/o 0.5 mm Hg, –60 ºC	99	99	< 1
4	w/o 0.5 mm Hg	97	99	< 1
5	w/o 0.5 mm Hg, –20 ºC	42	—	31
6	w/o 0.5 mm Hg, 0 ºC	16	—	38
7	w/o 0.5 mm Hg, w/o DMSO, 4 Å MS	34	—	1
8	w/o DMSO, 4 Å MS	86	87	1
9	heating for 0.5 h, skip 1h after addition of DMSO, 4 Å MS	97	99	< 1
10	entry 9, 0 ºC, w/o 4 Å MS	94	96	< 1
11	entry 9, w/o 4 Å MS, 10 mol% H_2O at –40 ºC	99	99	< 1
12	entry 9, w/o 4 Å MS, 10 mol% H_2O at rt	8	—	—
13	entry 9, $B(OPh)_3$ instead of BH_3•Me_2S	99	99	< 1
14	entry 9, $B(OPh)_3$ instead of BH_3•Me_2S, no heating	45	—	2

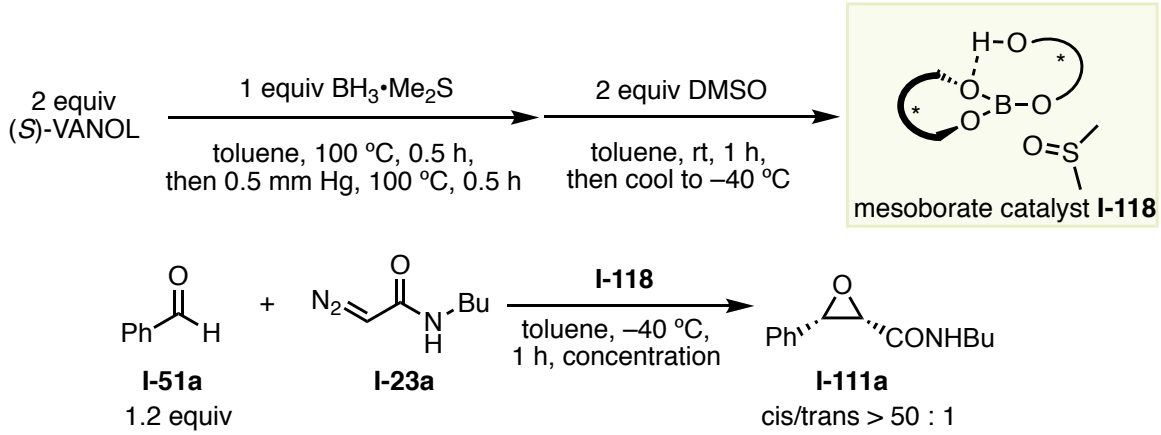
[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC. [c]Determined by ^1H NMR analysis of crude product using Ph_3CH as an internal standard.

It was decided to further optimize the *meso*borate system. Removing solvents after the precatalyst formation will presumably get rid of the unreacted borane and Me_2S molecules. This step proved to be worthwhile at higher temperature where the catalyst becomes less efficient (entry 6 vs 10, 7 vs 8, *Table 1.7*). The incorporation of 4 Å molecular sieves was thought to help increase the stability of the borate catalyst but it turned out to be unnecessary and even detrimental in many reactions. As shown in control experiments, the catalyst is sensitive to water but tolerant of water at low temperature

(entry 11 and 12, *Table 1.7*). These findings prompted us to omit the 4 Å MS from the optimal conditions and use a simple round bottom flask to run the reactions rather than in a Schlenck flask. The 30 min heating time for precatalyst formation was proved to be enough and no induction time was needed for DMSO to engage in the system (entry 9, *Table 1.7*). These procedural adjustments decreased the set-up time for the reaction significantly from 3 h to 1 h. Finally, triphenyl borate can be used as an alternative boron source. However, in contrast to boroxinate formation, heating is required for effective 2:1 *meso*borate catalyst generation (entry 13 and 14, *Table 1.7*).

Next experiments were carried out to figure out the limit of catalyst loading (*Table 1.8*). When the concentration of the catalyst was kept constant, the reaction was equally effective in the presence of 2.5 mol% catalyst. When 2.0 mol% catalyst loading was employed, the epoxide was obtained with excellent enantioselectivity, albeit in slightly lower yield. (entry 1-3, *Table 1.8*). Further decreasing the loading was impractical and caused a considerable loss in yield (entry 4-5, *Table 1.8*).

Table 1.8 Catalyst loading study

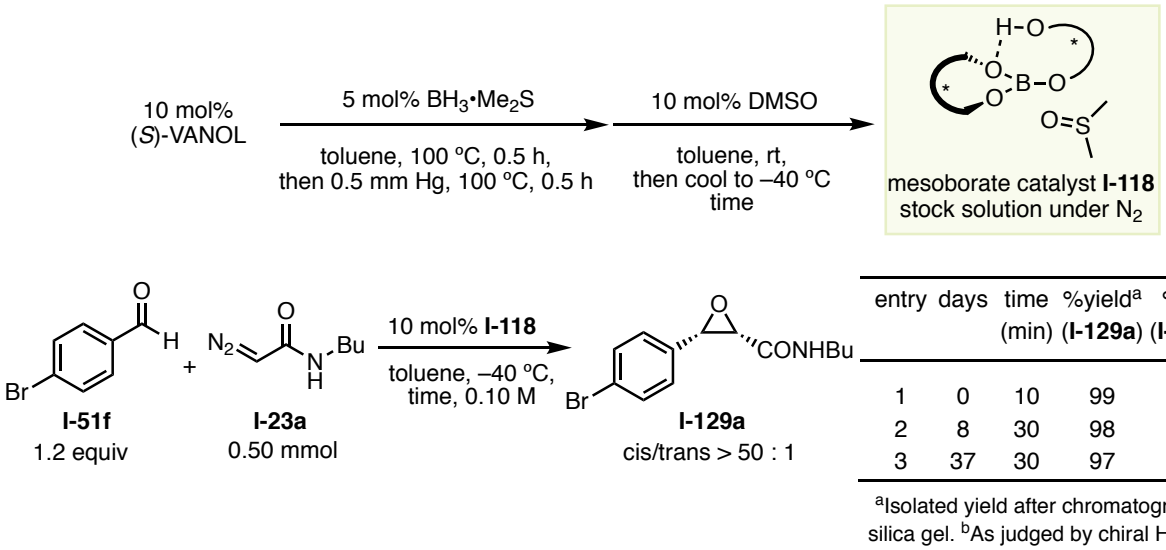


entry	mmol (**I-51a**)	concentration of **I-51a** (M)	mol% (**I-118**)	%yield[a] (**I-111a**)	%ee[b] (**I-111a**)
1	0.5	0.1	5	94	99
2	0.5	0.2	2.5	99	99
3	0.5	0.25	2.0	88	99
4	1.0	0.25	1.0	(48)	—
5	1.0	0.25	0.5	(5)	—

[a]Isolated yield after chromatography on silica gel. Yields in parentheses are determined by ^{1}H NMR analysis using Ph_3CH as an internal standard. [b]As judged by chiral HPLC. [c]*cis*/*trans* = 27:1

To test the idea of whether the reaction can be run with catalyst prepared in advance as a stock solution to avoid preparation of the catalyst each time before every reaction, a stability study was conducted (*Table 1.9*). The *meso*borate catalyst **I-118** was generated and stored in a Shlenk Flask under nitrogen atmosphere on the benchtop. The results showed that the catalyst is relatively stable under moisture-free conditions and maintained its catalytic ability over 5 weeks.

Table 1.9 Catalyst stability study



entry	days	time (min)	%yield[a] (**I-129a**)	%ee[b] (**I-129a**)
1	0	10	99	99
2	8	30	98	99
3	37	30	97	99

[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC.

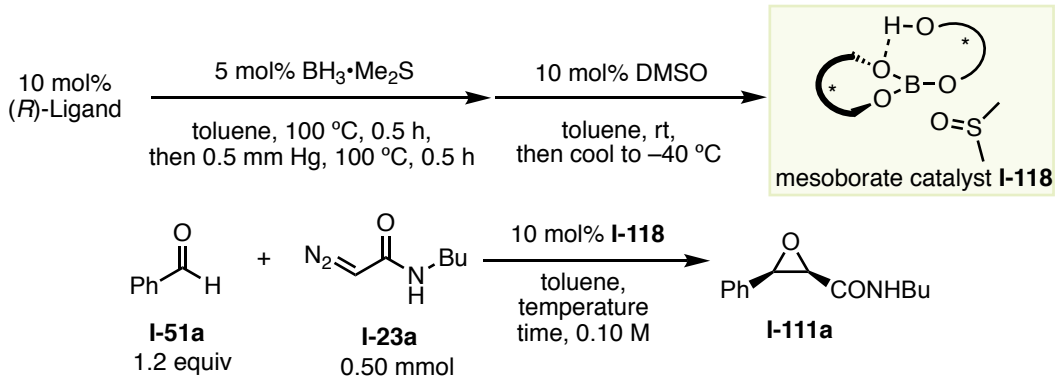
1.6 Ligand comparison and a distinction between two catalysts

The ligand effect was investigated with the 2:1 *meso*borate catalyst (*Table 1.10*). It was surprising to observe a dramatic decrease in yield when BINOL and VAPOL were used as ligands under the optimal condition (entry 1-3 vs 4, *Table 1.10*). It was decided to increase the reaction temperature in order to elevate their reactivity to produce a better comparison between the ligands. The reactions performed at 0 °C indicated that catalysts generated from VANOL are superior to BINOL and VAPOL in terms of yield and ee no matter whether DMSO is added or not. Oddly, BINOL and VAPOL catalyst performed better in the absence of DMSO (entry 5 vs 6 and 7 vs 8, *Table 1.10*). Moderate yield and ee of the epoxide was observed for BINOL catalyst while almost racemic epoxide was produced with the VAPOL catalyst (entry 5-8 vs 9-10, *Table 1.10*). The notable difference in performance of the 2:1 catalyst in the epoxidation might be explained by their inherent structural characteristics. First, the BINOL *meso*borate should have a wider crevice in the chiral pocket since the fused benzene rings are located distal to the phenol hydroxyl

groups. This would decrease the energy difference of the transition states leading to the major and minor enantiomers. Second, BINOL is reported to react with BH_3 generate *meso*borates[53] or propeller borates[34]. Under the conditions for the preparation of the 2:1 catalyst, the propeller borate could be generated as a byproduct. Both propeller borate and *meso*borate of BINOL could catalyze the epoxidation of aldehydes. It is likely that the propeller borate would be a less enantioselective catalyst than *meso*borate which causes the decrease in ee. On the other hand, VAPOL is more sterically hindered than VANOL in its chiral pocket. This might result in a lower conversion into *meso*borate. It would also be difficult for the aldehyde substrate to bind to the active catalytic site. Both factors might cause the lower conversion and enantioselectivity of VAPOL *meso*borate catalyst.

The question remains whether the active catalysts generated from 1:3 boroxinate or 2:1 *meso*borate conditions are distinct species or not. Although the epoxidation reactions under *meso*borate conditions were faster and more enantioselective for many substrates, it might be explained by a situation where the active catalyst is the same but generated in a more efficient manner under the 2:1 conditions. Indeed, the enantioselectivity can be hampered by adding 20 mol% phenol or by recombining the missing components from the boroxinate conditions (*Table 1.11*).

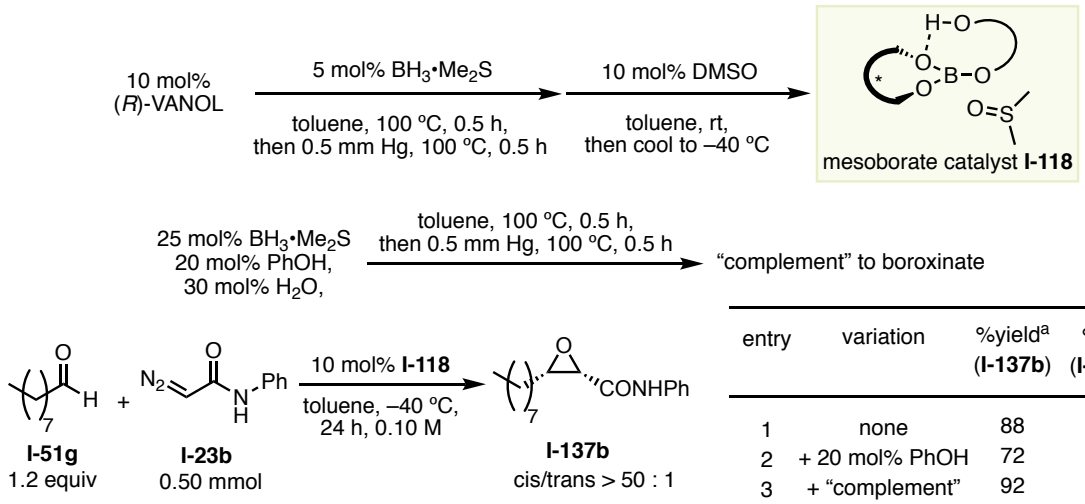
Table 1.10 Ligand effect in epoxidation catalyzed by *meso*borate **I-118**



entry	ligand	DMSO	temperature	time (h)	%conv[a] (**I-23a**)	%yield[b] (**I-111a**)	%ee[c] (**I-111a**)
1	BINOL	yes	–40 °C	24	47	(3)	—
2	BINOL	no	–40 °C	22	66	(12)	—
3	VAPOL	yes	–40 °C	24	73	(13)	—
4	VANOL	yes	–40 °C	1	100	97	99
5	BINOL	yes	0 °C	12	51	(5)	—
6	BINOL	no	0 °C	0.5	100	62	62
7	VAPOL	yes	0 °C	24	79	(23)	—
8	VAPOL	no	0 °C	24	91	43	6
9	VANOL	yes	0 °C	0.5	100	94	96
10	VANOL	no	0 °C	0.5	100	84	88

[a]Determined by ^{1}H NMR analysis of crude product using Ph_3CH as an internal standard. [b]Isolated yield after chromatography on silica gel. Yields in parentheses are determined by ^{1}H NMR analysis. [c]As judged by chiral HPLC.

Table 1.11 Effect of PhOH in epoxidation catalyzed by *meso*borate **I-118**



entry	variation	%yield[a] (**I-137b**)	%ee[b] (**I-137b**)
1	none	88	89
2	+ 20 mol% PhOH	72	63
3	+ "complement"	92	83

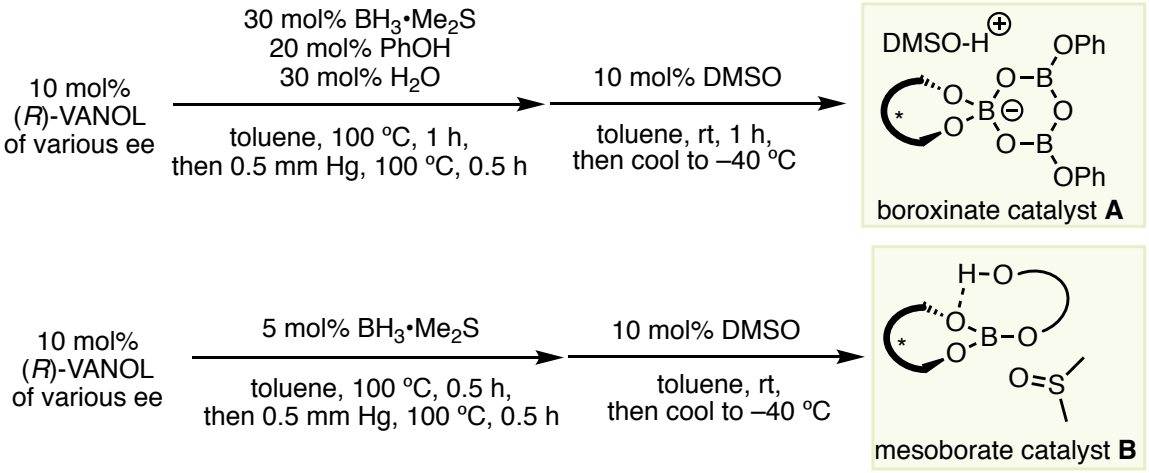
[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC.

To resolve this issue, it was decided to perform nonlinear effect (NLE) studies to investigate the nature of these two catalyst systems. Nonlinear studies have been employed to probe boron-catalyzed reactions, such as Yamamoto's BINOL-BLA catalyzed AHDA by James and Bull[55], boroxinate catalyzed aziridination by Wulff[95] and 3-borono-BINOL catalyzed aza-Michael additions by Maruoka[125].

The results of the experiment are shown below (*Table 1.11*, *Figure 1.3*, *Figure 1.4*). A large difference between these two catalysts in the epoxidation can be observed from the data and the graph. For the boroxinate catalyst, the yields of epoxide remain consistent when varying the enantiopurity of VANOL. And in support the proposed boroxinate catalyst, no nonlinear effect was observed in the graph, which is in agreement of the NLE studies in aziridination[95] and consistent with the structure **A** that a single molecule of the ligand in the catalyst. In contrast, the yields and rates of epoxidation increase as the enantiopurity of the VANOL in the *meso*borate catalyst increases. A significant (+)-NLE was revealed, providing strong experimental evidence that the active catalyst responsible for asymmetric induction under the 2:1 conditions contains more than 1 equivalent of VANOL.

Therefore, the catalysts generated from these two conditions are distinct boron catalysts. Both catalysts are effective in catalyzing epoxidation of aldehydes with diazoacetamides. But the *meso*borate has the edge over the boroxinate with regards to rate and enantioselectivity of reactions at higher temperatures.

Table 1.12 Nonlinear effect study on two catalytic systems



		catalsyt **A**		catalsyt **B**		
entry	%ee of VANOL	%yield[a] (**I-129a**)	%ee[b] (**I-129a**)	time (min)	%yield[a] (**I-129a**)	%ee[b] (**I-129a**)
1	0	68	0	30	55	0
2	10	69	11	30	52	23
3	19	67	21	30	56	57
4	32	67	33	30	75	69
5	39	69	43	30	91	82
6	50	68	51	10	70	85
7	57	68	58	20	86	95
8	69	68	69	10	93	97
9	79	73	74	10	96	98
10	93	61	84	10	88	98
11	>99	77	88	10	99	99

[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC.

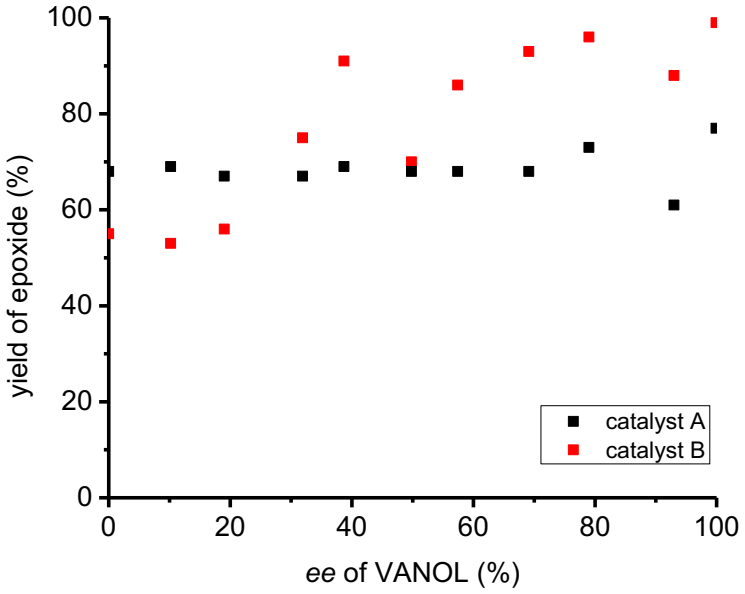


Figure 1.3 Yield of epoxide **I-129a** for non-linear studies

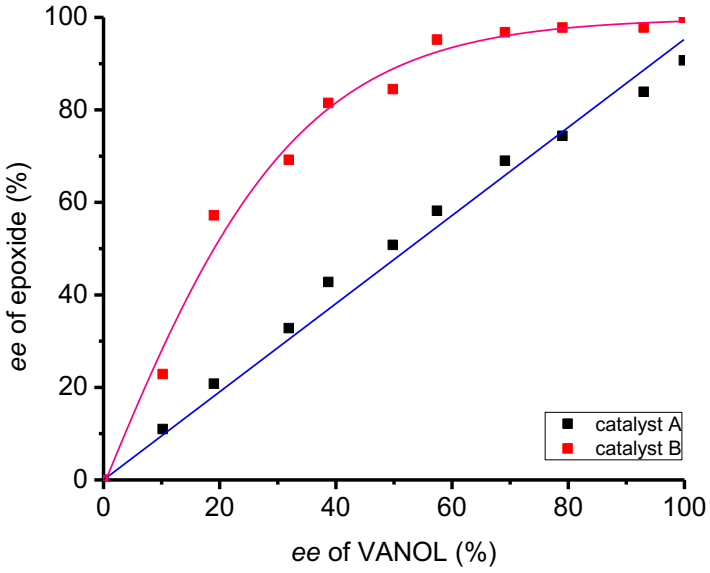


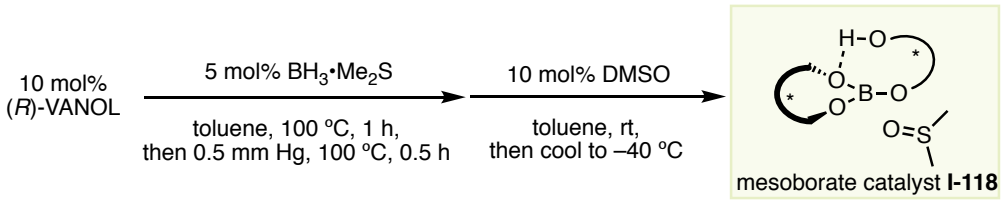
Figure 1.4 Non-linear effect studies on two catalysts

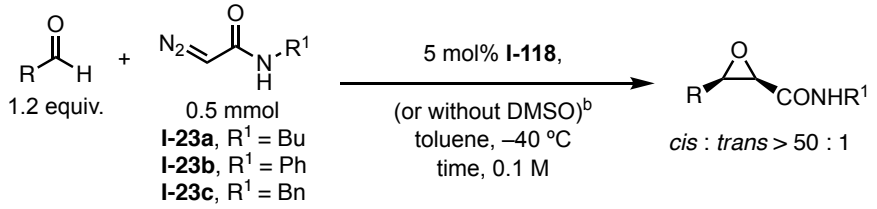
1.7 Reaction scope

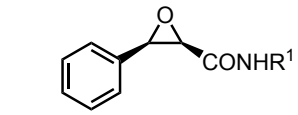
Having identified the optimal conditions for the asymmetric epoxidation catalyzed by the *meso*borate catalyst, attention was next turned to the evaluation of the scope of this reaction for the aldehyde component. As shown in *Scheme 1,14*, a wide variety of

aryl aldehydes were first investigated. In general, electronically varied benzaldehyde derivatives (**I-111**-**142**) underwent the epoxidation reaction in excellent yield with excellent asymmetric inductions. The reaction tolerates various functional groups including alkyl (**I-119**-**120**), methoxy (**I-123**-**124**), ester (**I-125**), halogen (**I-127**-**132**), nitrile (**I-133**), and nitro (**I-134**-**135**) moieties. The reactions of aryl aldehydes with substituents at *o*-position were slower and gave the epoxide with slightly lower ee (**I-119**, **121**, **123**, **127**). In addition, the substrates with electron withdrawing group on the phenyl ring underwent the reaction slower and gave lower asymmetric inductions (**I-133**-**135**). Epoxidation of 5-bromo-2-fluorobenzaldehyde gave **I-132** in 82% yield and with moderate induction after 24 h. The reaction of 4-methoxybenzaldehyde was sluggish even when 10 mol% of catalyst was employed. This might be due to the instability of the resulting epoxide under these conditions and the resulting ring-opened product might bind to the catalyst and cause inhibition. Subsequently, aliphatic aldehydes were examined. It was delightful to find that the epoxidation could be extended to both unbranched and α-branched aliphatic aldehydes with excellent asymmetric inductions (**I-136c**-**138c**). It was found that the *N*-benzyl diazoacetamide **I-23c** was more suitable for aliphatic substrates. Alkyl substituted *cis*-epoxides were obtained with almost perfect ees, although the reactions were slower and this is thought to be due to the lower solubility of **I-23c**. Reaction of α, α -bis-branched alkyl aldehyde was substantially slower and only gave moderate yield when 10 mol% catalyst was used (**I-139**). Reaction with an alkenyl aldehyde was unfruitful (**I-140**). However, alkynyl aldehdyes were well-tolerated, albeit giving only moderate yields (**I-141**-**142**).

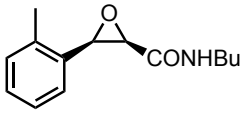
Scheme 1.14 Substrate scope of asymmetric epoxidation with *meso*borate catalyst **I-118**: variation of aldehydes[a]



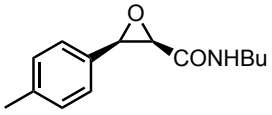




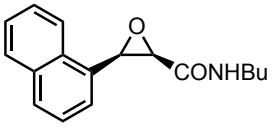
I-111a, R^1 = Bu, 0.17 h, 99%, >99% ee (2 h, 86%, 93% ee)
I-111b, R^1 = Ph, 12 h, 93%, 98% ee
I-111c, R^1 = Bn, 1 h, 88%, >99% ee (3 h, 98%, 97% ee)



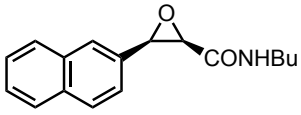
I-119, 2 h, 89%, 97% ee



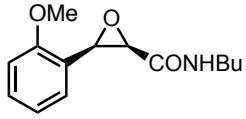
I-120, 0.17 h, 94%, 99% ee



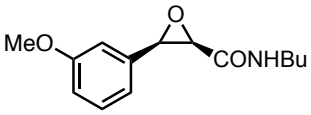
I-121, 1 h, 88%, 97% ee



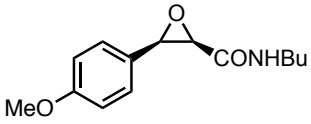
I-122, 0.25 h, 91%, >99% ee



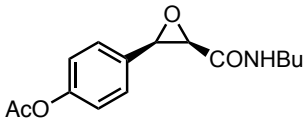
I-123, 0.17 h, 92%, 94% ee



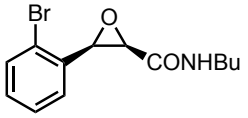
I-124, 0.17 h, 92%, 97% ee



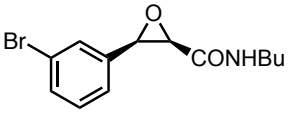
I-125, 24 h[c], 19%[d], —



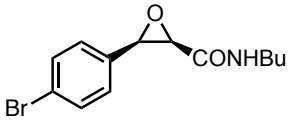
I-126, 0.25 h, 92%, >99% ee



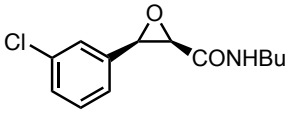
I-127, 0.5 h, 94%, 90% ee



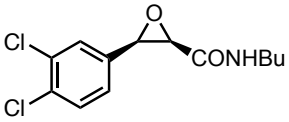
I-128, 0.17 h, 96%, 98% ee



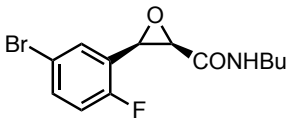
I-129a, 0.17 h, 99%, >99% ee (2 h, 72%, 90% ee)



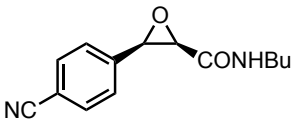
I-130, 0.17 h, 93%, 98% ee



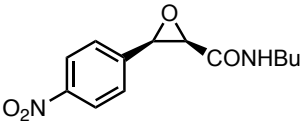
I-131, 0.25 h, 96%, 99% ee



I-132, 24 h, 82%, 63% ee

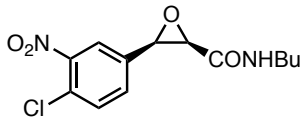


I-133, 0.25 h, 98%, 96% ee

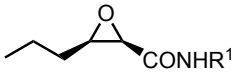


I-134, 3 h, 87%, 94% ee

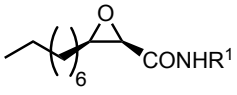
Scheme 1.14 (cont'd)



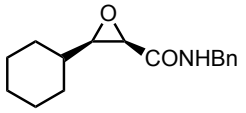
I-135, 1 h, 98%, 89% ee



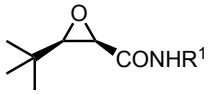
I-136a, R^1 = Bu, 0.25 h, 87%, 96% ee
I-136b, R^1 = Ph, 12 h, 94%, 90% ee
I-136c, R^1 = Bn, 12 h, 93%, >99% ee



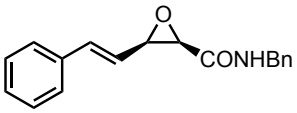
I-137b, R^1 = Ph, 12 h, 88%, 89% ee
I-137c, R^1 = Bn, 12 h, 93%, >99% ee
(12 h, 82%, >99% ee)



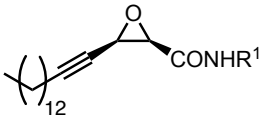
I-138b, R^1 = Ph, 12 h, 99%, 98% ee
I-138c, R^1 = Bn, 2 h, 92%, >99% ee
(1 h, 93%, >99% ee)



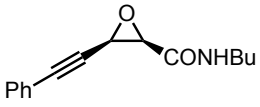
I-139b, R^1 = Ph, 36 h, 70%, 92% ee
I-139c, R^1 = Bn, 24 h[c], 47%[e], >99% ee



I-140, 24 h, <5%, –



I-141a, R^1 = Bu, 24 h, 63%, 91% ee
I-141c, R^1 = Bn, 24 h, 63%, >99% ee
(1 h, 79%, 93% ee)

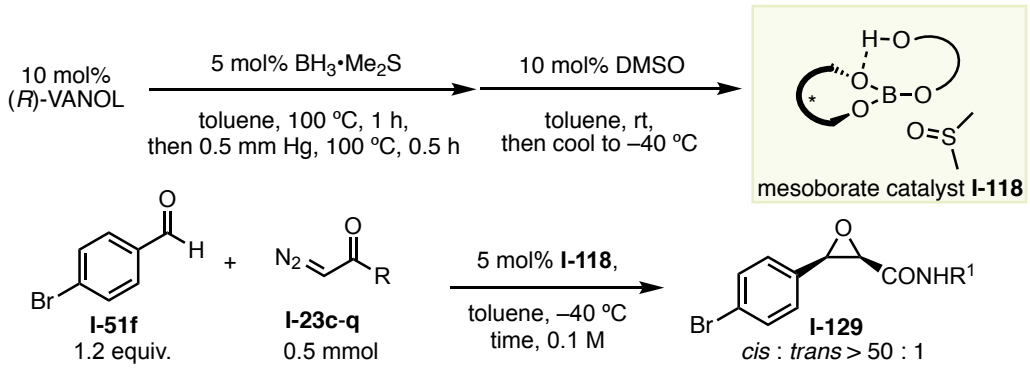


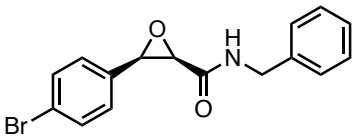
I-142, 4 h, 53%[f], 93% ee

[a]Reported are Isolated yields after chromatography on silica gel and ees judged by chiral HPLC. [b]Results of reaction without DMSO are shown in parentheses. [c]10 mol% catalyst was used [d]65% conversion. [e]78% conversion. [f]*cis* : *trans* = 26 : 1

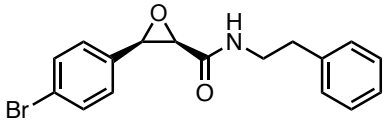
The scope of various *N*-substituted diazoacetamide or diazo esters with 4-bromobenzaldehyde **I-51f** was evaluated. The diazo acetamides **23c-o** were synthesized by the aforementioned procedure (*Scheme 1.12*). Pleasingly, the *N*-substituted diazoacetamides bearing phenyl, 2º and 3º alkyl, alkene, alkyne, ester and ether functional groups performed well in the reaction to afford the epoxides in moderate to good yields with excellent ees (**I-129c**-**129j**). Contrastingly, reactions with the *N*-substituted diazoacetamides bearing free hydroxyl, indole N-H, acidic sensitive Boc and acetal groups were sluggish and failed to go to completion. Our attempts to applied *N,N*-disubstituted acetamide **I-129o** and diazo esters **I-129p-q** were unsuccessful. These results suggested the important role of the amide group and amidic N-H in this epoxidation reaction.

Scheme 1.15 Substrate scope of asymmetric epoxidation with *meso*borate catalyst **I-118**: variation of diazo compounds[a]

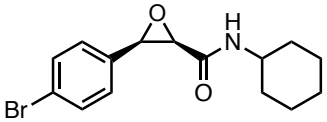




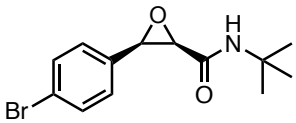
I-129c, 3.0 h, 90%, 99% ee



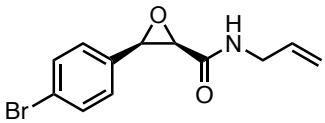
I-129d, 3.0 h, 88%, 99% ee



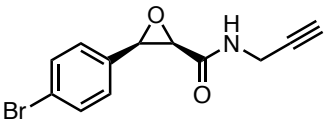
I-129e, 1.0 h, 91%, 99% ee



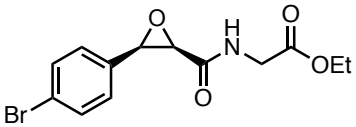
I-129f, 1.0 h, 87%, 99% ee



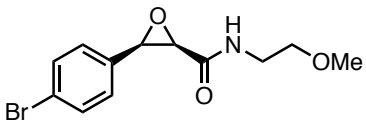
I-129g, 12 h, 47%, 99% ee



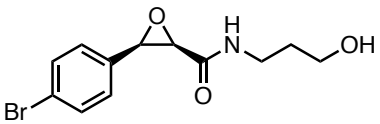
I-129h, 15 h, 97%, 94% ee



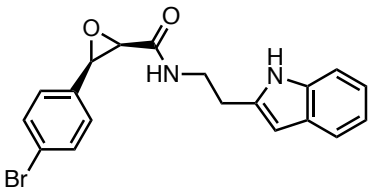
I-129i, 24 h, 90%, 99% ee



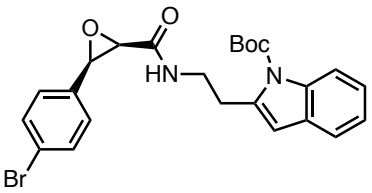
I-129j, 1.0 h, 93%, 99% ee



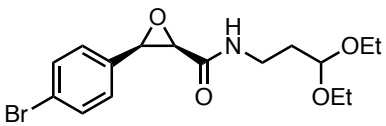
I-129k, 17 h, (9%)



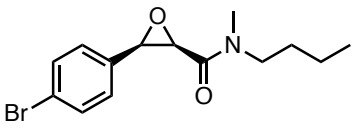
I-129l, 17 h, (35%)



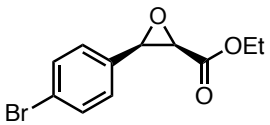
I-129m, 17 h, (24%)



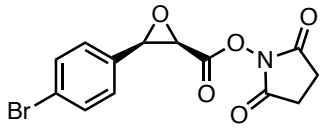
I-129n, 17 h, (30%)



I-129o, 24 h, 0%



I-129p, 24 h, 0%



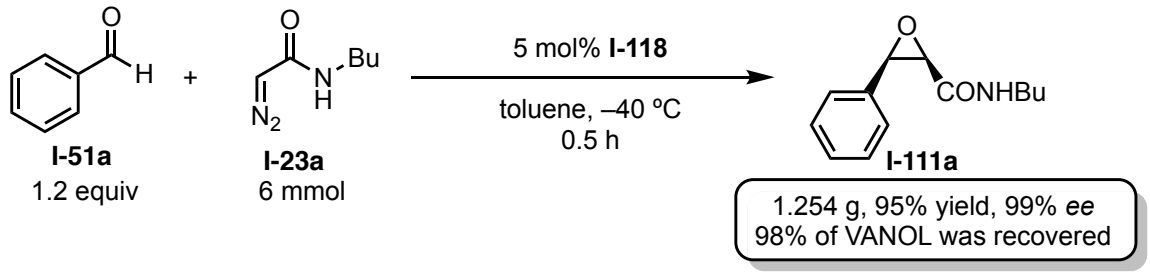
I-129q, 24 h, 0%

[a]Reported are Isolated yields after chromatography on silica gel and ees judged by chiral HPLC. Yield in parentheses are determined by ^{1}H NMR analysis. [c]10 mol% catalyst was used [d]65% conversion. [e]78% conversion. [f]*cis* : *trans* = 26 : 1

1.8 Gram-scale reaction and synthesis of Taxol-side chain

The asymmetric epoxidation of benzaldehyde with *N*-butyl diazoacetamide **I-23a** catalyzed by *meso*borate catalyst **I-118** could be easily scaled up 10-fold to afford 1.25 g of **I-111a** with >99%ee in 20 min. Pleasingly, we could recover 98.6% of VANOL ligand from the reaction mixture by chromatography. The gram-scale reaction was much slower in the presence of 4 Å MS. After 17 h only a 54% yield of **I-111a** was obtained with 92% ee and it delivered **I-111a** of 97% ee in 86% yield after 80 h.

Scheme 1.16 Gram-scale synthesis of *cis*-epoxide **I-108a**



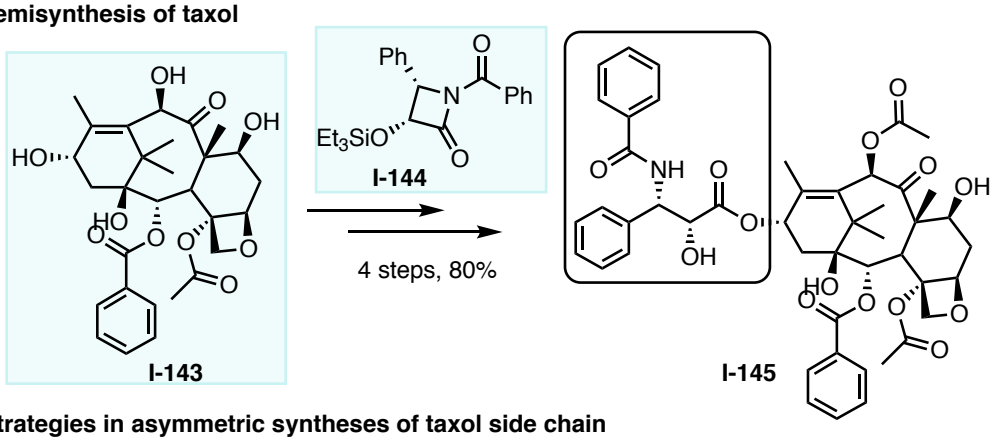
The synthetic usefulness of this methodology was demonstrated in the synthesis of taxol side-chain **I-146**. Taxol **I-145**, whose structure first elucidated[126] by Wani and coworkers in 1971, is one of the best-selling cancer drugs ever manufactured. Due of the limited amount of taxol that can be isolated from the yew tree (0.02%), organic chemists have been interested in the synthesis of taxol to meet its increasing demand. The first total synthesis of taxol was achieved[127-128] by Holton and coworkers in Dec 9th, 1993. However, the synthesis was not commercially viable due to the low yield and complexity. The large-scale production of taxol was made possible from a semisynthesis from 10-deacetyl-baccatin III **I-143**, which can be extracted from leaves of yew tree (0.1%). This process was first addressed[129] by Potier and developed by Holton. The key step is

installing the C-13 side chain by Ojima's lactam[130] **I-144** (a. *Scheme 1.17*). Therefore, the enantioselective synthesis of the taxol side chain has attracted the attention of many synthetic chemists. The first asymmetric synthesis of the taxol side chain was reported[131-132] by Greene et al. They used the Sharpless asymmetric epoxidation for the introduction of two chiral centers. The desired ester was isolated in 23% overall yield but recrystallization was needed to enrich the ee to >95%. Multiple pathways to the taxol side chain were developed by many other groups, including Ojima[133], Jacobsen[134], Yamamoto[135], Sharpless[136] and Shibasaki[137] etc., using different strategies (b. *Scheme 1.17*).

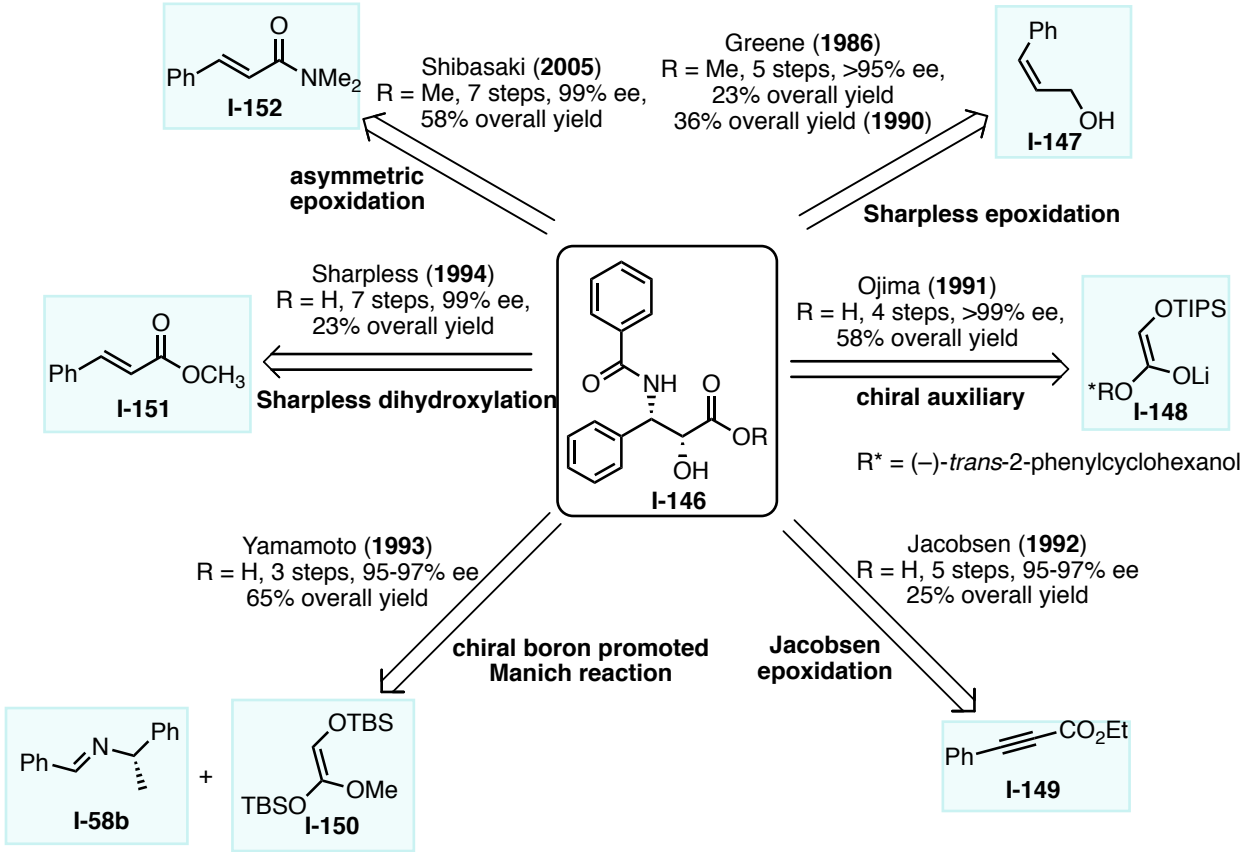
The synthesis of the taxol side chain begins with epoxide **I-111a** which was prepared by asymmetric epoxidation of benzaldehyde described in this chapter. Amide **I-111a** was first converted to ester **I-25** in 78% yield, a common intermediate in the synthesis by Greene[131] and Jacobsen[134]. The ethyl glycidate **I-25** was then reacted with $TMSN_3$ in the presence of $ZnCl_2$ to afford azido alcohol **I-153** in 96% yield. Benzoylation of followed by CuCl-catalyzed azide reduction[138] gave the desired ester **I-146** in 90% yield. In this way, the taxol side chain was isolated after 5 steps in 63% overall yield without erosion of ee.

Scheme 1.17 Synthetic strategies of taxol and the taxol side chain **I-146**

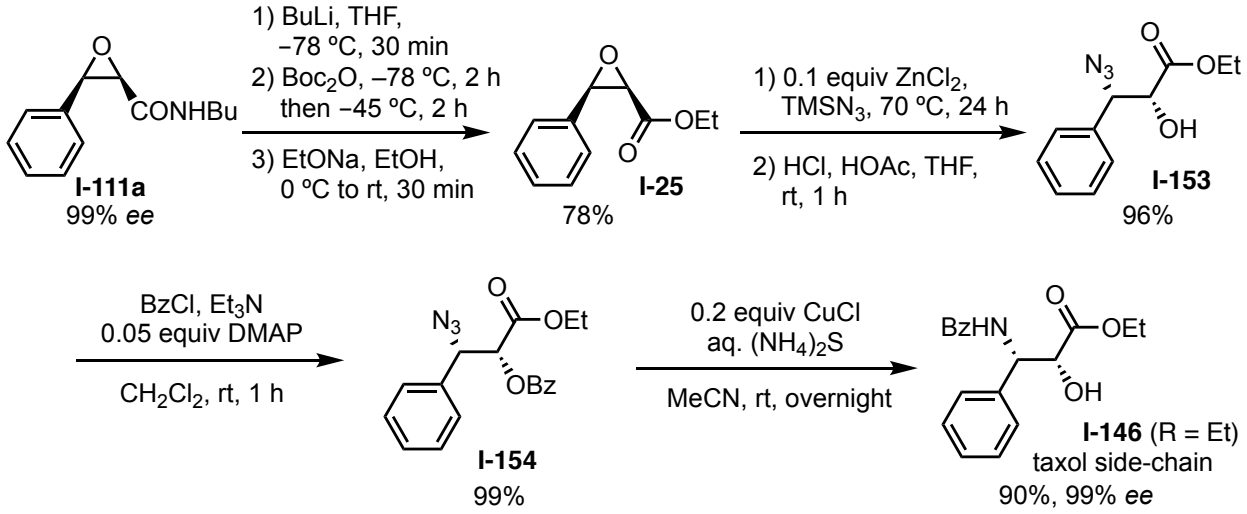
a. **Semisynthesis of taxol**



b. **Strategies in asymmetric syntheses of taxol side chain**



Scheme 1.18 Synthesis of the taxol side chain **I-146**



1.9 NMR studies and DFT calculations

For a better understanding the mechanism of the *meso*borate-catalyzed epoxidation of aldehydes with diazoacetamides and the role of DMSO, NMR studies were conducted by preparing a *meso*borate sample by the general procedure which was then subjected to ^{11}B NMR, ^{1}H NMR and ^{13}C NMR analysis.

In the DMSO titration studies, the ^{11}B NMR spectra clearly showed that the peak of *meso*borate at ~20 ppm shifts upfield to ~7.0 ppm gradually (a-f, *Figure 1.5*). The most upfield peak (6.7 ppm) results from 1.0 equiv DMSO. These observations suggest that the formation of a 1:1 complex with DMSO coordinating to the boron of the *meso*borate. In support of the coordination of DMSO, ^{13}C NMR spectra from the same studies showed that the change of chemical shift (40.9 ppm for e vs 35.3 ppm for b) and peak broadening of the methyl carbon signal of DMSO (b-d vs e, *Figure 1.6*). Addition of 1 equiv of benzaldehyde to the *meso*borate catalyst barely changed the characteristic tricoodinated boron peak of ~20 ppm in the ^{11}B NMR (b vs a, *Figure 1.7*). In contrast, in the presence

of 1 equiv DMSO, a distinctive shoulder peak at ~15 ppm could be observed (c, *Figure 1.7*). Obviously, the coordination of the *meso*borate with DMSO is more favorable than with benzaldehyde. Compared with the ^{1}H NMR spectrum of *meso*borate with 1 equiv benzaldehyde, the spectrum with an additional 1 equiv DMSO showed a notable increase in the intensity of a peak at 7.8 ppm and line broadening for most peaks in the aromatic region in the ^{1}H NMR spectrum (c vs b, *Figure 1.8*). In comparison, addition of 10 equiv of aldehyde to *meso*borate **I-118** revealed a peak at 6.1 ppm in the ^{11}B NMR, which suggested the coordination of aldehyde to boron of *meso*borate catalyst in the reaction conditions. Finally, the additive studies showed the different borate species resulting from addition of different additives with various pKas. For benzhydryl aldimine **I-176** (pKa = ~7) and 2-Aminophenol **I-117j** (pKa = 4.84), the *meso*borate was deprotonated to form an ionic *spiro*borate complex (~10 ppm sharp peak in ^{11}B NMR) with protonated imine/aniline (b & c, *Figure 1.9*). Benzaldehyde **I-52a** (pKa = –7), diazo acetamide **I-23a** (pKa = ~0) and DMSO (pKa = –2) were too weak to deprotonate the *meso*borate (d-f, *Figure 1.9*). Thus, the interaction was likely to be coordination to boron. The fact that the weaker base DMSO coordinates better than the diazoacetamide **I-23a** could be explained by the steric effect: DMSO is small enough to bind to the boron in the chiral pocket of the *meso*borate catalyst.

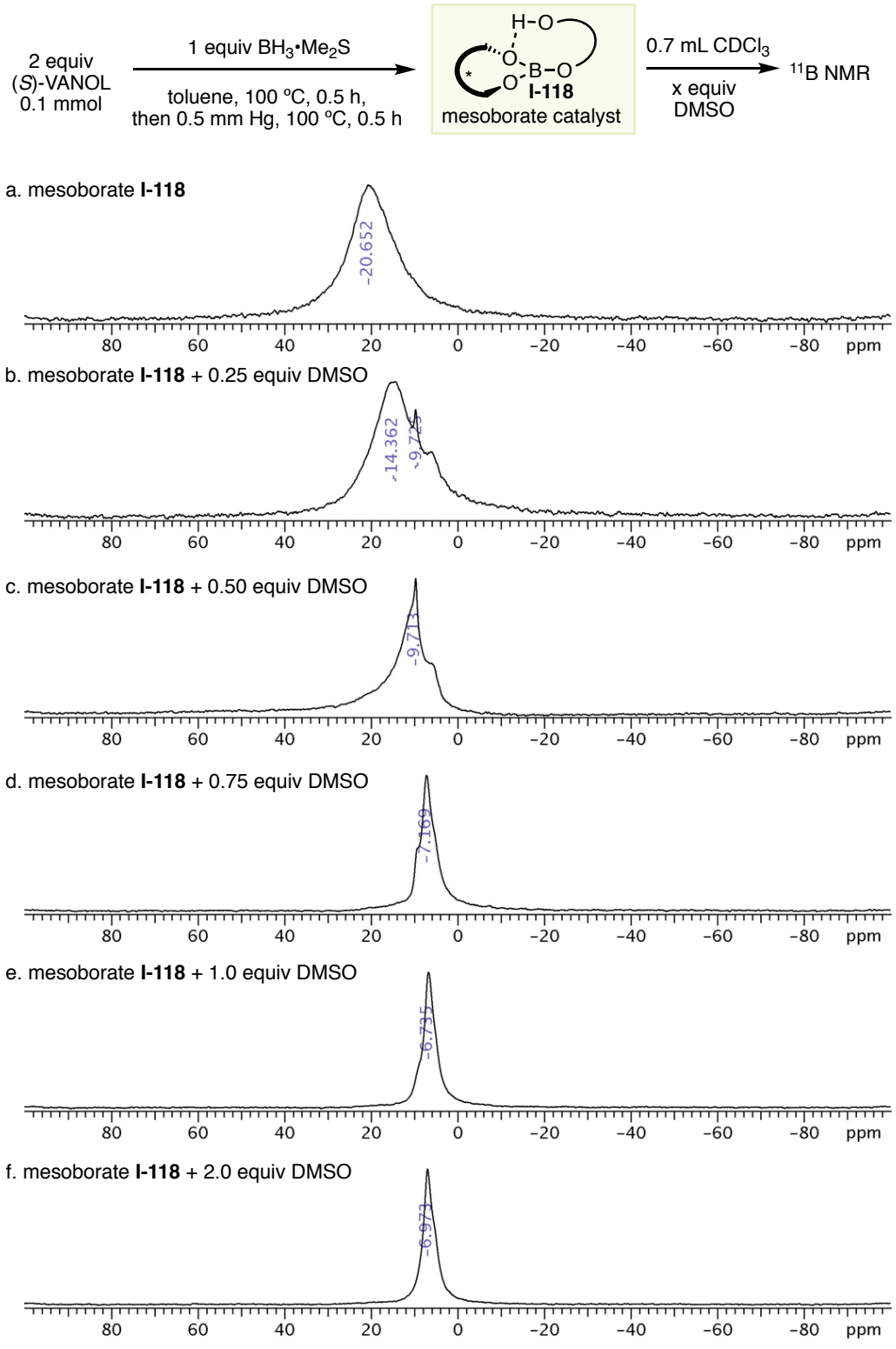


Figure 1.5 ^{11}B NMR spectra of *meso*borate **I-118** and DMSO titration studies

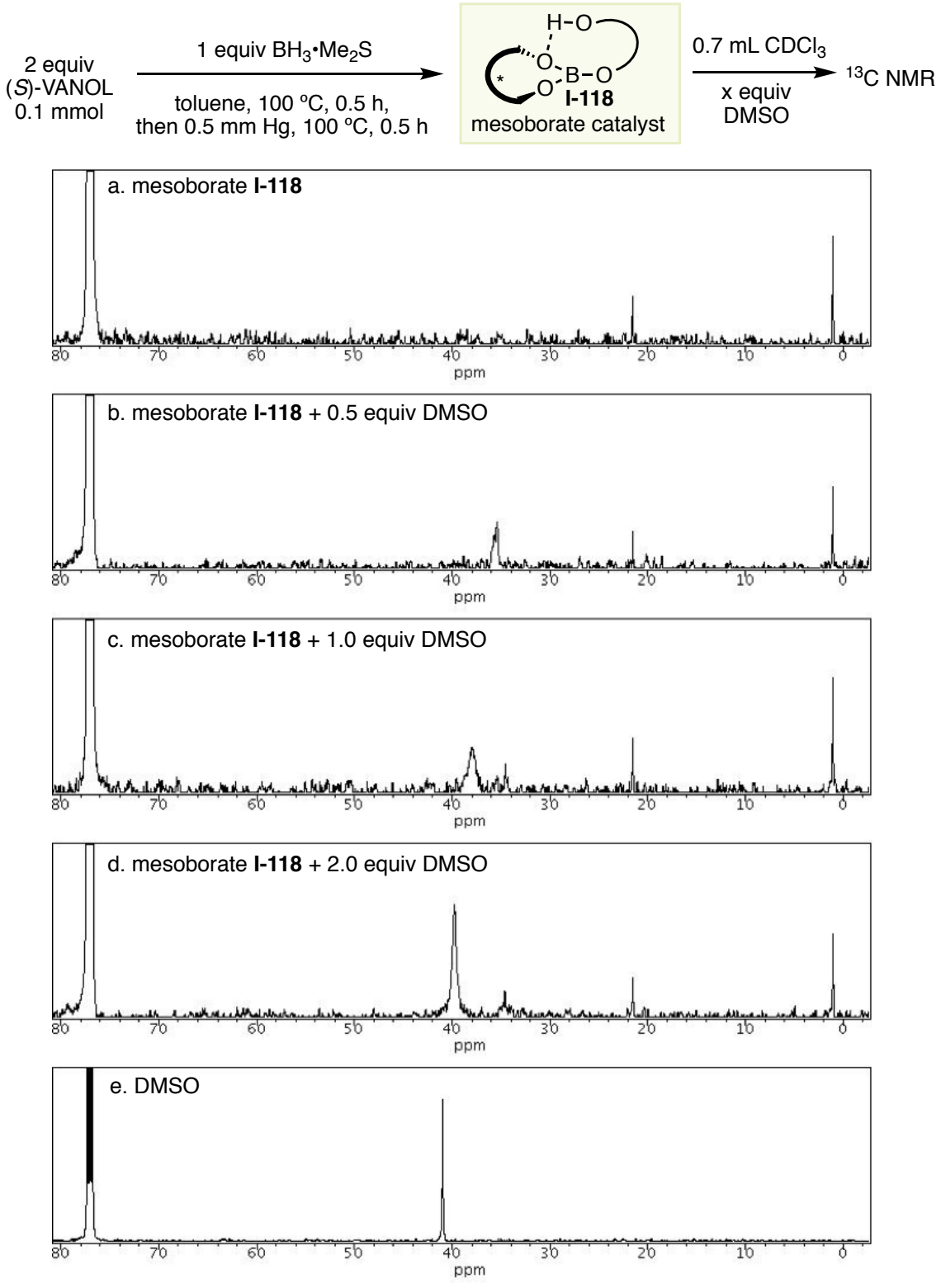


Figure 1.6 ^{13}C NMR spectra of *meso*borate **I-118** and DMSO titration studies

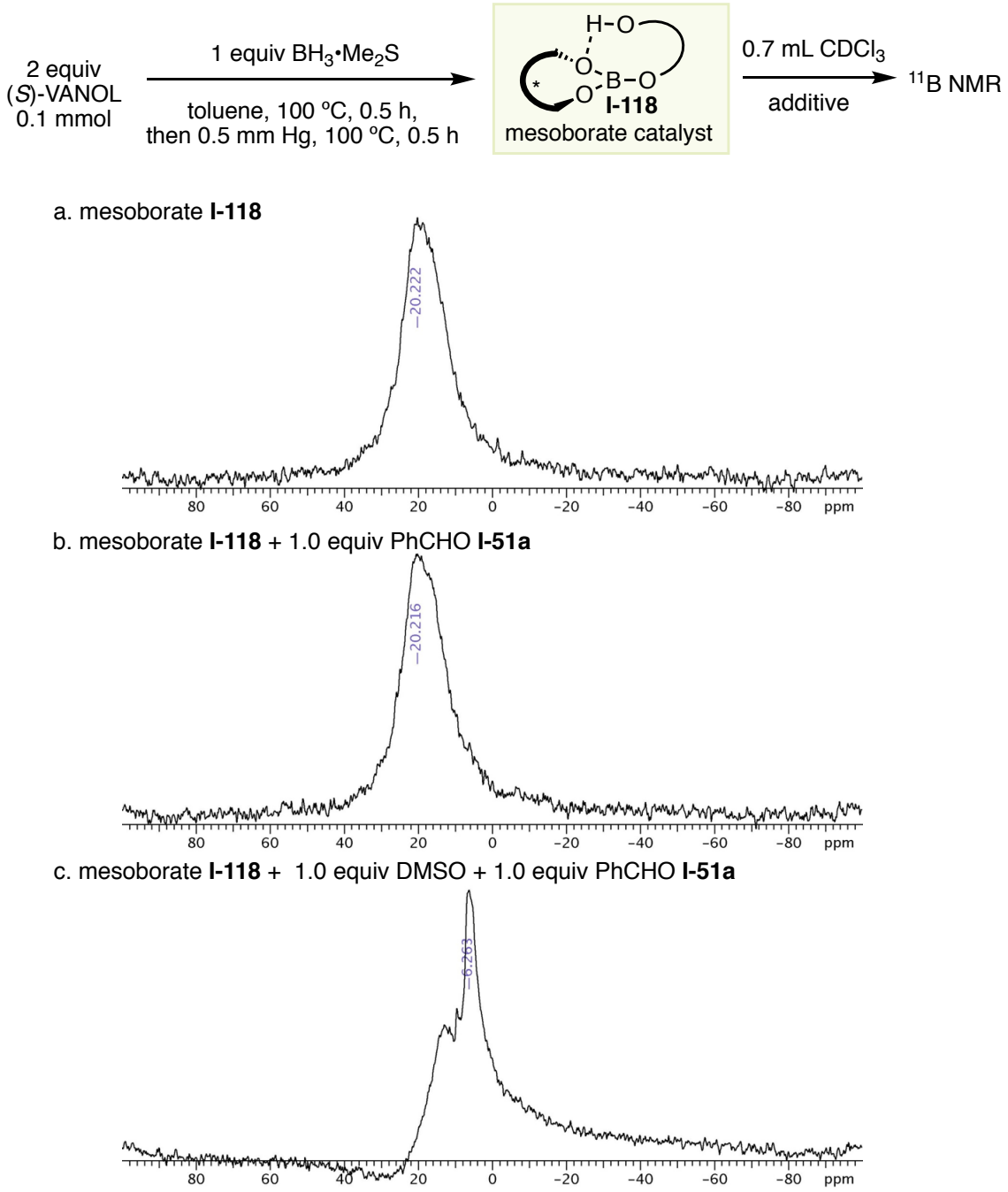


Figure 1.7 ^{11}B NMR spectra of *meso*borate **I-118** with benzaldehyde

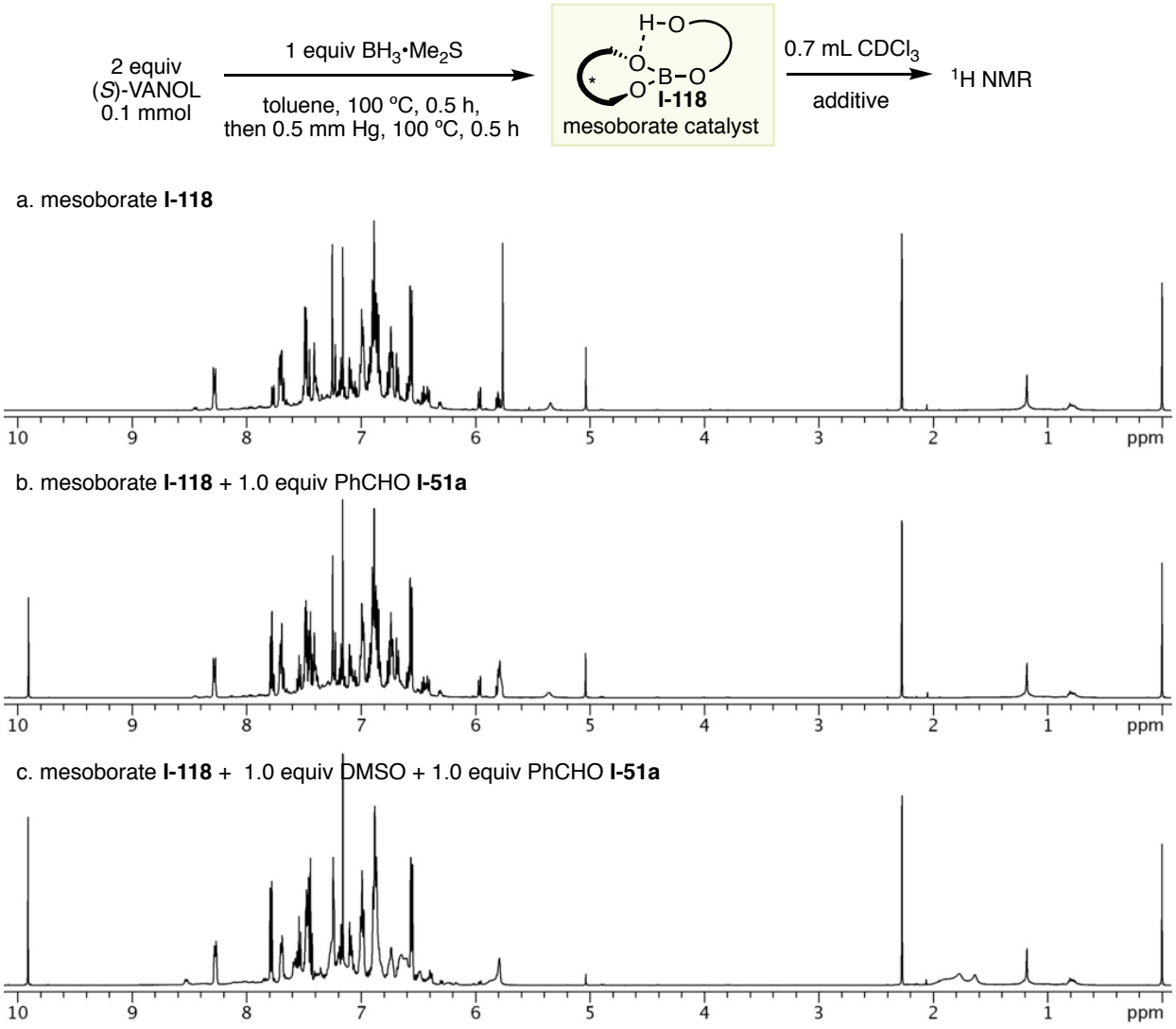


Figure 1.8 ^{1}H NMR spectra of *meso*borate **I-118** with benzaldehyde

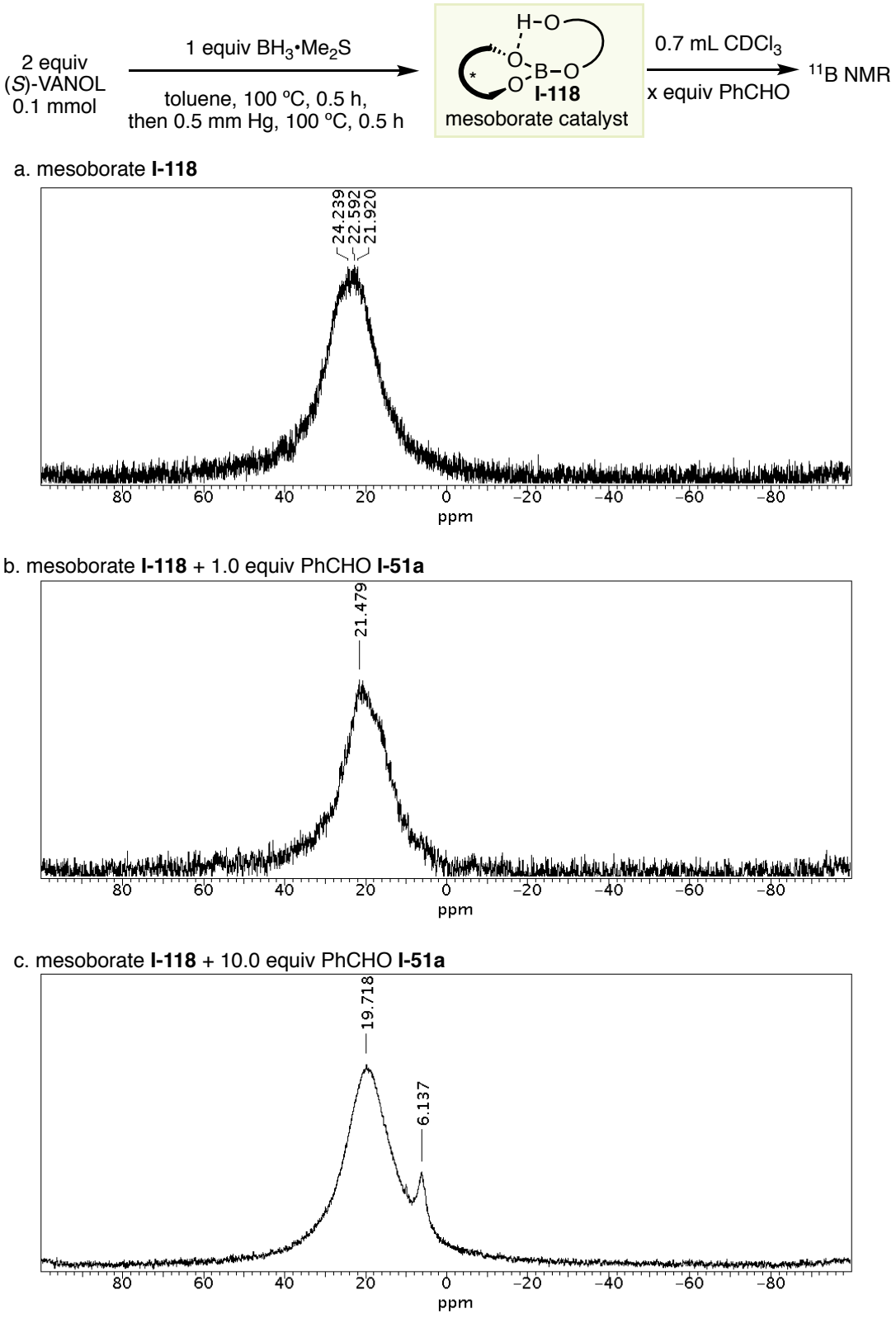


Figure 1.9 ^{11}B NMR spectra of *meso*borate **I-118** with 10 equiv benzaldehyde

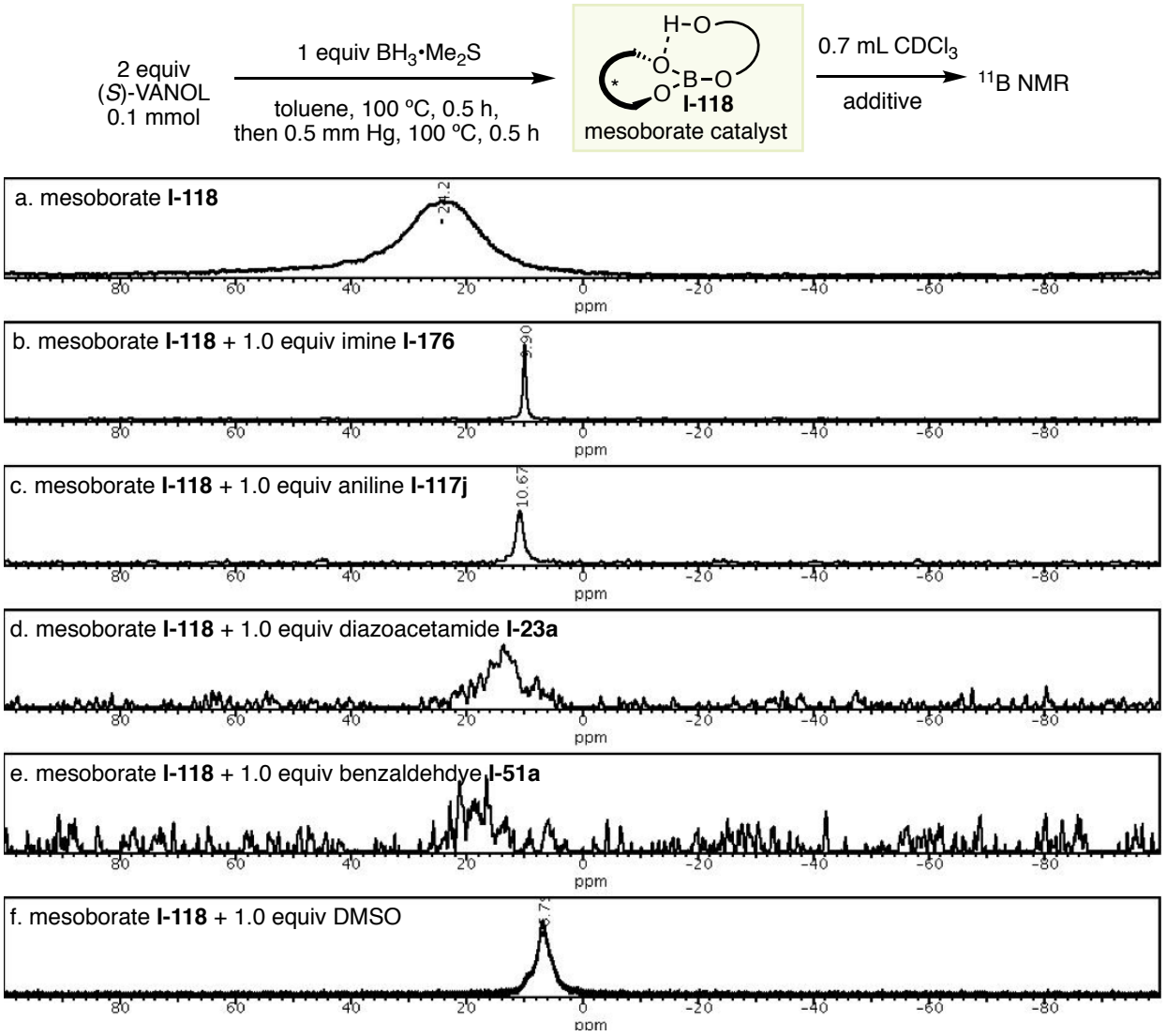


Figure 1.10 ^{11}B NMR spectra of *meso*borate **I-118** with additives

Computational modeling of the VANOL *meso*borate catalyst using density functional theory (DFT) revealed a minimum energy structure in which the boron is tricoordinated with three phenol hydroxyl group with the free hydroxyl H-bonding (2.07 Å) to an O of the other molecule of the ligand (*Figure 1.10*). Modeling the DMSO with different coordination patterns result in the lowest-energy structure where the oxygen of DMSO is bound to the boron from the same side of boron as where the H-bonding occurs

(*Figure 1.11*). The shorter distance of the H-bonding (1.73 Å) indicates the synergetic effect of the hydroxyl group (BLA).

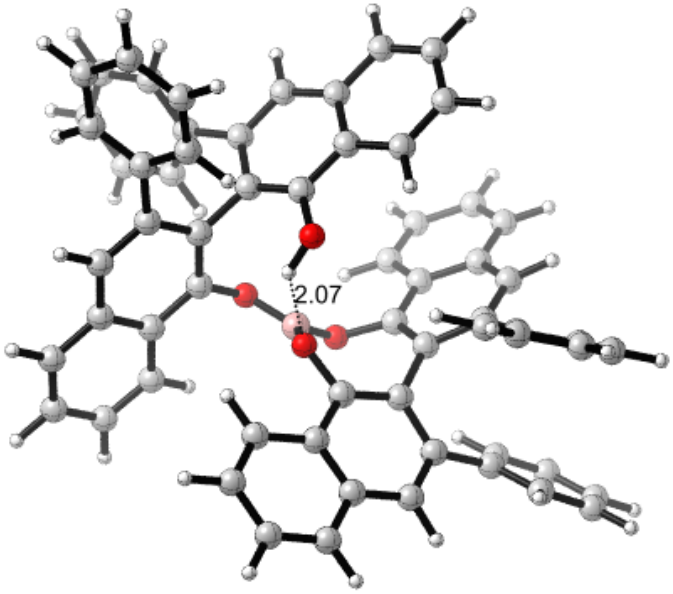


Figure 1.11 Lowest-energy ground-state structure of *meso*borate **I-118** at the B3LYP/6-31G(d) level

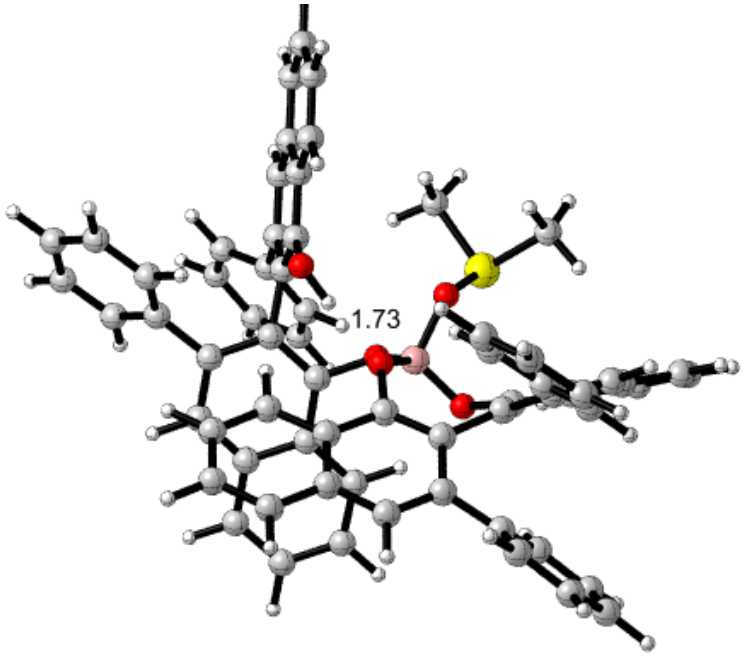


Figure 1.12 Lowest-energy ground-state structure of *meso*borate **I-118** bound to DMSO at the B3LYP/6-31G(d) level

The role of DMSO in improving the yields and ees for the epoxidation reactions is still not clear at this point. It would be reasonable to hypothesize that the DMSO molecule functions as a “recruiter”. Because an electrophilic sulfur atom that results upon coordination of the oxygen of the DMSO to the *meso*borate is more accessible than the boron in the *meso*borate, which is deep down in the chiral pocket. The DMSO could be replaced via a ligand exchange process to give structure **B**, where the aldehyde is activated by boron coordination (Lewis acid activation). Alternatively, the aldehyde can be activated by coordination to sulfur as shown in the structure **A**. On the other hand, DMSO molecule assembles the *meso*borate catalyst from various possible species of three-coordinated borate ester. Thus, this recruiting effect increases the rates of the reactions.

Meanwhile, the coordination of DMSO decreases the Brønsted acidity of the *meso*borate, which could possibly make the reaction more enantioselective if there is a less enantioselective Brønsted acid catalysis pathway that is operational.

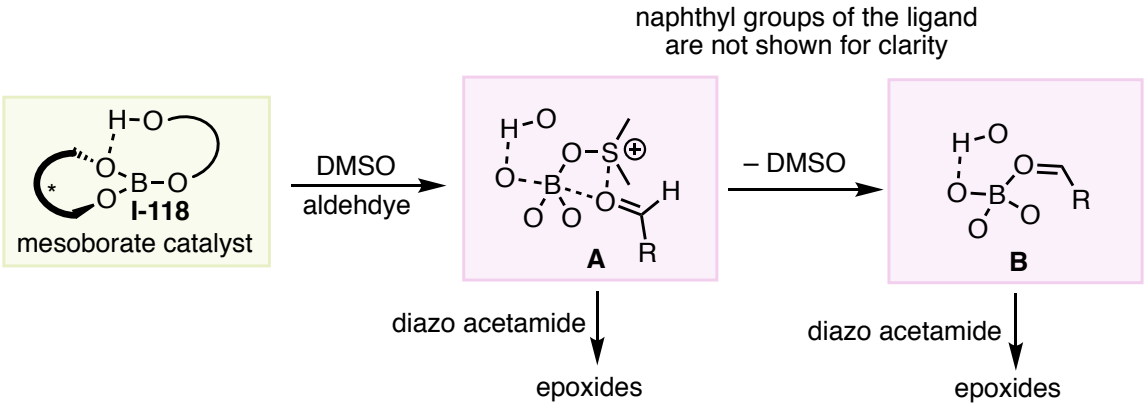
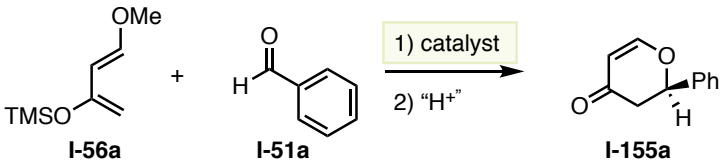


Figure 1.13 Proposed role of DMSO

1.10 Hetero Diels-Alder reactions (HDA) catalyzed by VANOL *meso*borates

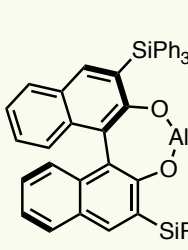
With the successful application of *meso*borate catalyst on asymmetric epoxidation of aldehydes, an attempt was made to extend this catalyst to other reactions with aldehydes. The catalytic asymmetric HDA reaction has been intensively explored[139] since Danishefsky et al reported[140] the first HDA with aldehydes catalyzed by $ZnCl_2$ in 1982. A wide variety of chiral Lewis acids have been developed for the HDA reaction of Danishefsky's diene with aldehydes (*Scheme 1.19*). Yamamoto and coworkers reported[141] the first efficient asymmetric HDA catalyzed by chiral aluminum catalyst **I-156**. Corey and coworkers employed[142] the chiral oxazaborolidine **I-157** to catalyze the formation of Mukaiyama aldol products. Subsequent acid treatment of the aldol products gave the formal HDA adducts **I-155** with high enantioselectivities. Chiral Cr(III) complex **I-158** was applied[143] by Jacobsen in HDA with various aldehydes to give **I-155** and derivatives with high enantioselectivities. Several highly efficient Lewis acid catalysts, including aluminum[144], titanium[145], zinc[146], magnesium[147] and zirconium[148] complexes generated from BINOL derivatives **I-159-162** were developed by Jørgensen, Ding and Kobayashi. In 2012, List and coworker reported[149] a highly enantioselective HDA reaction of aldehydes with **I-56a** and related catalyzed by chiral disulfonimide **I-163**. The HDA reaction was performed at –78 ºC for 4 days to afford a number of 2,6-disubstituted and 2,5,6-trisubstituted dihydropyrones in high yields (up to 97%) and excellent ees (up to 98%).

Scheme 1.19 Hetero Diels-Alder reaction of Danishefsky's diene **I-57a** with aldehydes

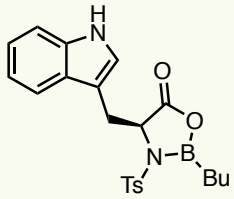


I-56a **I-51a** **I-155a**

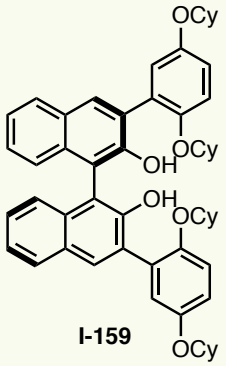
Danishefsky et al[138] (**1982**)	Yamamoto et al[139] (**1988**)	Corey et al[140] (**1992**)	Jacobsen et al[141] (**1998**)
0.5 equiv $ZnCl_2$ rt, 1-2 days	10 mol% **I-156** toluene, –20 ºC, hours	20 mol% **I-157** EtCN, –78 ºC, 14 h	2 mol% **I-158** tBuOMe, –30 ºC,
65%	71%, 67% ee (R)	100%, 82% ee (R)	85%, 87% ee (R)
Jørgensen et al[142] (2000)	**Ding et al[143] (2002)**	**Ding et al[144] (2002)**	**Ding et al[145] (2008)**
10 mol% **I-159**/$AlMe_3$ tBuOMe, –38 ºC,	0.05 mol% $Ti(OiPr)_4$/ **I-160** 1:2 neat, rt,	5 mol% **I-161**/Et_2Zn toluene, –25 ºC,	10 mol% **I-160**/$MgBu_2$ 1:1.5 toluten, rt,
97%, >99% ee (R)	99%, 99% ee (R)	99%, 97% ee (R)	99%, 99% ee (S)



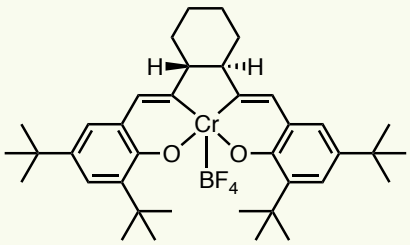
I-156



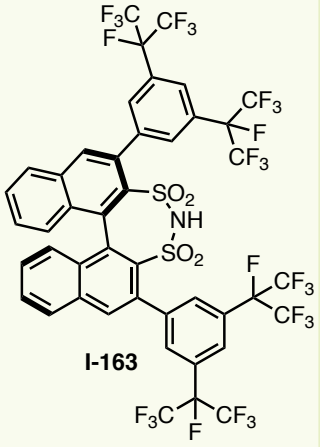
I-157



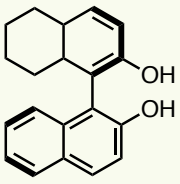
I-159



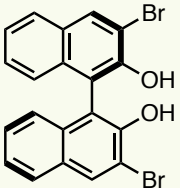
I-158



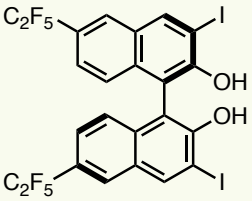
I-163



I-160



I-161

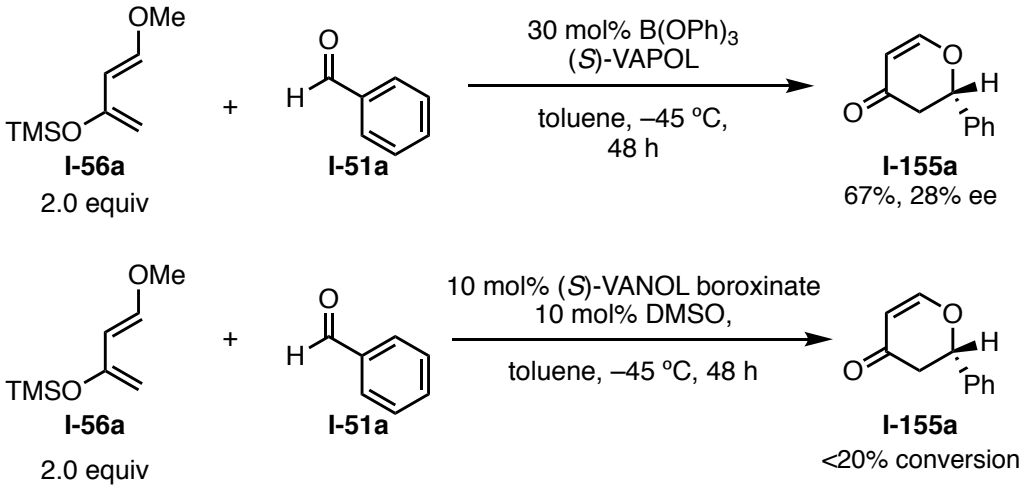


I-162

During the development of aza-Diels-Alder reaction of in situ generated imines, Newman and Wulff attempted the HDA reaction of benzaldehyde with **I-56a** catalyzed by

VAPOL/$B(OPh)_3$ 1:3 catalyst. The desired dihydropyrone was isolated in 67% yield with 28% ee. We then tested the same reaction with the VANOL boroxinate catalyst with DMSO under the same condition. The reaction gave low conversion (<20%) and the product was not isolated (*Scheme 1.20*).

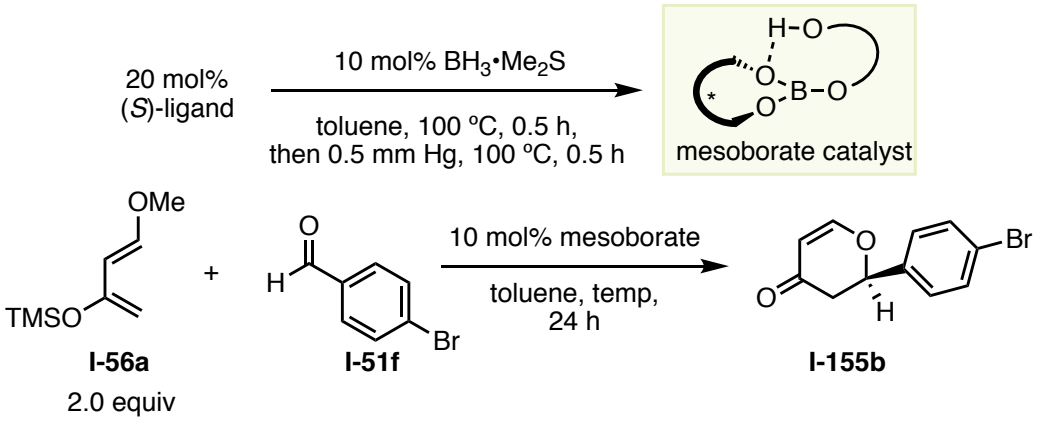
Scheme 1.20 HDA reaction of Danishefsky's diene **I-56a** with aldehydes catalyzed by boroxinate catalyst



It was pleasing to find that the HDA reaction of 4-bromobenzaldehyde with Danishefsky's diene catalyzed by VANOL *meso*borate catalyst gave **I-155b** in 84% yield and 40% ee at rt. In contrast to the epoxidation reaction, the enantioselectivity increase to 62% ee when DMSO was not added (entry 2 vs 1, *Table 1.13*). Decreasing the reaction temperature for the reactions with 20 mol% DMSO did not improve the ee but slowed down the rate significantly (entry 3 & 4 vs 1, *Table 1.13*). Attention was then turned to the study of the ligand effect (entry 5-7 & 1, *Table 1.13*). The reaction with BINOL *meso*borate gave a better result (94%, 83% ee) than VANOL. Compared with VANOL, the reaction catalyzed by *t*BuVANOL *meso*borate afforded **I-155b** in higher yield with comparable ee, while the reaction with VAPOL *meso*borate did not yield the desired product. This is quite

surprising because the steric hindrance of VAPOL and *t*BuVANOL are similar. It was delightful to see that lowering the reaction temperature to –40 ºC in the absence of DMSO had positive effects for both VANOL and BINOL. The dihydropyrone **I-155b** could be isolated in 89% with 83% ee for VANOL *meso*borate catalyst, and 96% with 91% ee for BINOL *meso*borate catalyst (entry 8 & 9, *Table 1.13*).

Table 1.13 Temperature and ligand screening for HDA reaction



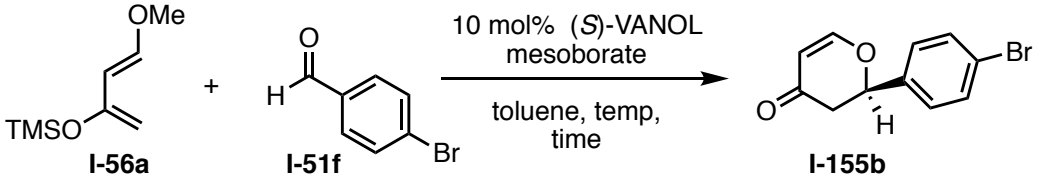
entry	ligand	DMSO	temperature	%yield[a] (**I-155b**)	%ee[b] (**I-155b**)
1	VANOL	20 mol%	rt	84	40
2	VANOL	—	rt	79	62
3	VANOL	20 mol%	0 ºC	82	25
4	VANOL	20 mol%	–40 ºC	40	37
5	BINOL	—	rt	94	83
6	VAPOL	—	rt	0	—
7	*t*BuVANOL	—	rt	90	64
8	VANOL	—	–40 ºC	89	83
9	BINOL	—	–40 ºC	96	91

[a]Isolated yield after chromatography on silica gel.
[b]As judged by chiral HPLC.

The reaction time was optimized. The reactions were completed within 1 h at rt and at –40 ºC (entry 1 vs 2, 3 vs 4, *Table 1.14*). However, a further decrease the reaction temperature to –78 ºC in an effort to increase the enantioselectivity proved to be fruitless. The reaction became very sluggish and did not go to completion for a longer period of

time (entry 5, 7-8, *Table 1.14*). As with the reaction with VANOL, the reaction with BINOL *meso*borate at –78 ºC was also affected, and to a greater extent. Both the yield and ee of the adduct were reduced substantially compared with that at –40 ºC (96%, 91% ee) (entry 6, *Table 1.14*). It is noteworthy that contrary to most of the HDA reactions in the literature, the VANOL *meso*borate catalyzed HDA did not require a treatment of acid to yield the cyclized product. This observation suggests that the reaction might proceed through a concerted [4+2] mechanism rather than the widely accepted[142, 149] stepwise pathway (Mukaiyama aldol then cyclization). Mechanistic investigations in this regard were not carried out.

Table 1.14 Studies of time and temperature for HDA reaction



I-56a 2.0 equiv + **I-51f** → **I-155b**

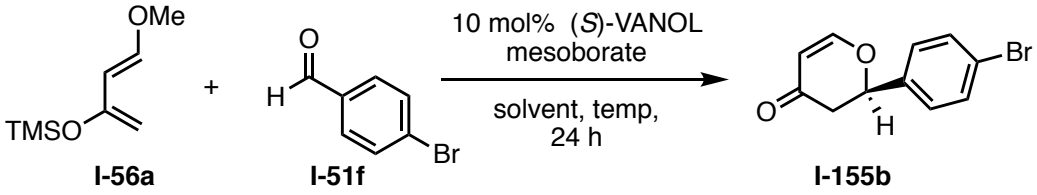
entry	temperature	time	%yield[a] (**I-155b**)	%ee[b] (**I-155b**)
1[c]	rt	24 h	79	62
2[c]	rt	1 h	83	59
3[c]	–40 ºC	24 h	89	83
4[d]	–40 ºC	1 h	92	84
5[e]	–78 ºC	1 h	49	83
6[ef]	–78 ºC	1 h	16	71
7[e]	–78 ºC	2 h	56	79
8[e]	–78 ºC	4 h	57	90
9[g]	–60 ºC	1.5 h	61	87

[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC. [c]Quenched by 1 M aq. HCl. [d]Quenched by TFA. [e]Quenched by Et_3N. [f]BINOL was used instead of VANOL. [g]Quenched by EtOH/H_2O

Next, the solvent effect was investigated for HDA reaction catalyzed by the VANOL *meso*borate at rt. Toluene appeared to be superior to the more polar solvents, such as

DCM and THF (entry 2 & 3 vs 1, *Table 1.15*). The optimal solvent system for *aza*-HDA reaction[113] delivered the product with higher yield, albeit slightly lower ee (entry 4, *Table 1.15*). The attempts to search for a better solvent for the *meso*borate catalyzed HDA reaction at –40 ºC were unsuccessful (entry 5-10, *Table 1.15*). The reaction in the polar solvent chloroform and the coordinating solvent Et_2O gave **I-155b** in low to moderate yield. In other aromatic solvents, including benzene, mesitylene and *m*-xylene, the reaction was much slower and gave similar enantioselectivity.

Table 1.15 Solvent screening for HDA reaction



I-56a 2.0 equiv **I-51f** **I-155b**

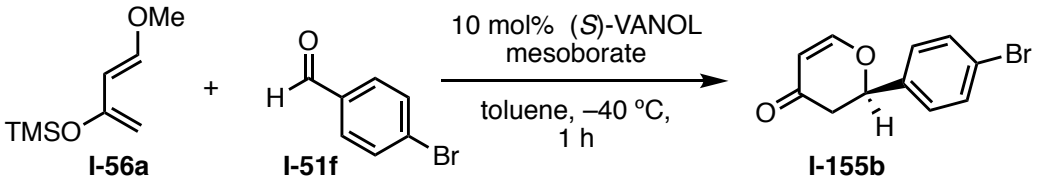
entry	solvent	temperature	%yield[a] (**I-155b**)	%ee[b] (**I-155b**)
1	toluene	rt	79	62
2	DCM	rt	65	54
3	THF	rt	56	48
4	DCM/toluene (1:1)	rt	88	59
5[c]	toluene	–40 ºC	79	81
6[c]	$CHCl_3$	–40 ºC	13	—
7[c]	benzene	–40 ºC	31	—
8[c]	Et_2O	–40 ºC	49	79
9[c]	mesitylene	–40 ºC	9	76
10[c]	*m*-xylene	–40 ºC	16	—

[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC.
[c] Quenched after 1 h

It was reasoned that the low reactivity in xylene and mesitylene could be caused by the water residue. In an attempt to improve the efficiency of the *meso*borate, effects of additives were investigated. The reaction gave comparable results in the presence of 4 Å MS or Na_2CO_3 (entry 2 & 3 vs 1, *Table 1.16*). The fact that the inorganic base Na_2CO_3

did not inhibit the reaction may be due to its low solubility in toluene at –40 ºC. In agreement with the reaction at rt (entry 2 vs 1, *Table 1.13*) DMSO was detrimental to the catalyzed reaction (entry 4 vs 1, *Table 1.16*). Addition of 20 mol% benzoic acid also had an adverse effect on the results, probably due to the formation of acyloxy borate (entry 5 vs 1, *Table 1.16*). Lastly, Et_3N shut down the reaction at –40 ºC as expected (entry 6, *Table 1.16*).

Table 1.16 Additive studies for HDA reaction

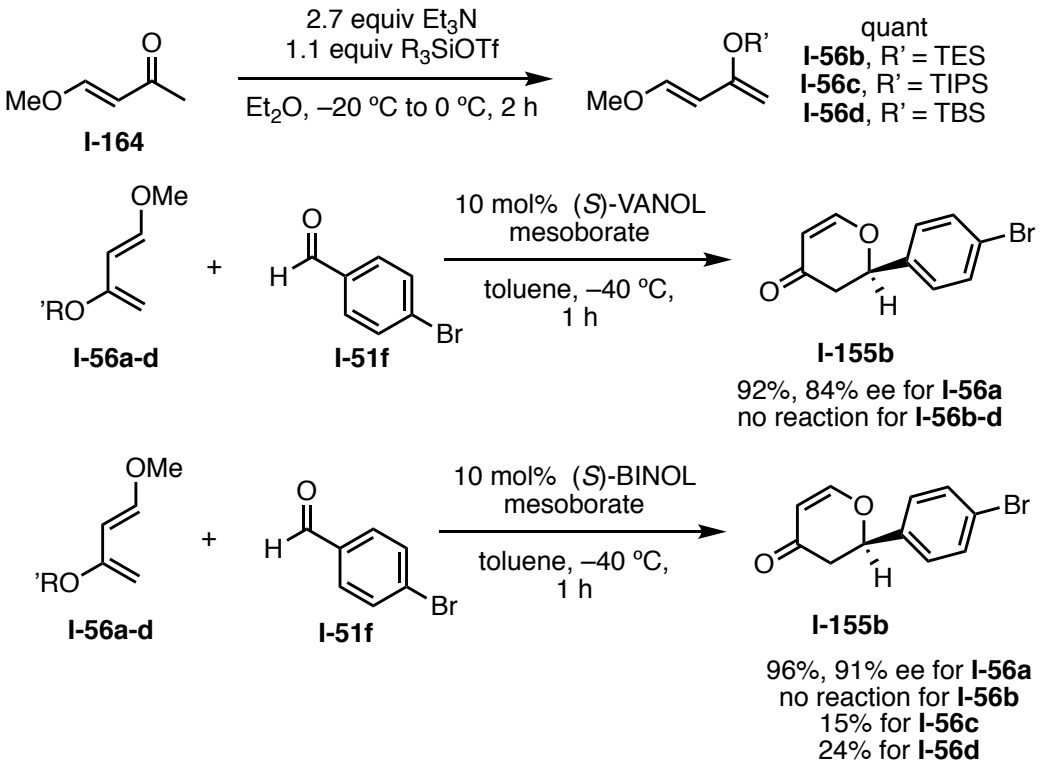


entry	additive	%yield[a] (**I-155b**)	%ee[b] (**I-155b**)
1	none	92	84
2	4 Å MS	91	83
3	20 mol% Na_2CO_3	91	83
4	20 mol% DMSO	17	—
5	20 mol% PhCOOH	47	74
6	20 mol% Et_3N	NR	—

[a]Isolated yield after chromatography on silica gel.
[b]As judged by chiral HPLC.

To investigate the effect of different silyl groups in the Danishefsky's diene, 3 other dienes **I-56b-d** was prepared by a modified procedure[150] in quantitative yields. It was a disappointment that employing the dienes with bulky silyl group such as TES, TIPS and TBS, slowed down the HDA reaction significantly with both VANOL and BINOL *meso*borate catalysts.

Scheme 1.21 HDA reaction of Danishefsky's diene **I-56** with different silyl group



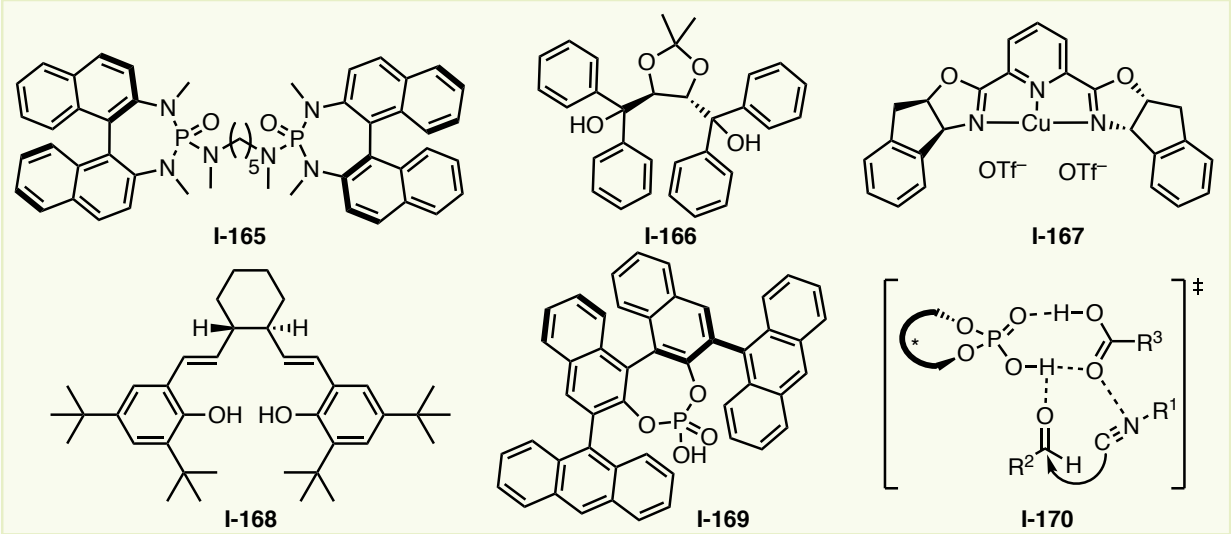
In summary, HDA reaction of Danishefsky's diene **I-56a** with 4-bromobenzaldehyde **I-51f** catalyzed by *meso*borate has been developed. By investigating the effect of temperature, time, ligand, solvent, additive and silyl group, the reaction under optimal condition afforded 89% dihydropyrone **I-155b** with 83% ee for VANOL *meso*borate, and 96% yield with 91% ee for BINOL *meso*borate.

1.11 Passerini reaction and aziridination reaction

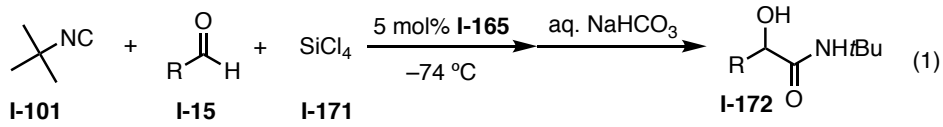
Another reaction of interest to test our *meso*borate catalyst on is the Passerini reaction. The Passerini reaction is a three-component (3C) reaction involving an isocyanide, an aldehyde (or ketone) and a carboxylic acid to afford an α-acyloxyamide with a chiral center. Although this reaction was discovered[151] about a century ago, only limited success has been achieved on a catalytic enantioselective version, since first of

which began to appear 14 years ago. Denmark and Fan reported[152] an asymmetric Passerini-type reaction without the carboxylic acid component catalyzed by a Lewis base catalyst, the chiral bisphosphoramide **I-165**. After aqueous workup, the reaction yielded α-hydroxyamides with high to excellent enantioselectivities for aromatic aldehydes but only moderate to high enantioselectivities was achieved for aliphatic or alkynyl aldehydes (eq 1, *Scheme 1.22*). The classic 3C Passerini reaction was first reported[153] in an asymmetric catalytic version by Dömling and coworkers by massive screening of hundreds of Lewis acid/ligand combinations. However, under the optimal conditions, the reaction promoted by complex Ti(O*i*Pr)$_4$-taddol **I-166** only afforded α-acyloxyamides with low enantioselectivities in low to moderate yields (eq 2, *Scheme 1.22*). Shreiber and coworkers developed[154] a Passerini 3C reaction catalyzed by the indan-pybox-Cu(II) complex **I-167**. High enantioselectivity was only observed when a chelating aldehyde was used (eq 3, *Scheme 1.22*). Zhu, Wang and coworkers demonstrated[155] that a chiral Al-salen **I-168** complex could catalyze the Passerini 3C reaction to afford moderate to good yield and good to excellent enantioselectivities only for a variety of aliphatic aldehydes (eq 4, *Scheme 1.22*). In 2015, Tan, Liu and coworkers achieved[156] a highly efficient asymmetric 3C Passerini reaction with a broad substrate scope by using the BINOL derived phosphoric acid **I-169**. Good yields and high to excellent ees were observed for the reaction with both aromatic and aliphatic aldehydes (eq 5, *Scheme 1.22*). The proposed transition state **I-170** involves activation of both aldehyde and isocyanide though hydrogen-bonding and ion pair interactions.

Scheme 1.22 Enantioselective Passerini reaction



Denmark (2003): Psserini-type Reaction

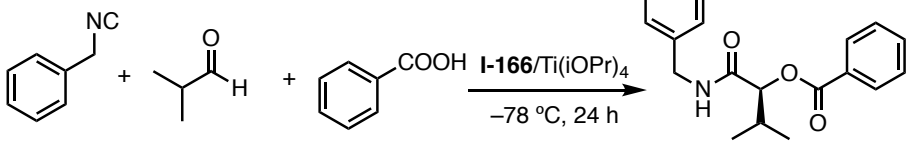


(1)

I-101 I-15 I-171 I-172

12 examples,
R = aryl or alkenyl,
81-93%, 84-99% ee
R = alkyl or alkynyl,
53-92%, 35-74% ee

Dömling (2003):

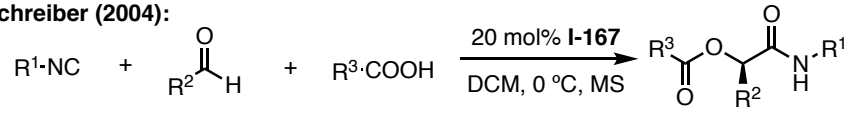


(2)

I-173a I-51h I-174a I-175a

6 examples,
12-48%, 32-42% ee

Schreiber (2004):



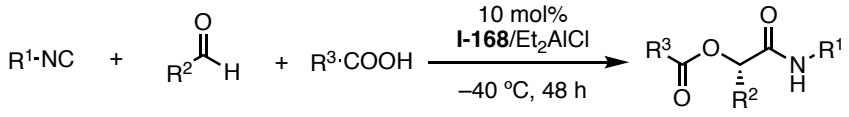
(3)

I-173 I-15 I-174 I-175

R^1 = alkyl; R^2 = alkyl, aryl with O or S groups; R^3 = Ph or Bn

16 examples,
75-98%, 60-98% ee

Zhu and Wang (2008):



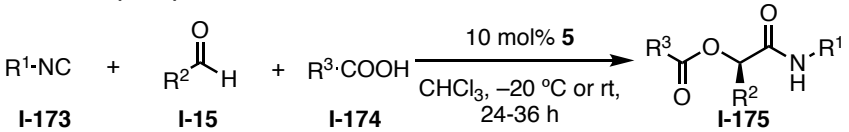
(4)

I-173 I-15 I-174 I-175

R^1 = aryl, alkyl; R^2 = alkyl; R^3 = aryl, alkyl

16 examples,
51-70%, 63-99% ee

Tan and Liu (2015):



(5)

I-173 I-15 I-174 I-175

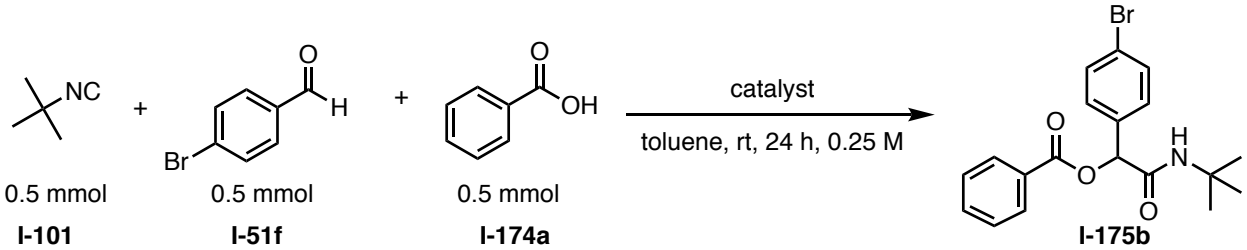
R^1 = alkyl; R^2, R^3 = aryl, alkyl

35 examples,
41-99%, 84-99% ee

Gupta and Wulff attempted[118] the Passerini 3C reaction of benzaldehyde, benzoic acid and *t*butyl isocyanide catalyzed by VANOL phosphoric acid (PA) in toluene at 80 ºC to afford the desired α-acyloxyamide with 6% ee in only 35% yield. In this work, the Passerini 3C reaction was examined with the *meso*borate catalyst described above which was effective for the epoxidations and AHDA reactions of aldehydes.

4-Bromobenzaldehyde was chosen instead of benzaldehyde for the model reaction since it is easier to handle and is relatively stable. The fact that the control reaction at rt without any catalyst gave a 49% yield of the desired product **I-175b** indicated a severe background reaction (entry 1, *Table 1.17*). Consistent with the result from the VAPOL PA catalyzed reaction, VANOL PA catalyzed the reaction at rt to afford 58% of **I-175b** with only –8% ee (entry 2, *Table 1.17*). The reaction catalyzed by either the *meso*borate or boroxinate catalyst gave a higher yield than the background reaction and both gave rise to the **I-175b** in 14% ee (entry 3 & 4, *Table 1.17*). Other Lewis acid systems that were effective in catalyzing reaction with imines[157] were also attempted. A Ti-VANOL complex was less effective. The Zr-VANOL[157] did not accelerate the Passerini reaction either with or without *N*-methyl imidazole (NMI) (entry 6 & 7, *Table 1.17*).

Table 1.17 Early attempts of asymmetric 3-component Passerini reaction



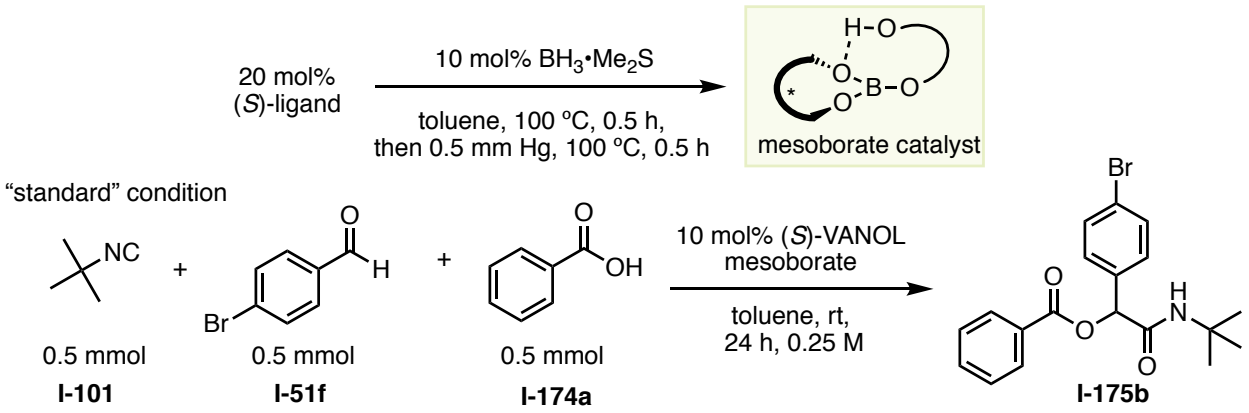
0.5 mmol **I-101** | 0.5 mmol **I-51f** | 0.5 mmol **I-174a** | **I-175b**

entry	catalyst	%yield[a] (**I-175b**)	%ee[b] (**I-175b**)
1	none	49	—
2	10% (*S*)-VANOL PA	58	–8
3	10 mol% (*S*)-VANOL mesoborate	68	14
4	20 mol% (*S*)-VANOL boroxinate	74	14
5	10 mol% (*S*)-VANOL/Ti[c]	56	–10
6	10 mol% (*S*)-VANOL/Zr[d]	46	–10
7	10 mol% (*S*)-VANOL/Zr/NMI[e]	45	–6

[a]Isolated yield after chromatography on silica gel.
[b]As judged by chiral HPLC. Absolute stereochemistry was not established.
[c]Catalyst was prepared by heating 20 mol% VANOL and 10 mol% $Zr(OiPr)_4$•(HOiPr) at 100 °C for 0.5 h, then pumping for 0.5 h
[d]Catalyst was prepared by heating 20 mol% VANOL and 10 mol% $Ti(OiPr)_4$ at 100 °C for 0.5 h, then pumping for 0.5 h
[e]10 mol% NMI was added to catalyst of entry 6

It was decided to further optimize the *meso*borate catalyst even though boroxinate gave slightly higher yield. Running the reaction at 0 °C increased the enantioselectivity while the yield dropped to 52% (entry 2 vs 1, *Table 1.18*). Adding 4 Å MS did not have a positive effect on the outcome (entry 4 vs 2, *Table 1.18*). A control reaction at 0 °C showed that the background reaction seriously competes with the catalyzed reaction (entry 3, *Table 1.18*). Further decreasing the temperature to –20 °C was not too rewarding. The ee of **I-175b** increased 5% but the loss in yield was 14% yield.

Table 1.18 Temperature screening of the Passerini reaction catalyzed by *meso*borate **I-118**



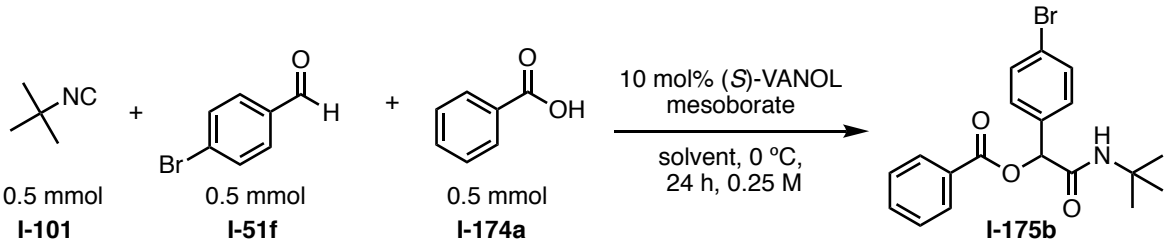
entry	variation from "standard"	%conv.[a] (**I-51f**)	%yield[b] (**I-175b**)	%ee[c] (**I-175b**)
1	none	91	68	14
2	0 ºC	81	52	35
3	0 ºC, w/o catalyst	87	54	—
4	0 ºC, 4 Å MS	60	56	34
5	–20 ºC	67	38	40

[a]Determined by ^{1}H NMR analysis of crude product using Ph_3CH as an internal standard. [b]Isolated yield after chromatography on silica gel.
[c]As judged by chiral HPLC. Absolute stereochemistry was not established.

Next, the effect of solvent and ligand was investigated on the *meso*borate catalyzed Passerini reaction at 0 ºC. Other common solvents including DCM, chloroform, THF and acetonitrile were screened (*Table 1.19*). Toluene gave the lowest yield of the product but with highest enantioselectivity among 5 solvents screened (entry 1, *Table 1.19*). Reaction in DCM afford **I-175b** in the highest yield of 71%, albeit with lower ee. The coordinating solvent THF gave the product with the lowest ee as expected (entry 4, *Table 1.19*). Toluene was used as the solvent for ligand screening. In contrary to the results from the AHDA reaction, BINOL *meso*borate was less effective than the corresponding VANOL/VAPOL catalysts (entry 2, *Table 1.20*). VANOL was superior ligand in terms of yield and ee of the product (entry 1, *Table 1.20*). Interestingly, same atropisomer of

VAPOL induced the opposite enantioselectivity for the reaction with VANOL and tBuVANOL *meso*borate catalyst (entry 3 & 4, *Table 1.20*).

Table 1.19 Solvent screening of Passerini reaction catalyzed by *meso*borate **I-118**

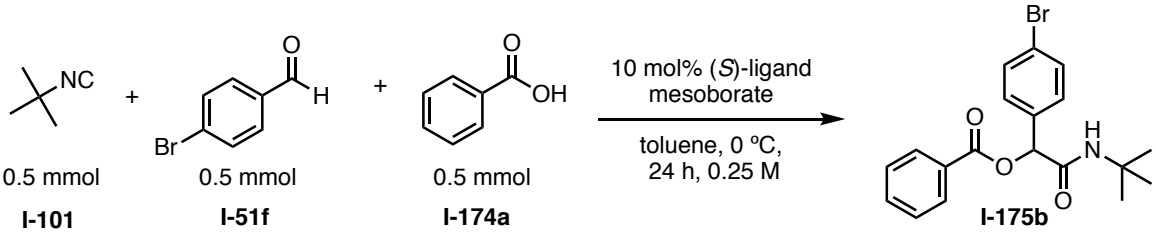


0.5 mmol **I-101** | 0.5 mmol **I-51f** | 0.5 mmol **I-174a** | **I-175b**

entry	solvent	%conv.[a] (**I-51f**)	%yield[b] (**I-175b**)	%ee[c] (**I-175b**)
1	toluene	81	52	35
2	DCM	86	71	27
3	$CHCl_3$	79	58	29
4	THF	70	60	15
5	MeCN	68	58	29

[a]Determined by ^{1}H NMR analysis of crude product using Ph_3CH as an internal standard.
[b]Isolated yield after chromatography on silica gel.
[c]As judged by chiral HPLC. Absolute stereochemistry was not established.

Table 1.20 Ligand screening of Passerini reaction catalyzed by *meso*borate **I-118**



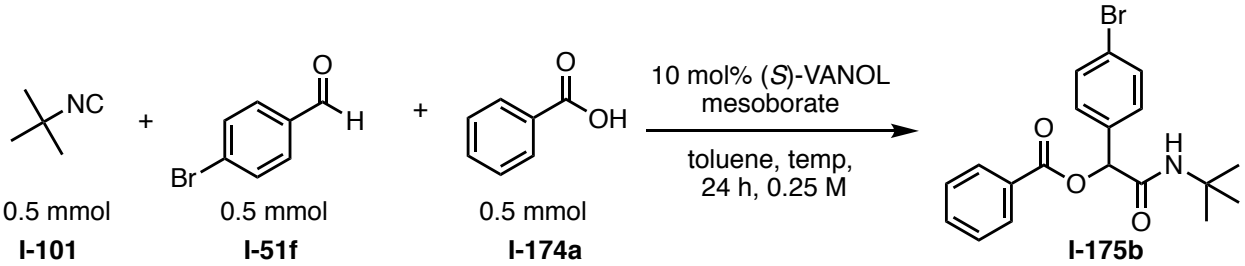
0.5 mmol **I-101** | 0.5 mmol **I-51f** | 0.5 mmol **I-174a** | **I-175b**

entry	ligand	%conv.[a] (**I-51f**)	%yield[b] (**I-175b**)	%ee[c] (**I-175b**)
1	VANOL	81	52	35
2	BINOL	78	26	–2
3	VAPOL	75	49	–23
4	*t*BuVANOL	78	21	24

[a]Determined by ^{1}H NMR analysis of crude product using Ph_3CH as an internal standard.
[b]Isolated yield after chromatography on silica gel.
[c]As judged by chiral HPLC. Absolute stereochemistry was not established.

Notably, in the presence of 20 mol% DMSO, the Passerini reaction catalyzed by *meso*borate afforded **I-175b** in higher yield but with slightly lower ee (entry 2 vs 1, 6 vs 5, *Table 1.21*). Control experiments revealed that the uncatalyzed reactions were not significantly affected either at rt or 0 ºC (entry 3 vs 4, 7 vs 8, *Table 1.21*). This might have suggested that DMSO was somehow engaged in the *meso*borate catalyst, which was helpful with the catalytic turnover.

Table 1.21 Effect of DMSO in Passerini reaction catalyzed by *meso*borate **I-118**



0.5 mmol **I-101** | 0.5 mmol **I-51f** | 0.5 mmol **I-174a** | **I-175b**

entry	catalyst	temp	DMSO	%yield[a] (**I-175b**)	%ee[b] (**I-175b**)
1	yes	rt	0	68	14
2	yes	rt	20 mol%	79	9
3	no	rt	20 mol%	45	—
4	no	rt	0	49	—
5	yes	0 ºC	0	52	35
6	yes	0 ºC	20 mol%	94	34
7	no	0 ºC	20 mol%	64	—
8	no	0 ºC	0	56	—

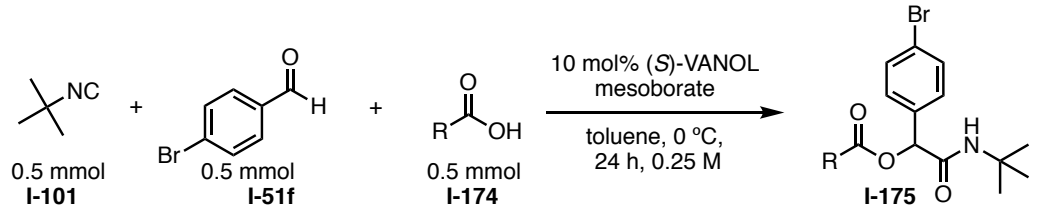
[a]Isolated yield after chromatography on silica gel. [b]As judged by chiral HPLC. Absolute stereochemistry was not established.

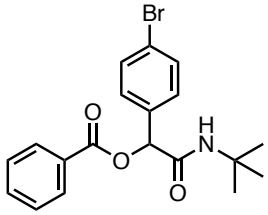
The enantioselectivity of the *meso*borate catalyzed Passerini reaction was hampered by competition with the uncatalyzed reaction. It was reasoned that by varying the acid component, it might be possible to slow down the background reaction, thus to increase the asymmetric induction of the reaction (*Scheme 1.23*).

With a more steric hindered 1-naphthoic acid, the reaction afforded **I-175b** in lower yield with minimal increase in ee. An aliphatic carboxylic acid was compatible in the reaction but did not improve the enantioselectivity (**I-175c**). The reaction with 4-substituted benzoic acids without DMSO was sluggish. Gratifyingly, in the presence of DMSO, the reaction of 4-methoxybenzoic acid afforded 50% of **I-175d** with 49% ee, while the 4-nitrobenzoic acid gave only 32% nearly racemic **I-175e**. This result was in agreement of our hypothesis that use of a weaker acid would slow down the background, thus increasing the ee of the product. However, the reaction with 3,4,5-trimethoxybenzoic acid did not afford **I-175f** with better ee, probably because of it's lower capability to donate a H-bond to the *meso*borate catalyst.

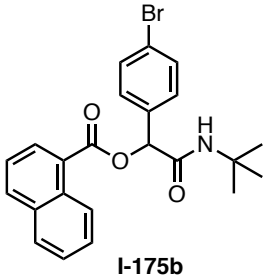
In summary, *meso*borate catalyst could be extended to 3C Passerini reaction to afford α-acyloxyamides with low to moderate enantioselectivities. In order to optimize it into a highly enantioselective reaction, one would need to develop a more reactive catalyst that can outcompete the uncatalyzed reaction. Perhaps this could be achieved by screening *meso*borates generated from a variety of VANOL derivatives.

Scheme 1.23 Screening of acid component for 3C Passerini reaction catalyzed by *spiro*borate **I-118**

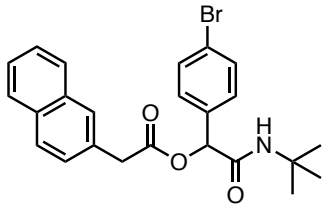




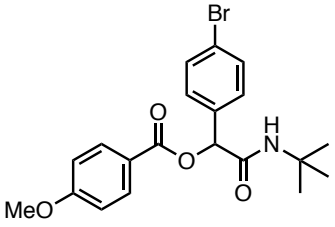
I-175a
81% conv.[a], 52%[b], 35% ee[c]



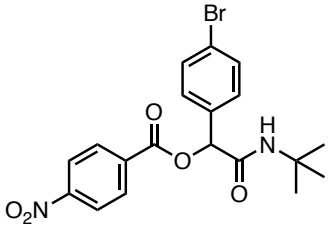
I-175b
69% conv.[a], 43%[b], 37% ee[c]



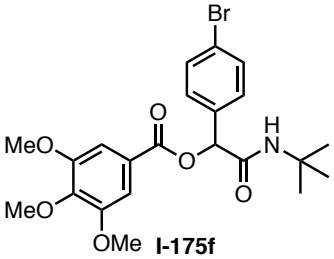
I-175c
72% conv.[a], 40%[b], 35% ee[c]



I-175d
55% conv.[a], 14% NMR yield[a]
(66% conv.[a], 50%[b], 49% ee[c])[d]



I-175e
62% conv.[a], 12% NMR yield[a]
(66% conv.[a], 32%[b], 3% ee[c])[d]



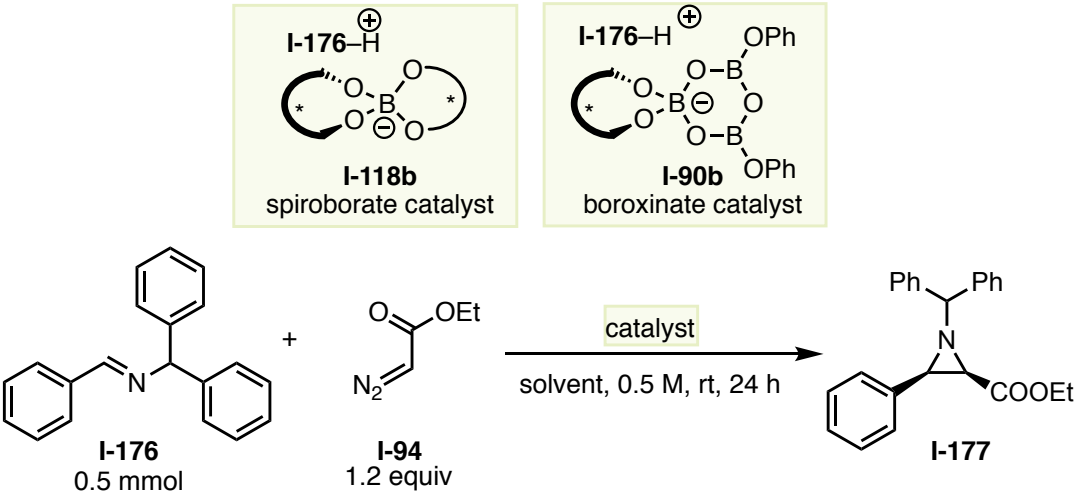
I-175f
(32%[b], 37% ee[c])[e]
(rt, 92%[b], 24% ee[c])[d]

[a]Determined by ^{1}H NMR analysis of aldehyde using Ph_3CH as an internal standard. [b]Isolated yield after chromatography on silica gel. [c]As judged by chiral HPLC. Absolute stereochemistry was not established. [d]With 20 mol% DMSO. [e]$B(OPh)_3$ was used for spiroborate formation instead of BH_3•Me_2S.

1.11 Asymmetric aziridination and future work

Asymmetric aziridination reactions catalyzed by BINOL *spiro*borate catalysts has been studied[56]. It was found that the BINOL *spiro*borate can catalyze the aziridination reaction of imine **I-176** and EDA **I-94** to afford the *cis*-aziridine **I-177** with the opposite ee compared to that with the BINOL boroxinate catalyst (entry 1 vs 2, *Table 1.22*). Furthermore, the BINOL *spiro*borate is formed alongside the boroxinate catalyst as a mixure under the 1:3 BINOL to boron conditions. Therefore, only low optical purity (13-20% ee) could be achieved by the boroxinate conditions (entry 2, *Table 1.22*).

Table 1.22 Asymmetric aziridination of imine **I-176** with EDA **I-94** catalyzed by *spiro*borate **I-118b** and boroxinate **I-90b**



entry	catalyst	method[a]	solvent	*cis*:*trans*[b] (**I-177**)	%yield[c] (**I-177**)	%ee[d] (**I-177**)
1	10 mol% BINOL-**I-118b**	A	DCM	8:1	44	–26
2	10 mol% BINOL-**I-118b**/**I-90b**[e]	B	DCM	18:1	58	24
3	5 mol% VANOL-**I-118b**	C	toluene	30:1	82	52
4	10 mol% VANOL-**I-90b**	D	toluene	>50:1	84	93

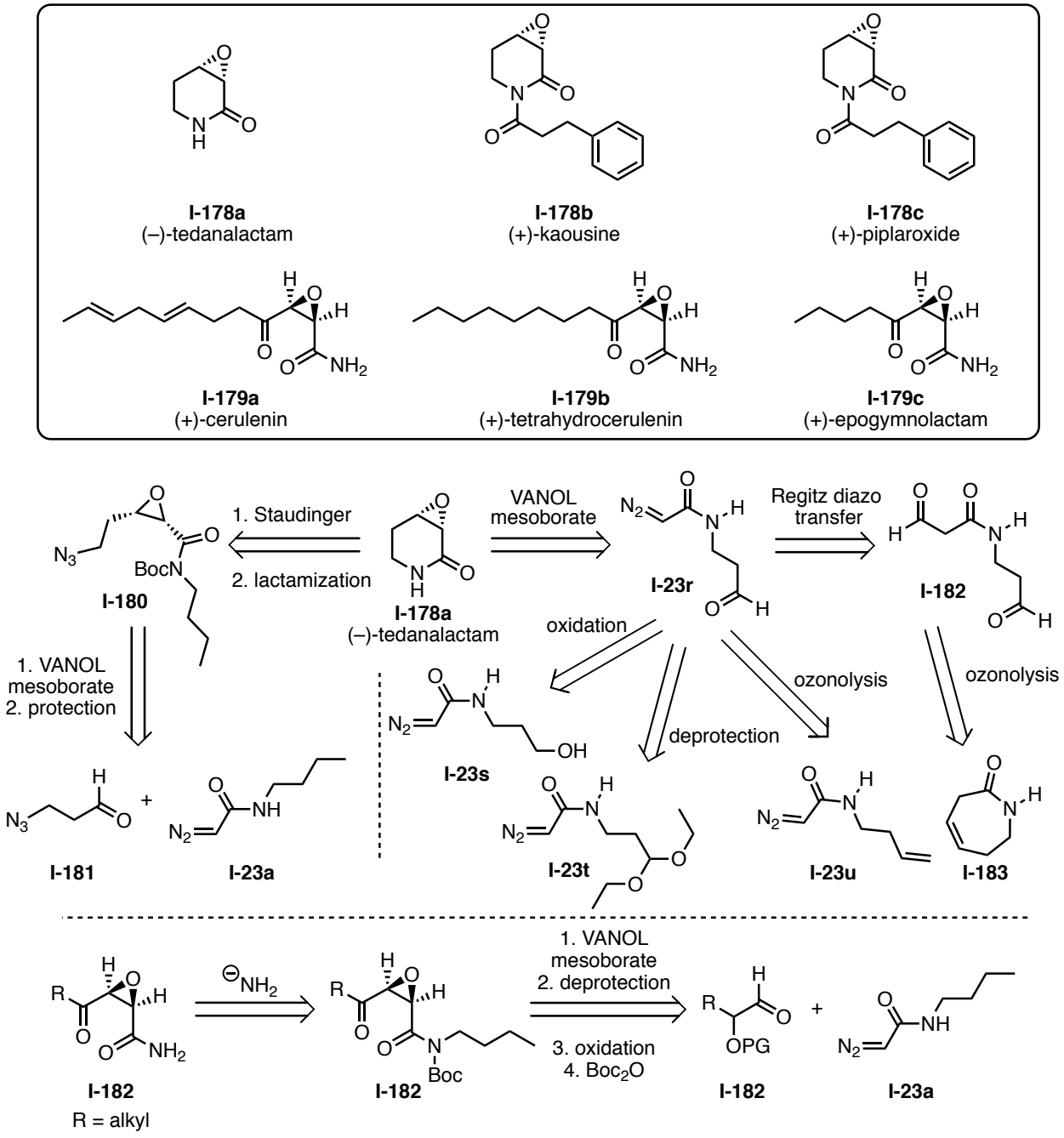
[a]A: precatalyst prepared by reaction of (*S*)-BINOL with 3 equiv of $B(OPh)_3$ in CH_2Cl_2 at 55 °C for 1 h and then removal of volatiles. B: reaction performed by adding 12 equiv of **I-94** to a CH_2Cl_2 solution of a (2:1:10) mixture of BINOL, $B(OPh)_3$, and imine **I-176.** C: precatalyst prepared by reaction of the 10 mol% (*S*)-VANOL and 5 mol% $BH_3{\cdot}Me_2S$ in toluene at 100 °C for 1 h and then removal of the volatiles. D: precatalyst prepared by reaction of the 10 mol% (*S*)-VANOL, $BH_3{\cdot}Me_2S$, PhOH, and H_2O (1:3:2:3) in toluene at 100 °C for 1 h and then removal of the volatiles. [b]As judged by ^{1}H NMR crude. [c]Isolated yield after chromatography on silica gel. [d]As judged by chiral HPLC. [e]The mixure of **I-118b**/**I-90b** was determined to be 5:2 by ^{11}B NMR.

It would be interesting to evaluate the VANOL *spiro*borate catalyst **I-118** in the aziridination of aldimines with EDA. The *spiro*borate precatalyst of VANOL was prepared by the general conditions and then was added imine **I-176**. EDA **I-94** was added after 5 min and the mixture was stirred at rt for 24 h. The reaction afforded the desired *cis*-aziridine in 82% yield with 52% ee. It was found that VANOL *spiro*borate gave better stereoselectivity than its BINOL analog (entry 3 vs 1, *Table 1.22*). In addition, VANOL

*spiro*borate gave the same enantiomer ((2*R*,3*R*)-**I-177)** as the VANOL boroxinate catalyst, albeit with much lower enantioselectivity (entry 3 vs 4, *Table 1.22*).

It was pleasing to find that by optimization of the protecting group in the imine and optimizing the ligand in the catalyst, a highly enantioselective aziridination has been developed[158]. The mechanism of this reaction is proposed to be a Brønsted acid catalyzed pathway. Deprotonation by imine to give a *spiro*borate precatalyst was supported by ^{11}B NMR studies and X-ray crystallography[158]. In addition, a Hammett plot study[158] with catalysts prepared from VANOLs having substituents with varying electronic properties in the 5,5'-postions was conducted. Preliminary results are in agreement with a Brønsted acid catalysis mechanism. It would be also worthwhile to investigate the mechanism of the *meso*borate-catalyzed epoxidation by a Hammett study and a KIE study. If the experimental evidence supports the Lewis acid pathway, these borate catalysts would be one of the rare cases of the "chameleon catalysts", which could catalyze different reactions by two distinct pathways (Brønsted vs Lewis acid catalysis) depending on the substrates.

Scheme 1.24 Potential applications of asymmetric epoxidation in total synthesis



Also in the future work, the asymmetric epoxidation could be applied in the total synthesis of natural products containing a 3,4-epoxy amide motif, such as (–)-tedanalactam **I-178a**, (+)-cerulenin **I-179a** and related compounds (*Scheme 1.24*). The enantioselective total synthesis of (–)-tedanalactam has been reported on three

occasions[159-161]. The source of chirality is produced by the Sharpless asymmetric dihydroxylation[159], from the chiral pool[160] and by a classical resolution[161]. Our approach is to introduce chirality by epoxidation of the azide containing aldehyde **I-181** with diazoacetamide **I-23a**, followed by Staudinger reaction and lactamization to finish the synthesis. Alternatively, a more challenging intramolecular epoxidation of **I-23r** could be employed as th last step to construct the *cis*-epoxide group asymmetrically. However, the synthesis of a diazo compound that contains an aldehyde functional group has not been reported. The synthesis of diazo compound **I-23s** containing a hydroxyl group and **I-23t** containing a diethyl acetal group was carried out (see Chapter 4 section 4.21) using general procedure and went well. But the attempts to oxidize the hydroxyl group into aldehydes using DMP, Swern oxidation and PCC oxidation failed to give **I-23r** due to the sensitivity of diazo group under those conditions. Deprotection of **I-23t** by a mild I_2/acetone condition also failed due to the decomposition of the diazo compound. Other protecting groups for aldehyde such as silyl cyanohydrin acetals would be worth trying. Alternatively, **I-23r** could be prepared by Regiz diazo transfer reaction from **I-182** or by ozonolysis of compound **I-23u** if the diazo group can survive the ozonolysis process.

Another interesting compound cerulenin **I-179a**, an antifungal antibiotic that has been the target of several racemic[162-165] and enantioselective[166-168] total syntheses. Natural (+)-cerulenin and related compounds have been synthesized from chiral synthon $_D$-glucose[166], $_D$-tartaric acid[167] and using the Sharpless asymmetric epoxidation[168]. The shortest synthesis[168] was reported by Mani and Townsend, with the longest linear sequence of 8 steps and 26% overall yield. Our approach is straight forward: the

epoxidation of racemic protected α-hydroxy aldehyde **I-182** with diazo acetamide **I-23a** would afford the epoxide with the correct stereochemistry. Hopefully, the asymmetric epoxidation would display a high catalyst-controlled rather than control by the stereocenter of the hydroxyl group in the aldehyde substrates. After several steps of functional group manipulation, the natural product (+)-cerulenin **I-179a** could hopefully be accessed. The related compound (+)-tetrahydrocerulenin **I-179b** and (+)-epogymnolactam **I-179c** could also be synthesized in the similar manner.

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CHAPTER TWO

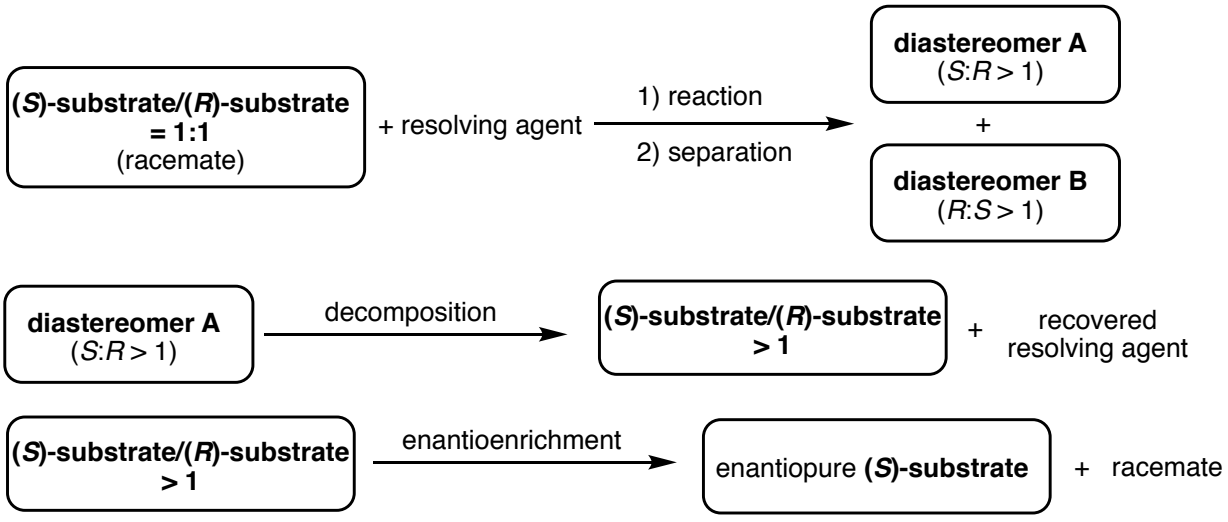
CHIRAL RESOLUTION OF VANOL/VAPOL DERIVATIVES

"Sometimes life is going to hit you in the head with a brick. Don't lose faith."
–Steve Jobs

2.1 Strategies in optical resolution

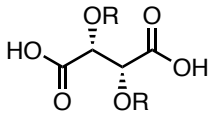
The importance of chirality in the pharmaceutical and agrochemical industry has been widely recognized. More than half or all the FDA-approved new molecular entities are single enantiomers for the 2001-2011 period[1] and in 2015, nine of the top-10 global selling small molecule drugs have chiral active ingredients[2]. Over the last few decades, the field of asymmetric synthesis enjoyed tremendous advances. However, the alternative method – preparation of a racemic mixture followed by resolution can still be attractive, especially when both enantiomers are desired[1].

Scheme 2.1 General scheme of classical resolution

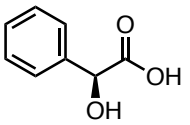


Since the first demonstration by Louis Pasteur in 1848[3], optical resolution has been the most important method for obtaining enantiomers from racemates[4]. The proper choice of resolving agent to form diastereomers is essential to realize the "classical resolution" (*Scheme 2.1*). Two main categories of diastereomers can be distinguished: 1) non-covalent diastereomers and 2) covalently bound diastereomers. Resolution by non-covalent diastereomers is the most often used method of resolution. This involves salt formation when the substrates are acidic or basic, and less efficiently, complex with neutral racemates. Some commonly used acidic or basic resolving agents[4] are shown (*Scheme 2.2*). Most frequently used resolving agents in pharmaceutical industry are natural $_{L}$-tartaric acid **II-1** and its derivatives, followed by (*R*)- or (*S*)-mandelic acid **II-2** due to their relative stability, commercial availability and cost. Basic resolving agents, represented by α-methylbenzylamine **II-4** and natural alkaloids **II-5** to **II-10** are useful for resolving acidic racemic compounds. Although the enantiomers of these natural products are often not available (two pair of cinchona alkaloids are pseudoenantiomers), natural alkaloids were used in about 25% of all resolutions reported in the 1990s[5]. A less commonly used method for resolution, mostly when the substrate is not amenable to salt formation, is by forming a covalent bond with the resolving agent. If these two strategies of resolution fail for a compound, resolution of a simple derivatives could be attempt. Examples of using these strategies to resolve BINOL will be given in the next section.

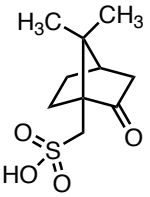
Scheme 2.2 Commonly used resolving agents



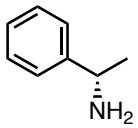
R = H, (*R*,*R*)-tartaric acid
(*R*,*R*)-**II-1**



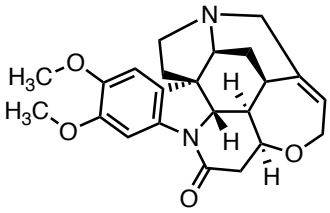
(*S*)-mandelic acid
(*S*)-**II-2**



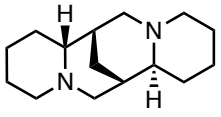
(+)-Camphor-10-sulfonic acid
(+)-**II-3**



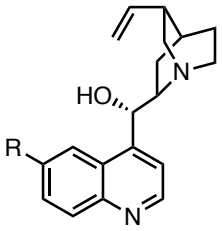
(*S*)-1-phenylethylamine
(*S*)-**II-4**



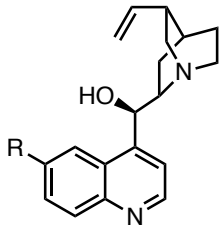
brucine
II-5



(–)-sparteine
(–)-**II-6**



R = H, (+)-cinchonidine **II-7**
R = OMe, (+)-quinidine **II-8**



R = H, (–)-cinchonine **II-9**
R = OMe, (–)-quinine **II-10**

Despite several researchers' attempts to searching for a rational guide by many approaches such as empirical correlations[6], physical and phase properties[7], analysis of crystal structure data[8] and computational modeling[9-10], no methodology has been developed to predict the resolution efficiency of a diastereomeric pair. Selecting a resolving agent remains a method of trial and error instead of an engineering approach. Moreover, a subtle structural change in the resolving agent or substrate would cause unpredictable changes in the crystal structure of the diastereomers, thus affect the efficiency of a resolution process substantially[11]. Therefore, there is only a limited number of reported resolution process that could be applied to a broad scope of substrates[12-14].

In spite of our lack of theory to predict the solubility difference between two diastereomeric compounds, many approaches have been developed to facilitate the searching for the optimal resolving process. Vries and coworkers first reported[15] the "family approach" in 1988 which was also known as "Dutch resolution". In their method,

a mixture of (usually three, sometimes two) resolving agents with structural similarity (family members) were used, and the results (yield and ee) of most cases were superior to those achieved by any of the resolving agents alone. The chance of obtaining solid salts with significant dr were improved from 20-30% for classical resolution to 90-95%[16]. High-throughput screening and analysis were employed by pharmaceutical companies in selection of resolution agent and condition optimization to aid pharmaceutical development[17]. The resulting increase in productivity has allowed rapid access to pure enantiomer of active pharmaceutical ingredient (API) in the early stage of development.

Once a suitable resolving agent is identified, the rest of the process development is usually fast and easy, which is a fundamental advantage compared to other stereoselective process. To develop an effective resolution, several parameters have to be optimized, such as solvent system, concentration, temperature, time etc. Moreover, chiral resolution does not always provide a product with an ee meeting the requirement (>99% ee for chiral ligand). Often times, enantioenrichment by crystallization will be required[18].

2.2 Resolution of Bi-2-naphthol (BINOL)

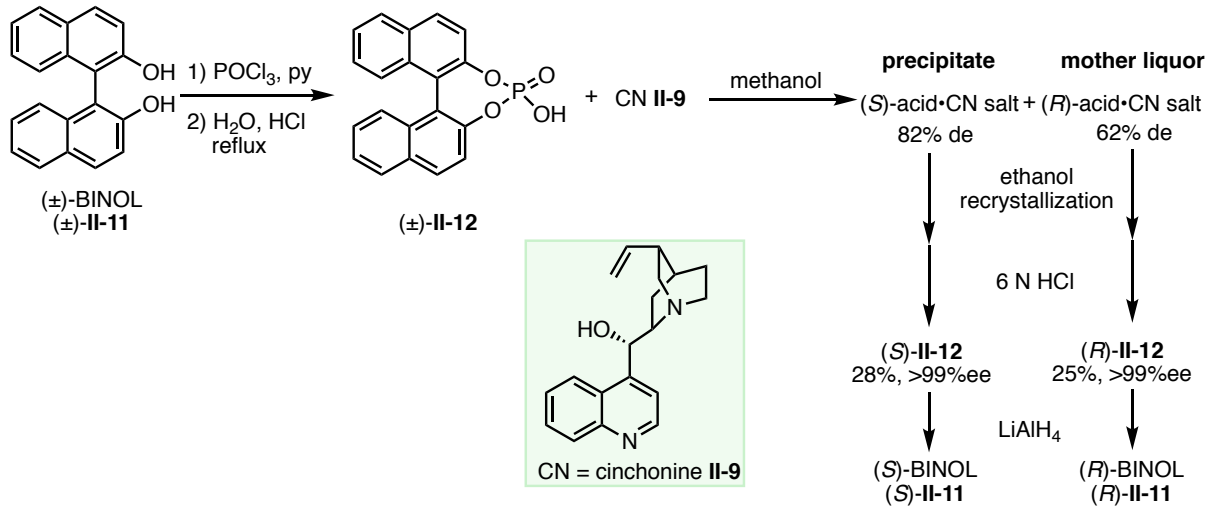
Even though BINOL was first synthesized by von Richter[19] via oxidative coupling of 2-naphthol using $FeCl_3$ in 1873 (also independently reported[20] by Pummerer and coworkers in 1926), its potential for providing a stereospecific process was not recognized until nearly 100 years later. In 1971, Jacques and coworkers reported[21] the first resolution of BINOL **II-11**, procedures involving preparation of its phosphoric acid derivatives **II-12**, resolution via cinchonine salt, followed by liberation by $LiAlH_4$ (*Scheme 2.3*). They also

described the resolution of chiral amines utilizing optically pure BINOL phosphoric acid. Two years later, Cram synthesized chiral crown ethers from optically pure BINOL and demonstrated their application in chiral recognition[22]. The first application of BINOL in asymmetric synthesis was reported[23] by Noyori and coworkers, using a BINOL aluminum hydride complex to reduce ketones and aldehydes in 1979. Over the last 30 years, BINOL and its derivatives have been successfully used as chiral ligands in a broad range of transformations in asymmetric synthesis[24-25].

Although many asymmetric syntheses of BINOL by enantioselective oxidation of 2-naphthol have been developed[24], chemical resolution is still the general approach to obtain optically pure BINOL and its derivatives. Resolution of BINOL has been extensively studied in the 1990s[26]. All of the reported examples can be categorized into the aforementioned approaches. Selected examples for each approach are provided in *Scheme 2.3 to 2.6.*

1) Via salt formation with phosphoric acid derivatives (*Scheme 2.3*)

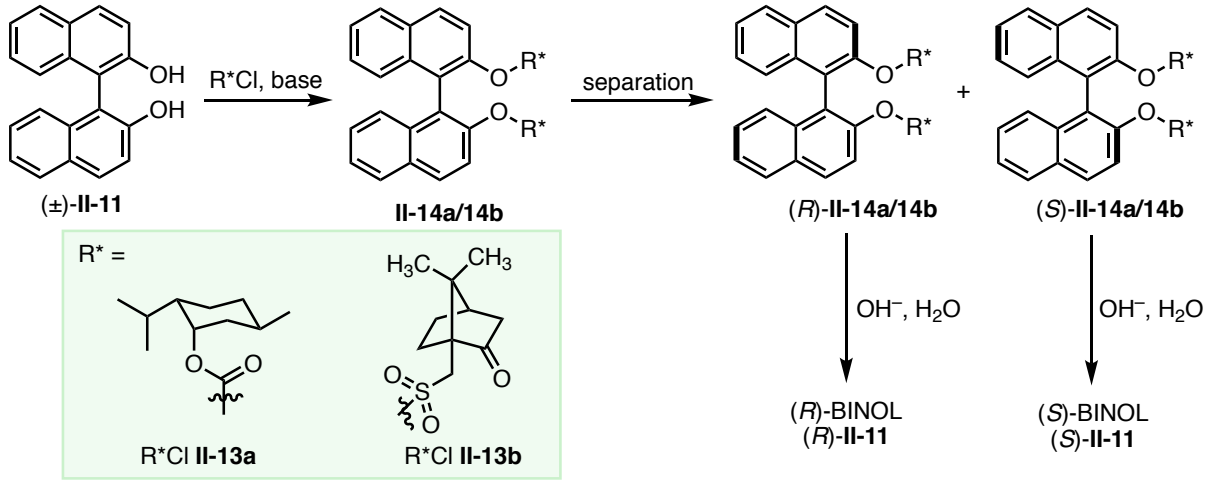
Scheme 2.3 Resolution of BINOL (1)



A large-scale procedure[27] was developed by the Jacques and coworkers and had been utilized by the Cram group. Instead of using cinchonine **II-9** for (*S*)-BINOL and cinchonidine **II-7** for (*R*)-BINOL as in the original report, the complexes of cinchonine **II-9** with both enantiomers of BINOL can be obtained in moderate yield by recrystallization from ethanol, followed by cleavage using $LiAlH_4$. The 7,7'-bis(benzyloxy) analog was similarly resolved[28] using the same procedure. The drawback of this procedure is that some reagents involved ($POCl_3$ and $LiAlH_4$) require special handling.

2) Via diastereomeric esters (*Scheme 2.4*)

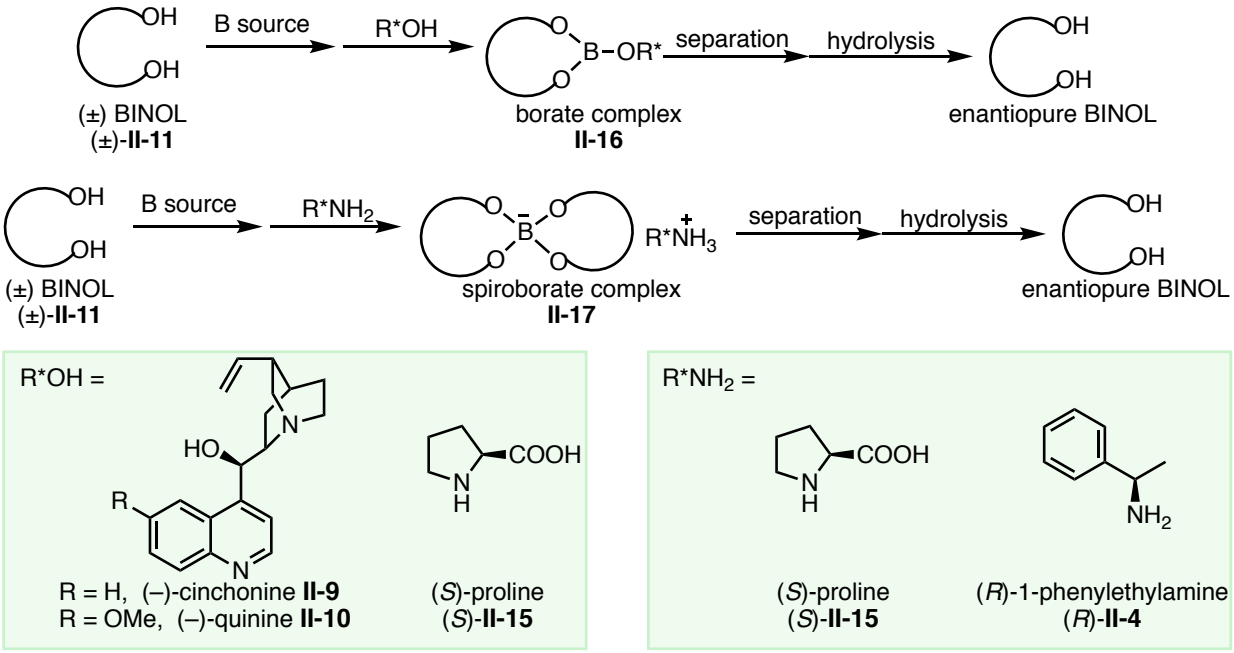
Scheme 2.4 Resolution of BINOL (*2*)



Diastereomeric BINOL bis-carbonates[29-30] and bis-sulfonates[31] can be derived from racemic BINOL with commercially available chiral acyl chloride **II-13a** and sulfonyl chloride **II-13b**. The diastereomer can be easily separated either by recrystallization or column chromatography. After hydrolysis, both BINOL enantiomers can be obtained in high yield.

3) Via diastereomeric borates (*Scheme 2.5*)

Scheme 2.5 Resolution of BINOL (3)



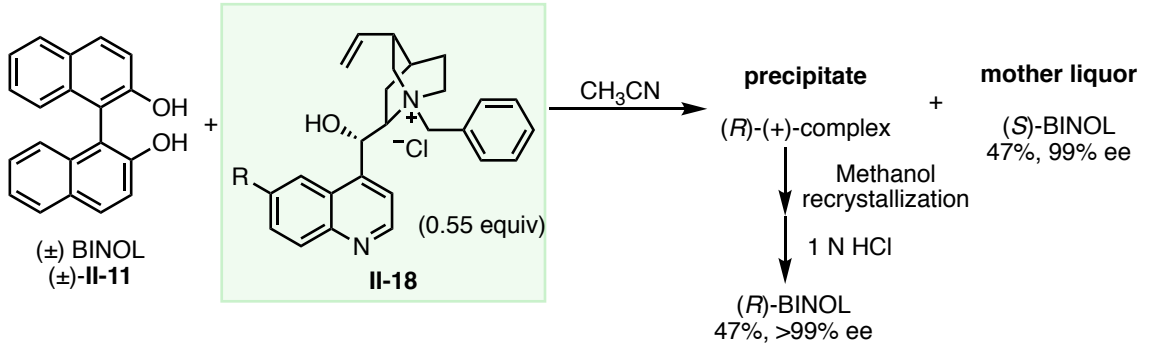
Resolution of BINOL via cyclic borate esters was first reported[32] by Shan and coworkers. Compared to resolution via other diastereomeric esters, the procedure with borate ester is more convenient because formation and cleavage of B-O bonds are easier. In their first report, BINOL-quinine complex **II-16** was synthesized using either BH_3•Me_2S or $B(OMe)_3$ as boron source. (*S*)-BINOL complex precipitates from THF and then is separated by filtration. Both (*R*)- and (*S*)-BINOL can be obtained with 100% ee in high yield from hydrolysis and then recrystallization from Et_2O. Subsequently, they developed a complementary procedure[33]. Employing cinchonine **II-9** as the resolving agent provides (*R*)-BINOL complex as a precipitate from toluene. The same methodology

using (*S*)-proline **II-15** has been reported[34] with lower efficiency but was later improved[35] by the same group.

Periasamy et al. discovered[36] that racemic BINOL forms a 2:1 *spiro*borate ionic complex **II-17** with (*S*)-proline **II-15** during their efforts at preparing the borate ester. Although only moderate resolving efficiency was achieved using (*S*)-proline **II-15**, they developed a procedure employing boric acid and readily accessible chiral amine, (*R*)-α-methylbenzylamine (*R*)-**II-4** to obtain both BINOL enantiomers in high yield after recrystallization enantioenrichment.

4) Via diastereomeric inclusion complexes (*Scheme 2.6*)

Scheme 2.6 Resolution of BINOL (4)



equivalent	1.0	1.1	1.0	0.5
solvent	DCM/CH_3OH 10:1	toluene	benzene/hexane 4:1	THF/ethanol 1:1.5
precipitate	(*S*), 32%, 78% ee	(*R*), 45%, >99% ee	(*S*), 36%, 100% ee	(*R*), 37%, 70% ee

Toda and coworker first applied[37] inclusion crystallization in the resolution of BINOL using a chiral host molecule. In their original report, the amide derivative (*R,R*)-**II-**

20 from inexpensive (*R*,*R*)-tartaric acid was utilized as the host compound. A complex of (*S*)-BINOL was formed and was recrystallized. Upon column chromatography, enantiopure (*S*)-BINOL was separated from the amide host. In 1993, they applied[38] the same methodology using commercially available *N*-benzylcinchonidinium chloride **II-18** as the host compound. Subsequently, this procedure was optimized[39-40] by the Pu group and the Merck process team, and it was later applied[41] to the synthesis of BINAP. This process is arguably one of the most effective methods accessing both enantiomers of BINOL in the literature. Only 0.55 equivalent of **II-18** is required, with (*R*)-BINOL complex crystallizing in very high yield, leaving 95% (*S*)-BINOL with >99%ee in the supernatant. The same procedure can be applied[39, 42] to four BINOL analogs with substituents on the 6-, 7- or 8-position, giving similar results. Other chiral host compounds, such as (*S*)-proline **II-15**[43-45], (*S*)-5-oxopyrrolidine-2-carboxanilide **II-21**[46] and (1*R*,2*R*)-diaminocyclohexane **II-19**[47,48] were also explored and proved to be efficient by other researchers.

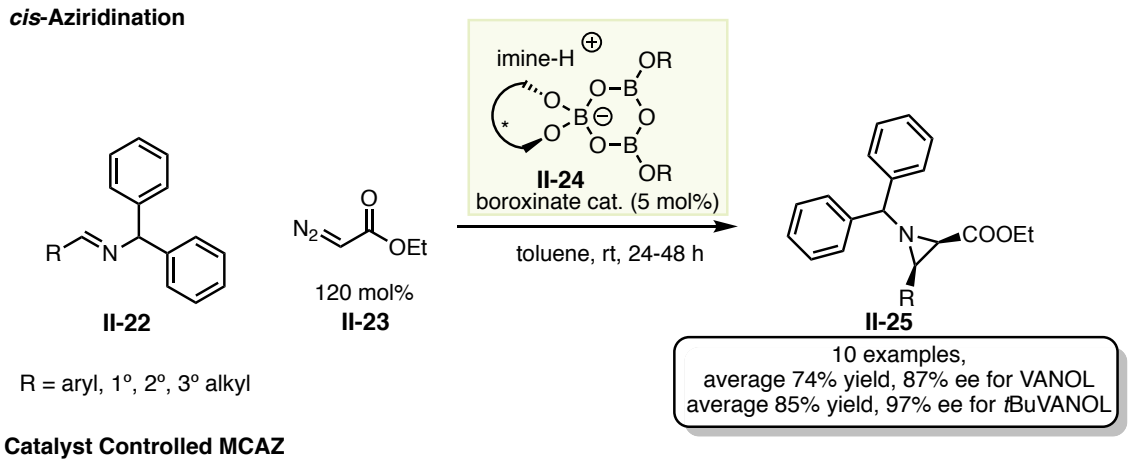
2.3 VANOL/VAPOL derivatives and deracemization

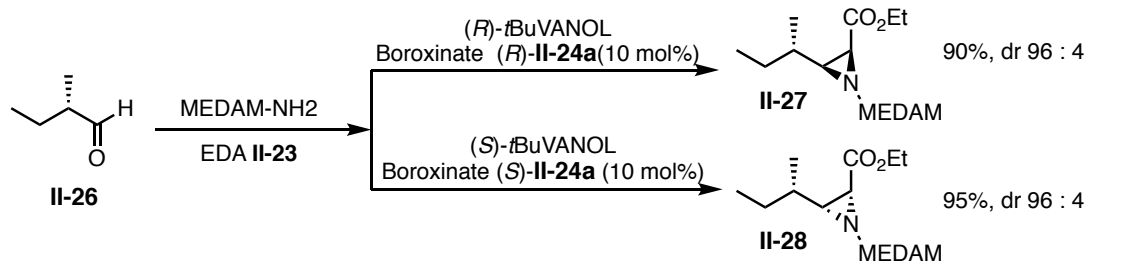
Vaulted 2,2′-binaphthol (VANOL) and vaulted 3,3′-biphenanthrol (VAPOL) were introduced[49] in asymmetric catalysis by the Wulff group in 1993. They have been successfully applied to a wide range of asymmetric reactions[50] over the last two decades. Comparing with BINOL, VANOL and VAPOL provide a deeper chiral pocket around the metal center, thus usually give distinct results in the same system[49, 51-57].

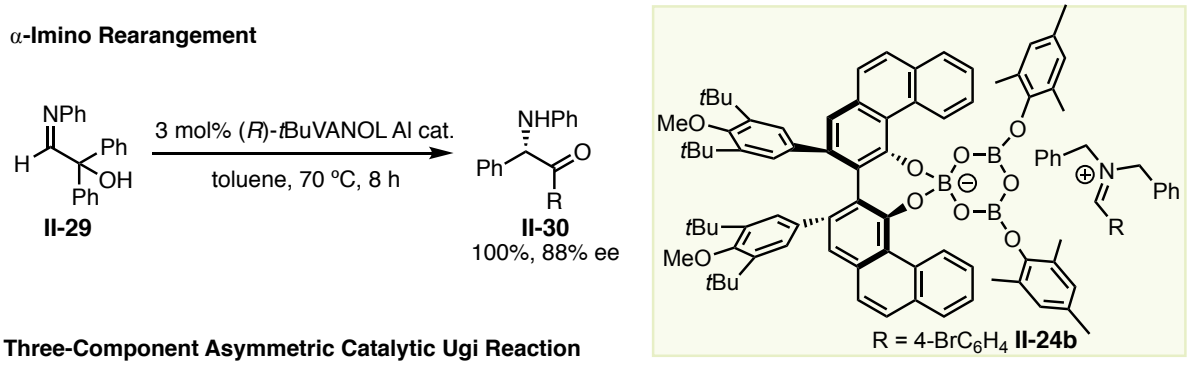
Modifying BINOL by introduction of substituents within the framework has proven to be effective to improve their catalytic systems[25, 58]. In most cases, by introducing

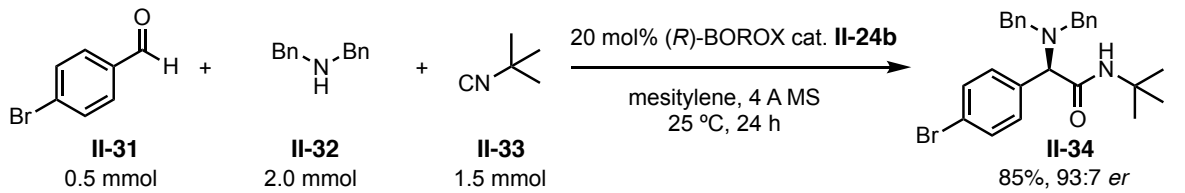
different functional groups into 3,3'- and 6,6'-positons, one can modify the steric and electronic characteristics of BINOL, respectively, thereby changing the yield and enantioselectivity of the reaction. Derivatives of VANOL and VAPOL were synthesized and used in screening for aziridination[59] and Ugi reaction[56] by Wulff and coworkers. The structure-activity relationship study on VANOL-BOROX catalyst in the aziridination[59] of benzhydryl imine and ethyl diazo acetate indicated that substituents in the 7,7' positons lead to improved asymmetric inductions in most cases, while substituents in 4,4'- and 8,8'-positions provide a negative impact. 7,7'-tBu_2VANOL (*t*BuVANOL) was identified as the optimal ligand, giving higher yield and ee than VANOL for 10 different imine substrates. In the report of the first catalytic asymmetric three-component Ugi reaction, 13 biaryl ligands including two VANOL derivatives and five VAPOL derivatives were screened. The best result was obtained with a boroxinate catalyst **II-24b** prepared from a VAPOL derivative (*Scheme 2.7*). *t*BuVANOL was also found to be effective in aluminate-catalyzed α-iminol rearrangement[60], catalyst-controlled multicomponent aziridination with chiral aldehydes[61], and very recently, zirconium-catalyzed Kabachnik-Fields reaction[62] (*Scheme 2.7*).

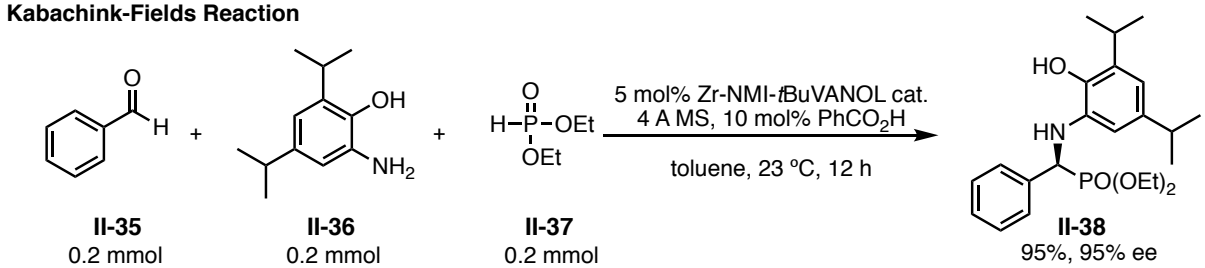
Scheme 2.7 Application of *t*BuVANOL and VAPOL derivatives



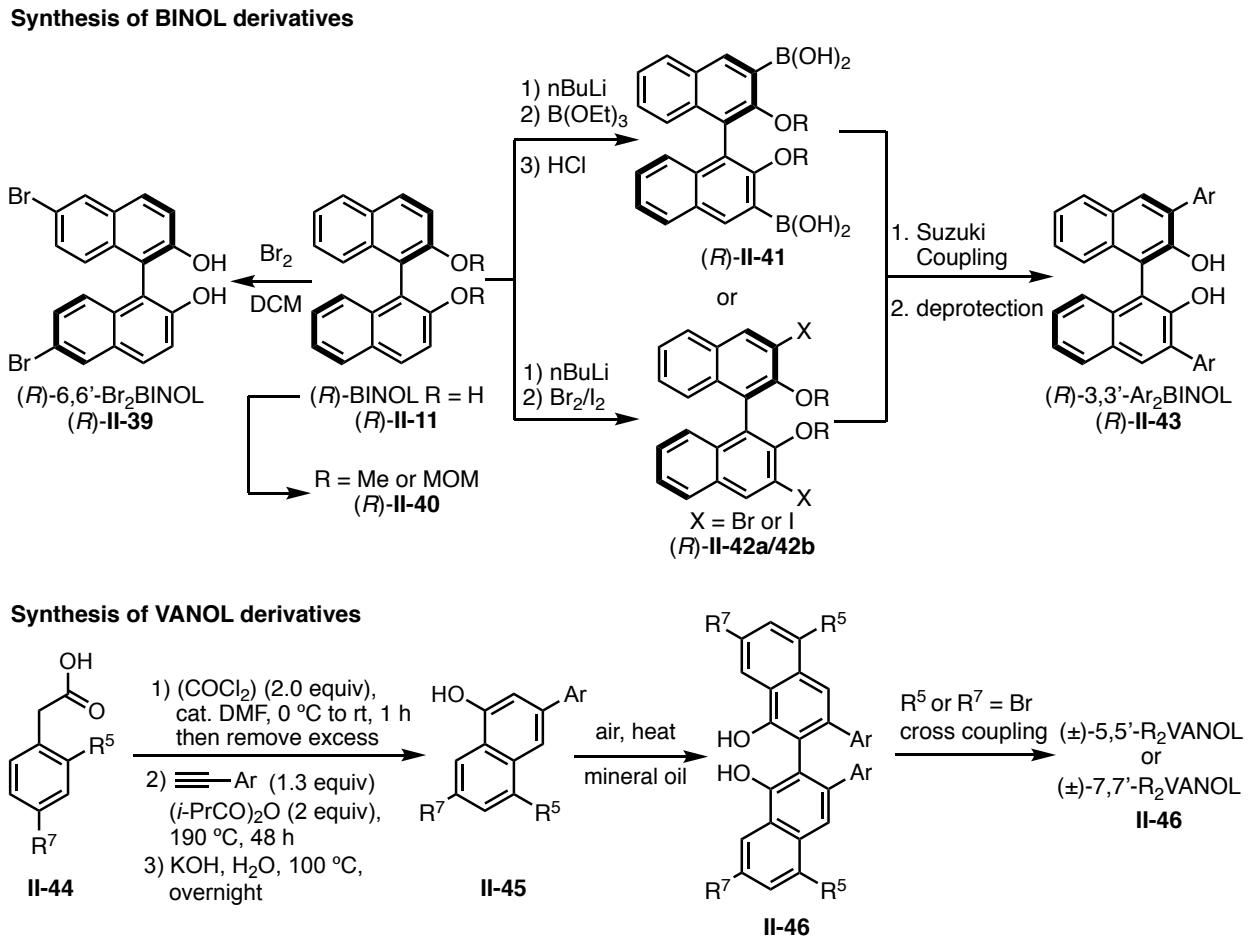




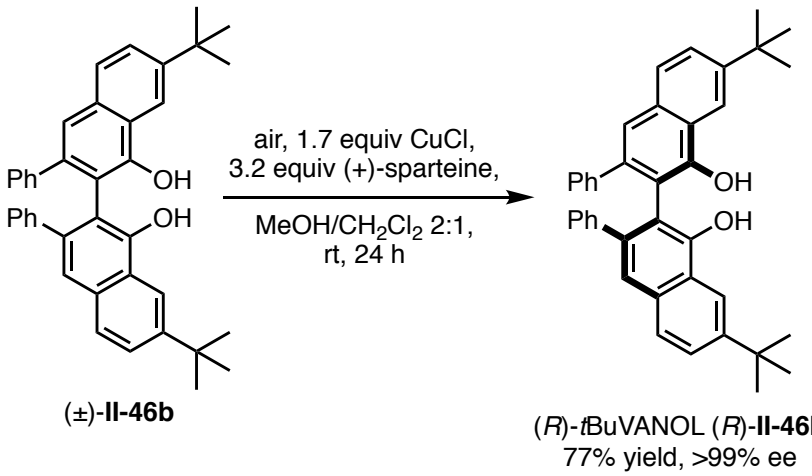




Scheme 2.8 Most commonly used route to BINOL and VANOL derivatives



Scheme 2.9 Deracemization of *t*BuVANOL **II-46b**

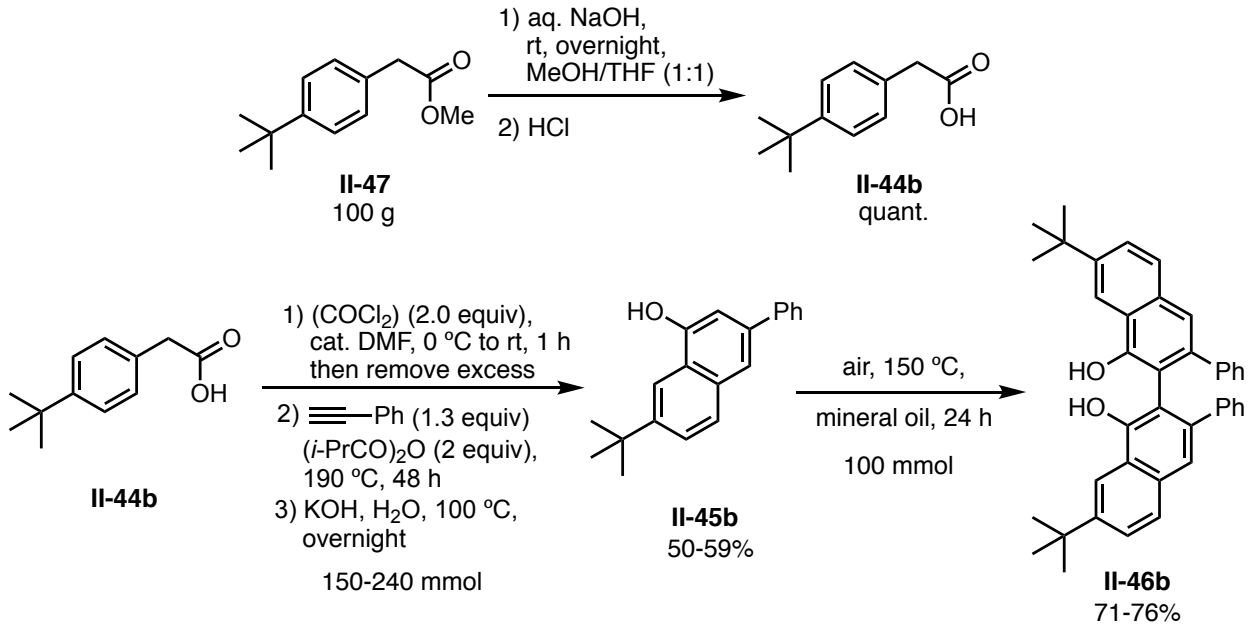


Unlike BINOL derivatives mostly being synthesized by modification of optically pure binaphthol scaffold, VANOL and VAPOL derivatives are usually obtained[56, 59] from a cycloadditon/electrocyclization cascade (CAEC) process[63] followed by oxidative coupling (and then cross-coupling) (*Scheme 2.8*). To get access to the enantiopure ligands, Wulff and coworkers developed[64-65] a deracemization procedure involving a copper complex of (–)- or (+)-sparteine (*Scheme 2.9*). This procedure has been proved to be general and reliable on the laboratory scale, successfully being applied to >20 different ligands[56, 59]. One notable drawback in this deracemization process is that, it usually requires >2.8 equivalent of sparteine which is expensive and not always available[66]. Very recently, a gram-scale synthesis of (–)-sparteine was reported[67] by O'Brien and coworkers. This 10-step synthesis, including an enzymatic resolution to introduce stereochemistry, afforded (–)-sparteine in 31% yield but is nevertheless lengthy and not practical for large scale process. In addition, a large amount of solvent (135 mL for 1 mmol) was used in the process, making it less practical for a large-scale process.

2.4 Discovery of resolution system for *t*BuVANOL by trial and error

To make both enantiomers of VANOL and VAPOL derivatives easily accessible to the Wulff group and the scientific community, it was desired to develop a simple, practical resolution process using inexpensive resolving agent. Racemic *t*BuVANOL was chosen as our target substrate since it gave better performance in a variety of asymmetric reactions (*Scheme 2.7*). The synthesis of (±)-*t*BuVANOL **II-46b** was carried out by modification of the reported procedure[59] (*Scheme 2.10*).

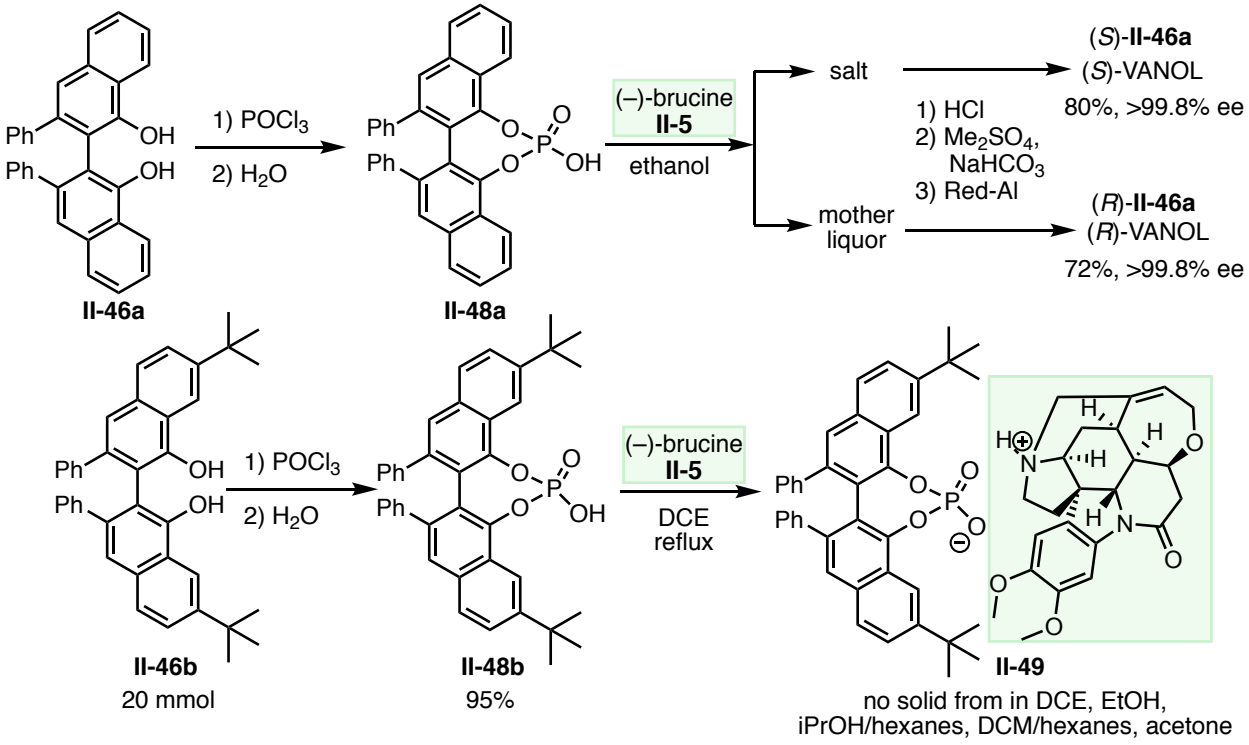
Scheme 2.10 Synthesis of (±)-*t*BuVANOL **II-46b**



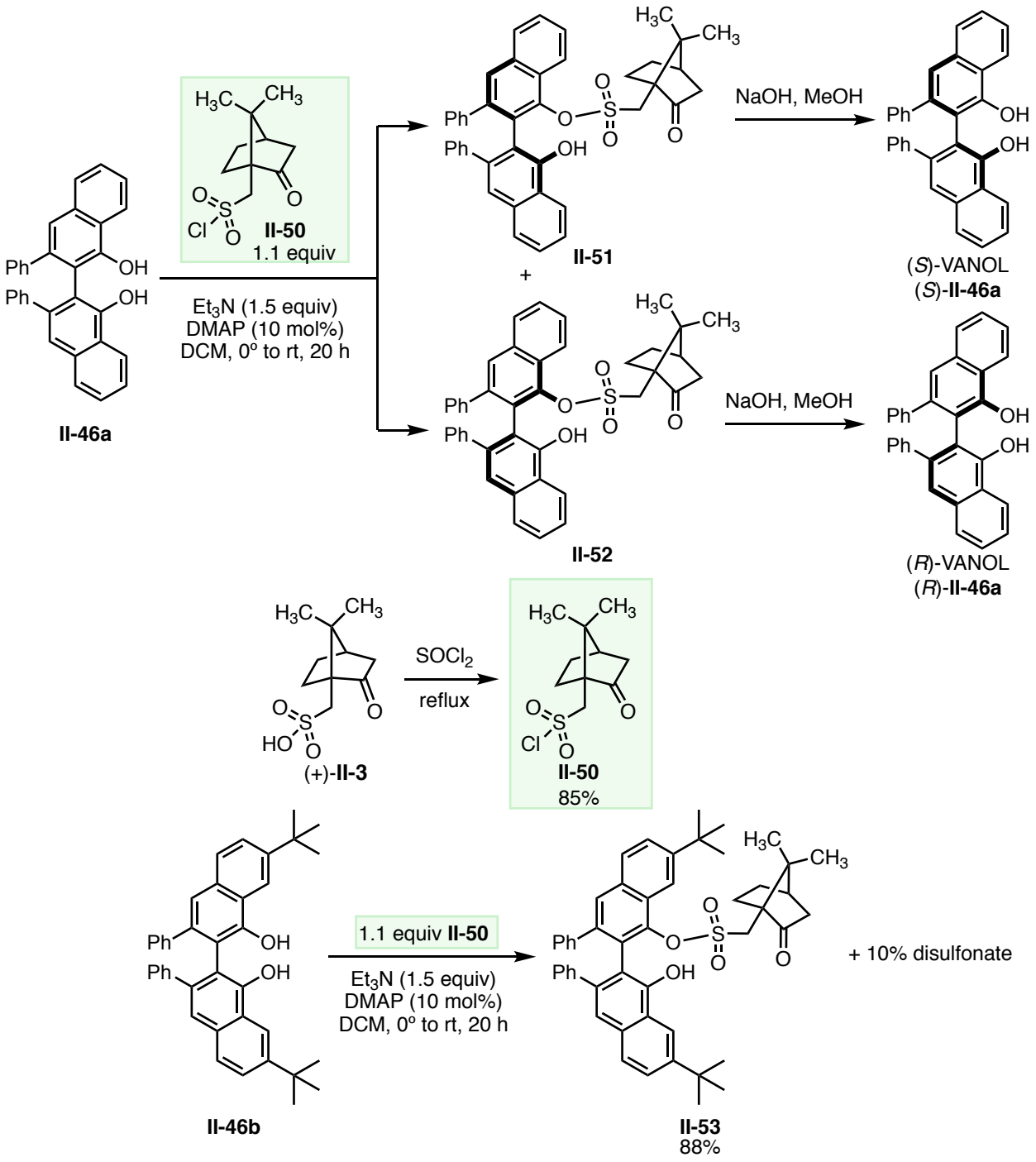
We were determined to find a suitable resolution method for *t*BuVANOL by trial and error. It was obvious that the resolution process of its congener, VANOL should be first attempted (*Scheme 2.11*). VANOL **II-46a** was first resolved[68] via its cyclic diester with phosphoric acid by salt formation with (–)-brucine **II-5**. The cyclic phosphoric acid of *t*BuVANOL **II-48b** was prepared in the same manner with excellent yield and its (–)-brucine salt **II-49** formation was carried out in DCE. After removing the solvent, recrystallization condition was screened on a 2 mmol scale. No solid was observed in 5 mL of DCE, EtOH, 2:1 *i*PrOH/hexanes, 2:1 DCM/hexanes, and acetone at room temperature. Only a trace amount of solid was observed from 2:1 *i*PrOH/hexanes and acetone after cooling at –20 ºC for 12 h. However, no solid was obtained after filtration was performed at rt. One patent[69] on the chiral resolution of VANOL drew our attention. They separated the diastereomers of VANOL camphor sulfonate by column chromatography and then hydrolyzed to obtain pure (*R*)- and (*S*)-VANOL. (+)-

Camphosulfonyl chloride **II-50** was prepared and used in the synthesis of *t*BuVANOL camphorsulfonate **II-53** (*Scheme 2.12*). The reaction gave an 88% yield of the monosulfonate **II-53** along with a 10% yield of the disulfonate. Unfortunately, the diastereomers of the mono-camphorsulfonate did not show any separation on TLC using the reported 1:10 EtOAc/hexanes as eluent and other combinations of Et_2O, DCM, toluene and benzene. The recrystallization was also performed in DCM, EtOH, iPrOH, Acetone, EtOAc, hexanes and Et_2O. Solid was observed in iPrOH, EtOAc and hexanes. However, the diastereomeric ratio of the solid were always 1:1 based on the ^{1}H NMR spectra.

Scheme 2.11 Resolution of VANOL with (–)-brucine and 1st attempt with *t*BuVANOL



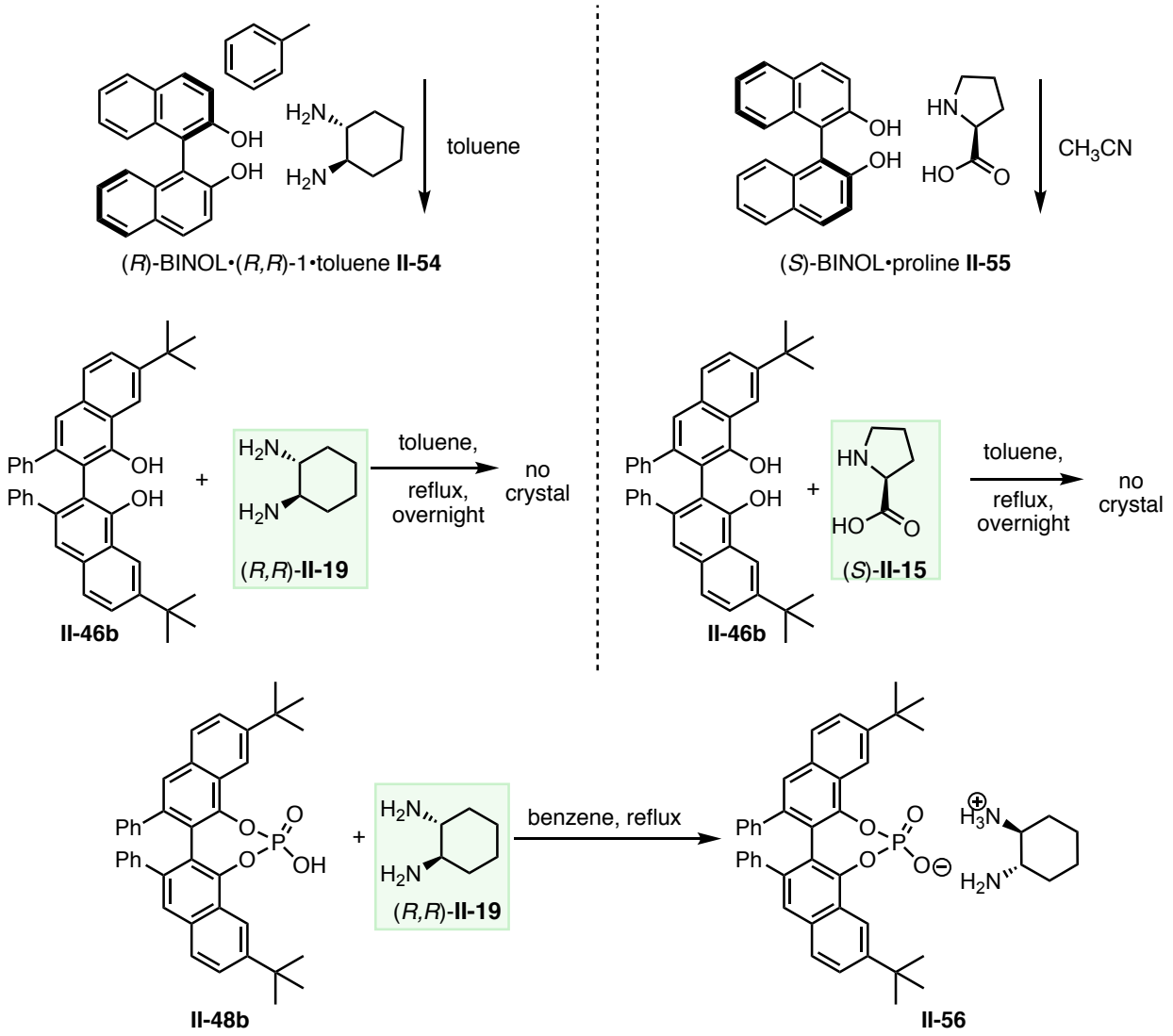
Scheme 2.12 Resolution of VANOL via Camphorsulfonate and 2nd attempt with *t*BuVANOL



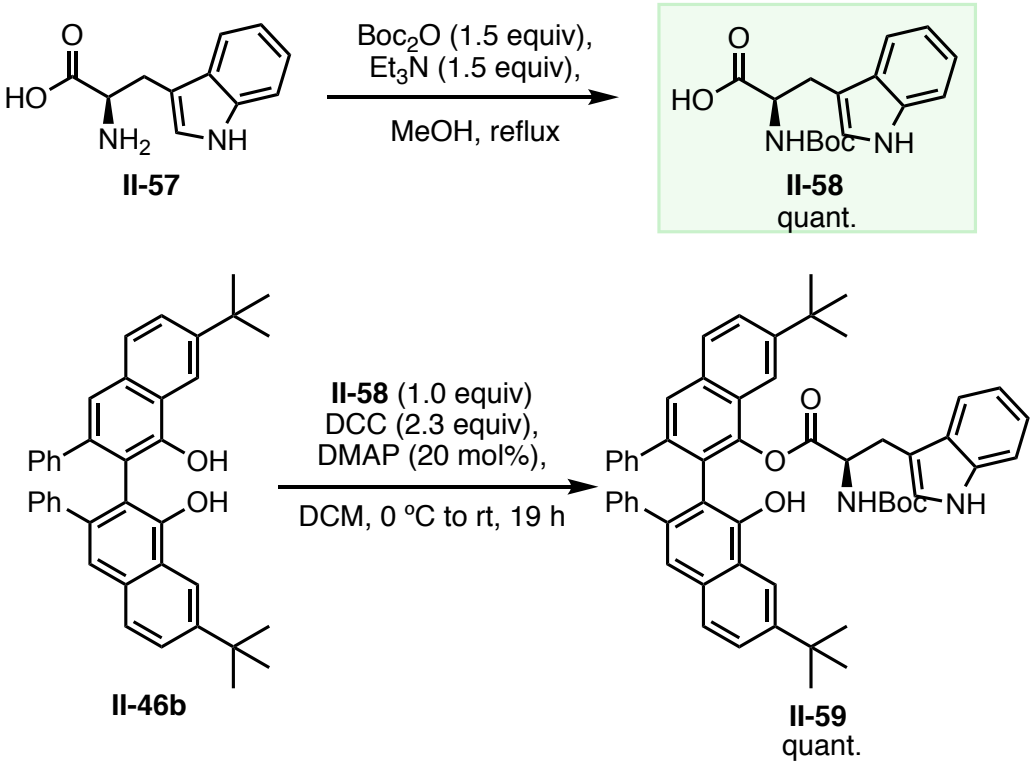
To continue to pursue the resolution of *t*BuVANOL, attention was then turned to the reported methods for the resolution of its biaryl analogue BINOL **II-11** (*Scheme 2.13*).

The literature was surveyed and attempted resolution of *t*BuVANOL using the same procedure reported for BINOL if 1) the resolving agent is an inexpensive, commercially available compound or easily accessible from such a compound; 2) the synthesis and separation are efficient and convenient. It was reported that BINOL could form diastereomeric inclusion complexes **II-54** and **II-55** with (*S*)-proline[45] and (1*R*,2*R*)-diaminocyclohexane[48]. Such complexes were readily separated and crystallized to obtain both enantiomers of BINOL in high ee. When *t*BuVANOL was employed under the same conditions with (*S*)-proline **II-15** and (1*R*,2*R*)-diaminocyclohexane **II-19**, no crystallization occurred after cooling to –20 ºC for an extended period of time. Salt formation with (*R*,*R*)-**II-19** and *t*BuVANOL phosphoric acid **II-48b** was also attempted. Although salt **II-56** formed, enantioenrichment by crystallization failed from benzene and EtOH, as judged by the ^{31}P NMR. In one report by Einhorn and coworkers, BINOL was efficiently resolved by chromatography via *N*-Boc tryptophan esters[70]. We carried out the synthesis of *N*-Boc tryptophan esters of *t*BuVANOL by Boc protection of tryptophan **II-57** and then DCC coupling (*Scheme 2.14*). The mono ester **II-59** was obtained in excellent yield, however the diastereomeric esters did not separate by TLC upon eluting with 95:5 DCM/ether which is the reported condition for BINOL. Other combinations of common eluting solvent, such as Et_2O, DCM, toluene and benzene, were also attempted. In contrast to a 0.2 R_f difference between the BINOL diastereomeric esters, only negligible separation was observed with the *t*BuVANOL analogues.

Scheme 2.13 Resolution of BINOL via inclusion complex formation and 3rd and 4th attempt with *t*BuVANOL

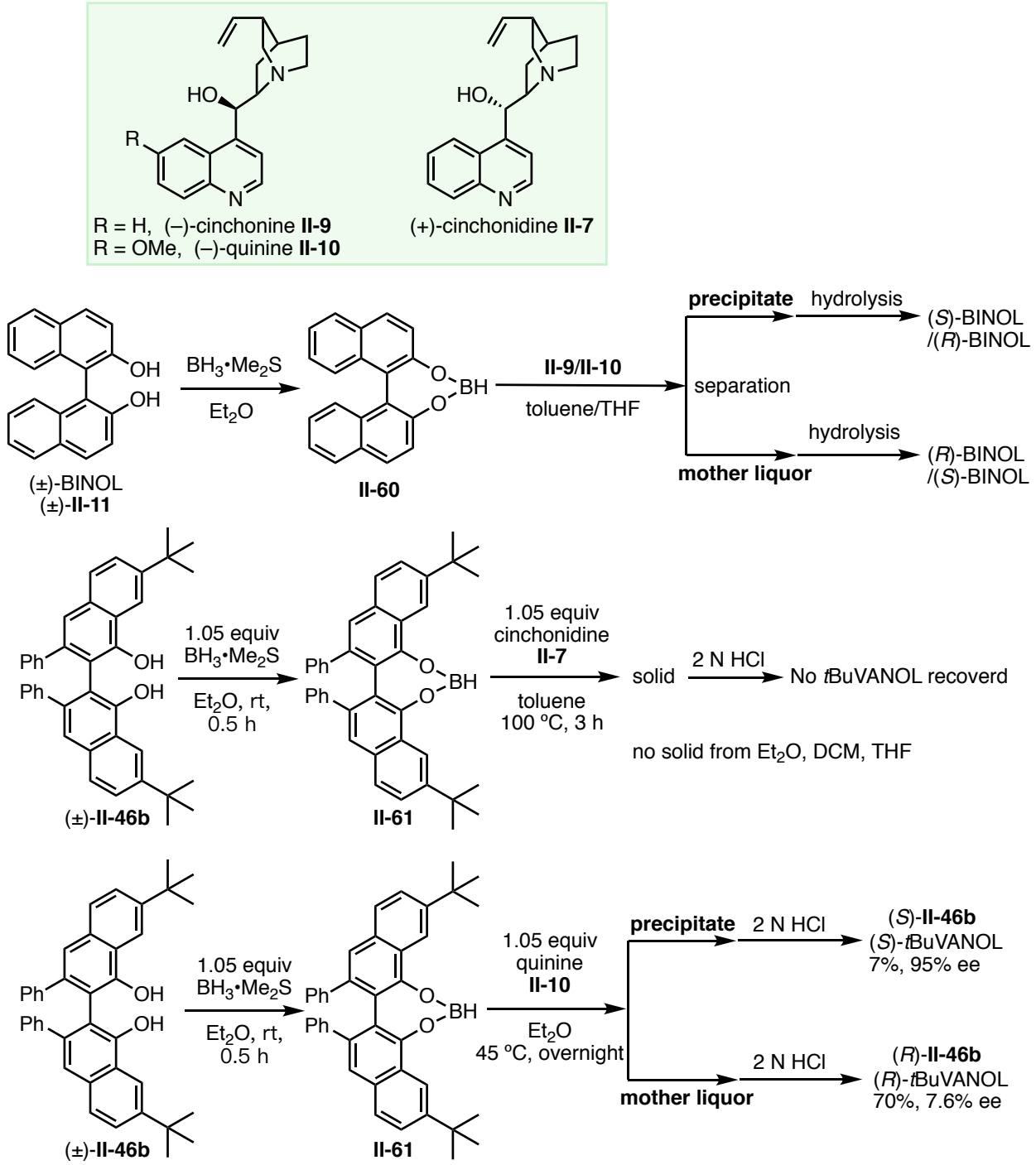


Scheme 2.14 5th resolution attempt via Boc-tryptophan ester



Focus was quickly moved on to a protocol reported[32] and improved[33] by Shan and coworkers. They resolved racemic BINOL via a cyclic borate ester formed from the reaction of BINOL and borane with cinchona alkaloids (*Scheme 2.15*). One diastereomer was found to be soluble under their conditions while the other precipitates. After filtration and simple hydrolysis, optically pure BINOL could be obtained in high yield and with excellent ee. It was found that the (*S*)-BINOL quinine borate precipitates from THF in 42% yield and with excellent ee, whereas the (*R*)-BINOL cinchonine borate precipitates from toluene to obtain optically pure (*R*)-BINOL in 35% yield after hydrolysis. Resolution of *t*BuVANOL was attempted using their most recent procedure[33] with cinchonidine **II-7**. *t*BuVANOL and 1.05 equivalent of borane dimethyl sulfide complex were stirred in Et_2O at rt for 0.5 h. The formation of cyclic borane **II-61** was complete when the gas revolution ceased. The solvent can be switched after removing Et_2O using a rotavapor. Cinchonidine

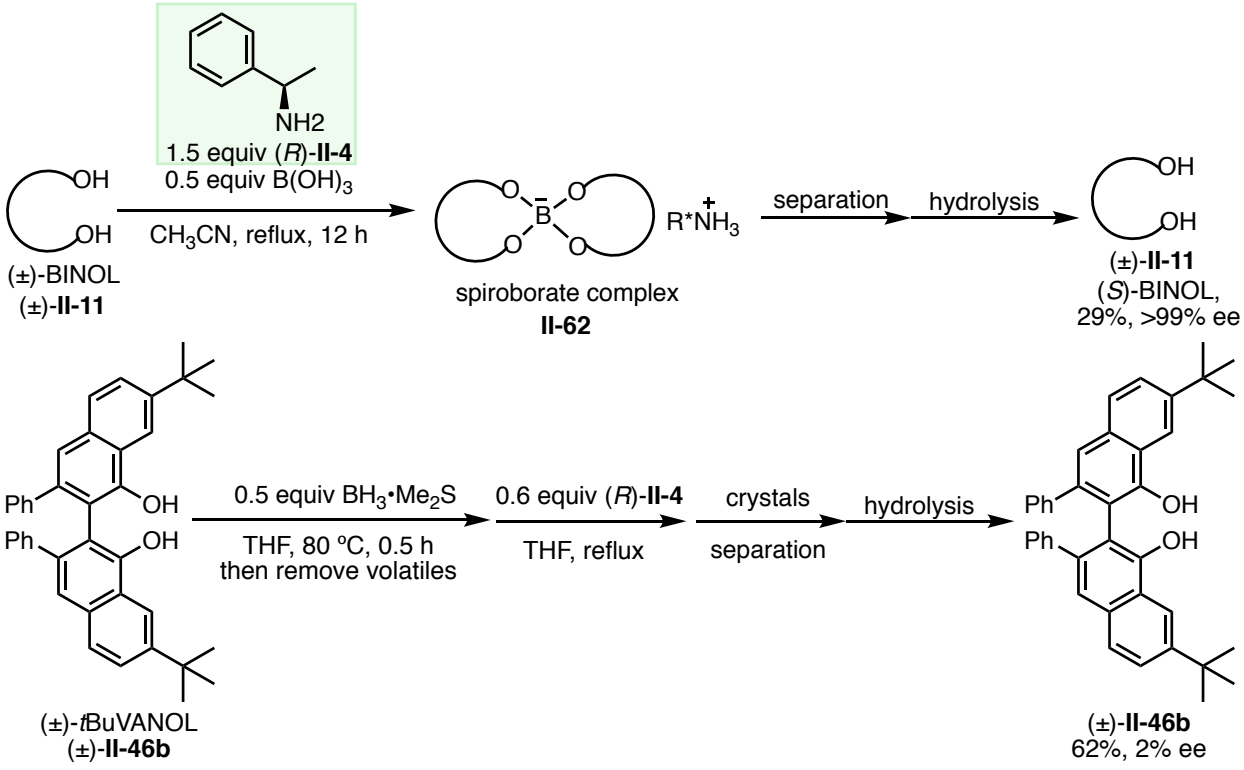
Scheme 2.15 Resolution of BINOL via cyclic borate ester with quinine and 7th attempt with *t*BuVANOL



II-7 was then added and the mixture was heated to reflux for 3-12 h. Solid was obtained from toluene but not from DCM, Et_2O or THF. However, no *t*BuVANOL was isolated after

hydrolysis, which suggested that the solid might be cinchonidine borate. We went back to their original procedure[32] using quinine **II-10**. After the cyclic borate was formed, 1.05 equivalent of quinine was added and the mixture was refluxed. A precipitate was observed after 30 min. After 12 h, solid was filtered and hydrolyzed in 2 N HCl solution for 30 min. It was delightful to find out that (*S*)-*t*BuVANOL was obtained with 95% ee from the precipitate, leaving 70% of *t*BuVANOL in the mother liquor with an excess of the *R*-enantiomer. Another related BINOL resolution[36] via *spiro*borate formation with chiral ammonium as gegen cation was also attempted (*Scheme 2.16*). Unfortunately, the solid precipitating from THF was *meso-spiro*borate rather than chiral *spiro*borate.

Scheme 2.16 Resolution of BINOL via *spiro*borate ester with quinine and 8th attempt with *t*BuVANOL

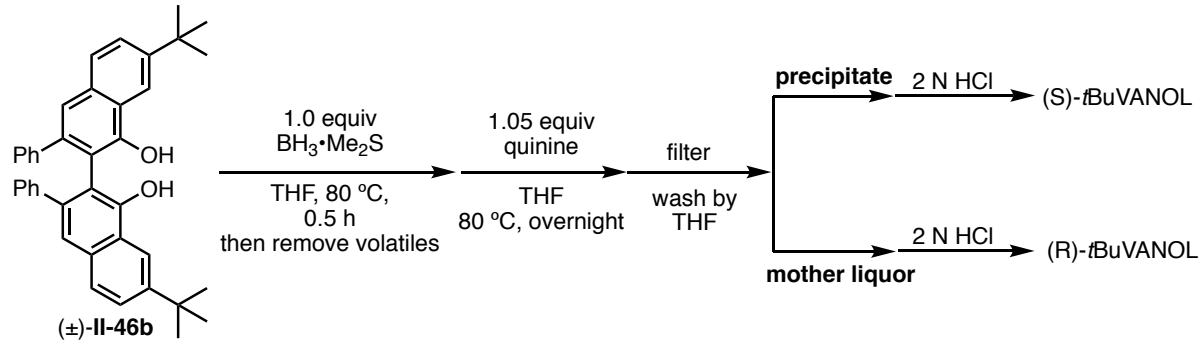


In summary, we successfully identified one resolution process that gave enatioenrichment for *t*BuVANOL after a number of failed trials. We decided to further

optimize this protocol using quinine due to the readily availability of quinine and convenience of the reaction procedure.

2.5 Condition optimization and scale up

Table 2.1 Optimization of the Resolution of *t*BuVANOL



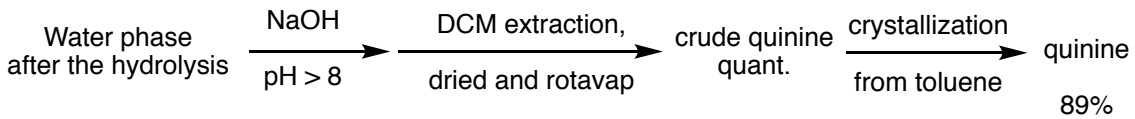
entry	scale (mmol)	THF (mL/mmol)	THF wash (mL/mmol)	%yield of (*S*)-*t*BuVANOL	%ee of (*S*)-*t*BuVANOL	%yield of (*R*)-*t*BuVANOL	%ee of (*R*)-*t*BuVANOL
1	2.0	7.5	5.0	28	>99	58	54
2	4.0	5.0	2.5	40	95	45	72
3	4.0	3.75	2.5	44	85	45	92
4[a]	4.0	5.0	4.0	19	>99	85	18
5[a]	4.0	2.5	2.5	28	98	64	41
6	16.0	4.0	4.0	36[b]	>99[b]	48[b]	86[b]
7[c]	16.0	4.0	4.0	30	>99	ND	ND

[a]0.525 equiv quinine was used. [b]Average of 5 runs. [c]Recovered quinine was used. ND = not determined.

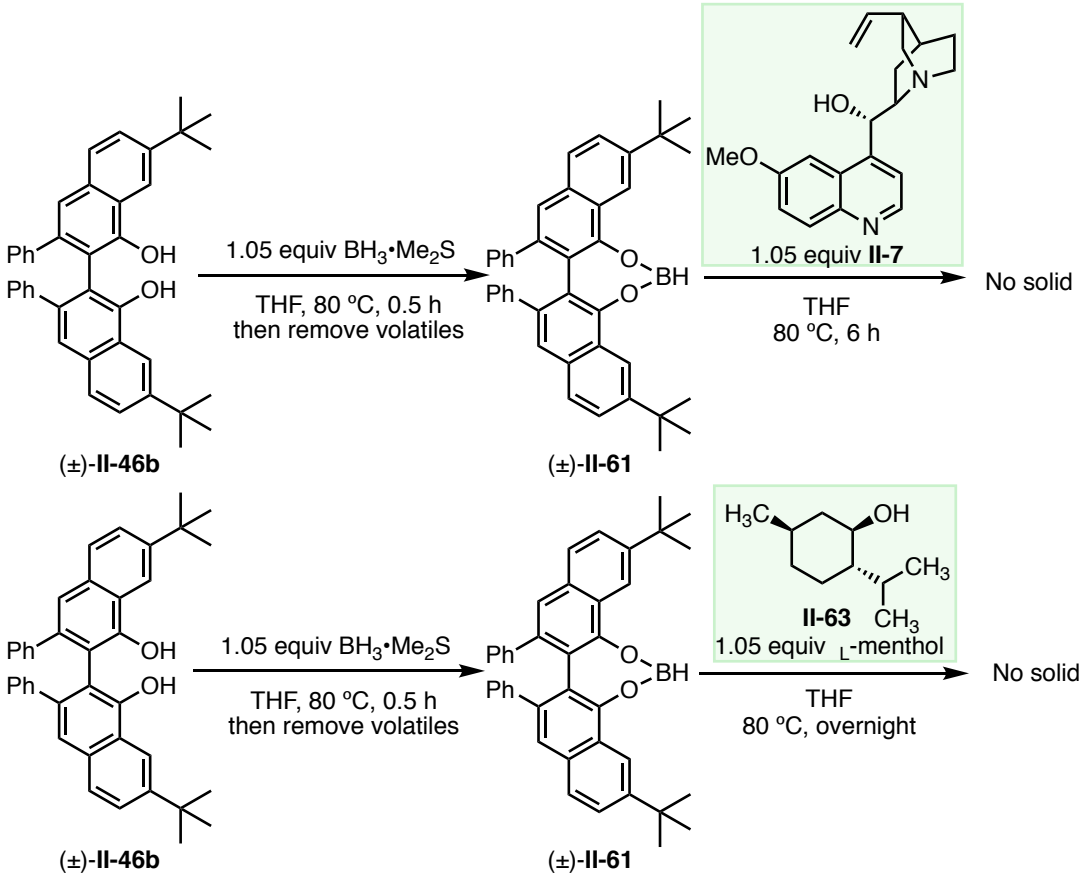
It was found that the resolution was more efficient using THF rather than Et_2O as solvent (entry 1, *Table 2.1* vs *Scheme 2.15*) which was the solvent used in reported resolution for BINOL[32]. The precipitate crashed out after 10 minutes of reflux subsequent to the addition of quinine. By decreasing the volume of THF used in the formation of the quinine borate complex, the yield of (*S*)-*t*BuVANOL increase at the sacrifice of ee (entry 1, 2 and 3, *Table 2.1*). The optimal volume was expected to be between 5.0 and 3.75 mL/mmol. The volume of THF used in the wash of the filter cake was found to affect the result as well. Unsurprisingly, the more THF used in the wash, higher ee and lower yield

was observed for (*S*)-*t*BuVANOL. We determined that the optimal volume for the wash is between 2.5 and 5.0 ml/mol. We also briefly tested resolution of *t*BuVANOL with a half-equivalent of resolving agent. This strategy was applied in many processes[71] since its first report in 1899[72]. Although less efficient, the process proved to be effective using less THF solvent (entry 4 and 5, *Table 2.1*). After weighing the pros and cons, we chose to develop the more reliable procedure with 1.05 equivalent of quinine which is a reasonably inexpensive natural product. In addition, the quinine used in the resolution could be easily recycled (*Scheme 2.17*). The aqueous layer containing quinine after hydrolysis and extraction was neutralized by addition of NaOH at 0 ºC until the pH > 8.0. The cloudy solution was extract with DCM and dried. The crude quinine can be further purified by crystallization from toluene (89% recovery). The conditions (indicated in entry 6, *Table 2.1*) with 1.05 equivalent of quinine at reflux in 4.0 mL/mmol THF and using 4.0 mL/mmol THF for the wash was chosen for the multigram-scale (8.812 g) trial (entry 6, *Table 2.1*). The procedure is robust and effective. Optically pure (*S*)-*t*BuVANOL could be prepared with an average 36% yield in 5 separated runs (32-41%). And the remaining (*R*)-*t*BuVANOL is recovered in an average of 48% yield (46-51%) and 82% ee (67-89% ee). The recovered crystallized quinine was employed a second time in the resolution under the same conditions (entry 7, *Table 2.1*), and proceed well with a slightly diminished yield.

Scheme 2.17 Recovery of quinine



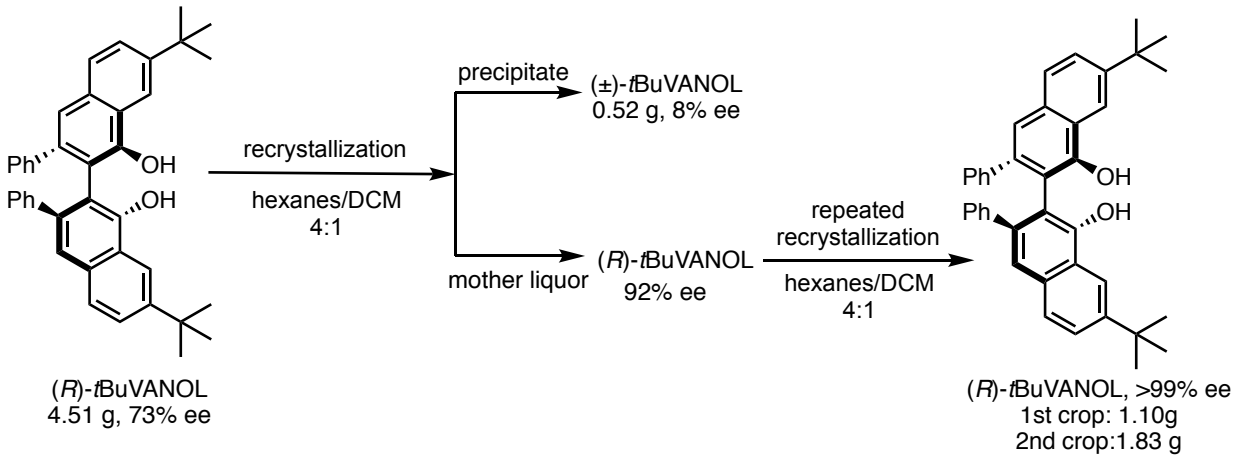
Scheme 2.18 Attempted resolution to get access to (*R*)-*t*BuVANOL



Access to enantiopure (*R*)-*t*BuVANOL via resolutions using cyclic borates was also examined with other resolving agents (*Scheme 2.18*). The pseudo enantiomer quinidine **II-7** was first tested. In contrast to the *t*BuVANOL quinine borate, the quinidine derived borate did not yield any precipitate after reflux in THF. Another inexpensive natural chiral alcohol (–)-menthol **II-63** was also applied to the same process. No solid was formed either. Other than repeated resolution using another resolving agent, enantioenrichment of (*R*)-*t*BuVANOL can be achieved simply by recrystallization. It is well known that crystallizations of scalemic VANOL and its derivatives produce solid of racemates rather than conglomerates. By performing crystallization, the racemic VANOL will crystallize first, leaving the mother liquor with higher enantiomeric purity. To improve the purity of

(*R*)-*t*BuVANOL with 73% ee, crystallization was performed (*Scheme 2.19*) from 4:1 hexanes/DCM. It was not surprising that a racemic powdery solid was formed first. The ee of the mother liquor was boosted to 92%. Repeated crystallization under the same conditions, however led to solids with two distinct crystal forms. Aside from the powdery racemate sitting in the bottom of the flask, a unique crystalline solid grew from the saturated solution. As a tribute to Pasteur, the crystals were manually separated from the powdery solid and then wash by the filtrate (*Figure 2.1*). The ee of the crystal was determined to be >99%. To develop a reliable and convenient procedure, we adopted an existing "wash in DCM" method for enantioenrichment of VANOL. Instead of using DCM, we found that the enantiopure *t*BuVANOL is very soluble in hexanes while the racemic is not. Therefore, after we mixed and stirred *t*BuVANOL with high ee in hexanes for one hour, the racemic *t*BuVANOL would crashed out. After filtration, ee of the *t*BuVANOL in the mother liquor was enhanced to >99%. The racemic precipitate can be recovered (*Scheme 2.20*). This enantioenrichment procedure was practical and simple, providing reproducible results from 5 separate runs.

Scheme 2.19 Enantiomeric excess enhancement by recrystallization



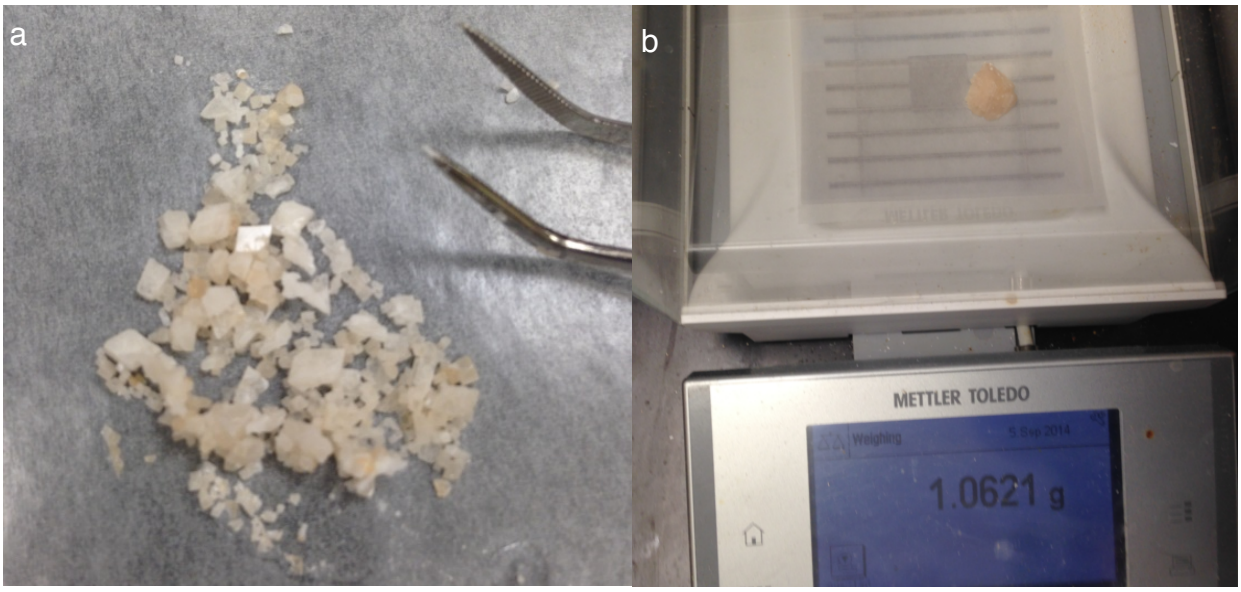
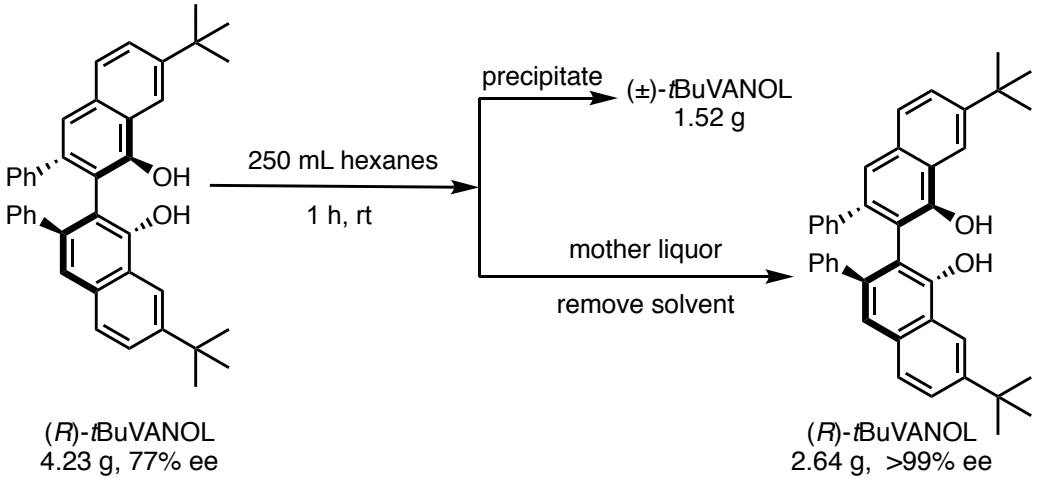


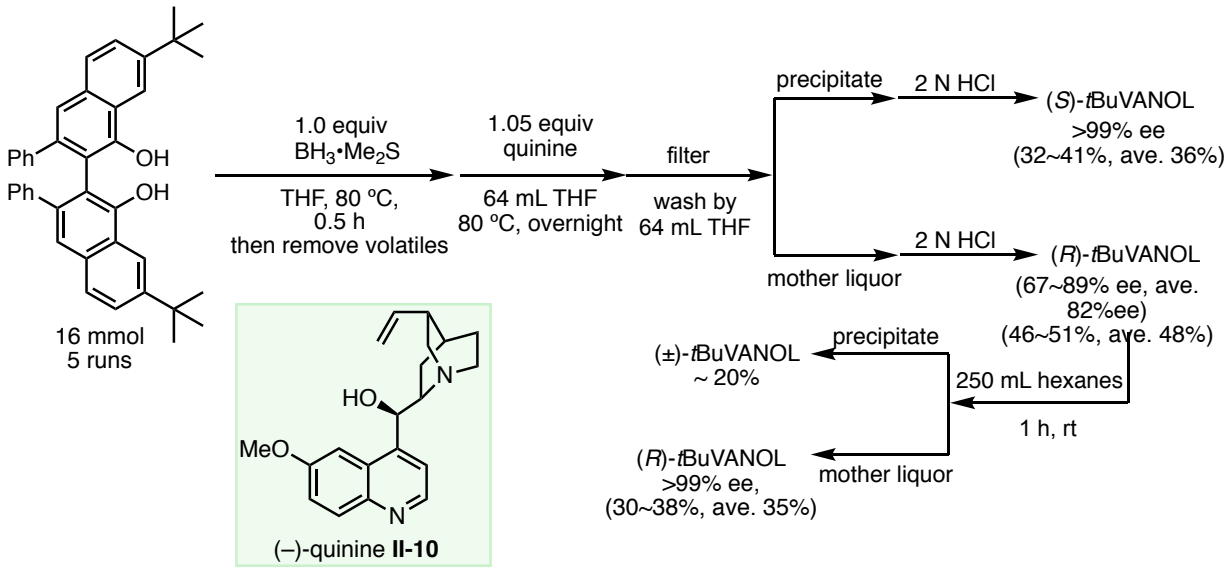
Figure 2.1 a) Sorting (*R*)-*t*BuVANOL crystals by tweezers; b) One (*R*)-*t*BuVANOL crystal

Scheme 2.20 Enantiomeric excess enhancement by hexanes wash



Finally, the overall procedure for the optimal resolution for *t*BuVANOL is shown in *Scheme 2.21*. It is worth noting that, the resolution procedure is convenient and time-efficient. One cycle of the resolution of *t*BuVANOL only takes less than 24 hours to access both (*S*)- and (*R*)-*t*BuVANOL as pure enantiomers in good yield (30-38% for each; maximum is 50%). Moreover, most of the quinine (89%) and about 20% of racemic *t*BuVANOL could be recovered by simple manipulations.

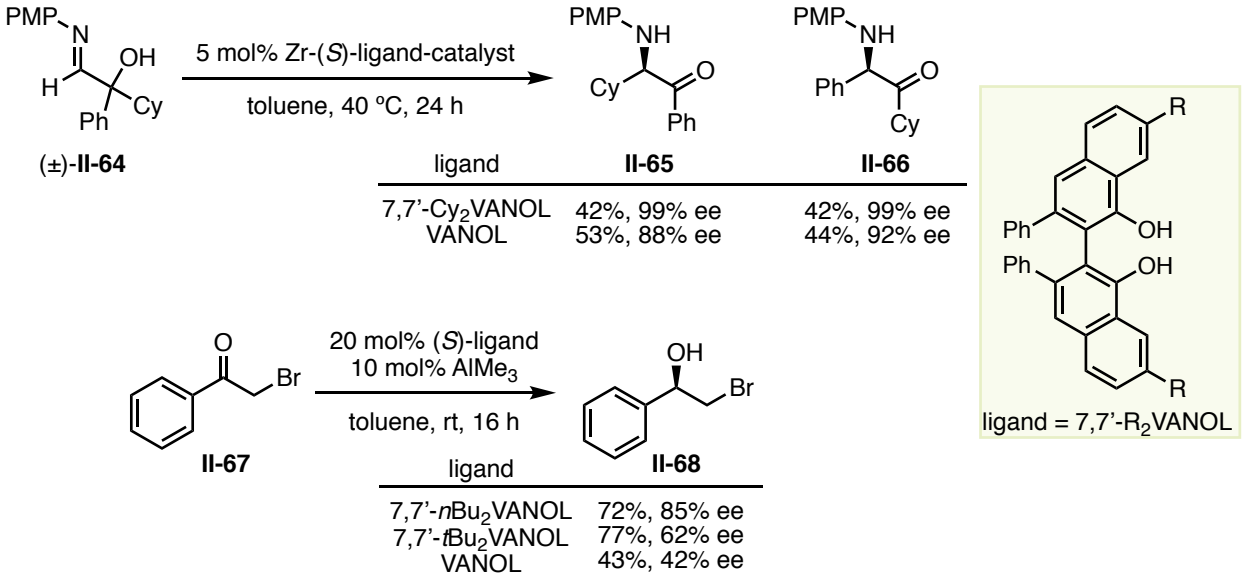
Scheme 2.21 Resolution of *t*BuVANOL



2.6 Synthesis and resolution of VANOL derivatives

One of the objectives of this project is to develop a general resolution that can be applied to a broad scope of VANOL derivatives. By introducing different substituent in the chiral ligand, we can modify the electronic and steric effect of the catalyst to accommodate the substrate. On most occasions, the optimal catalyst for various reactions (or even for different substrates in the same reaction) are different. For example, the 7,7'-Cy_2VANOL proved to be superior in the parallel kinetic resolution of racemic α-iminol[73]. In the case of MPV reduction of α-bromoacetophenone, VANOL with a longer linear alkyl chain at the 7,7'-positions gave the best results[74] (*Scheme 2.22*). A library of optically pure VANOL derivatives would be useful in developing new methodology and elucidating reaction mechanisms.

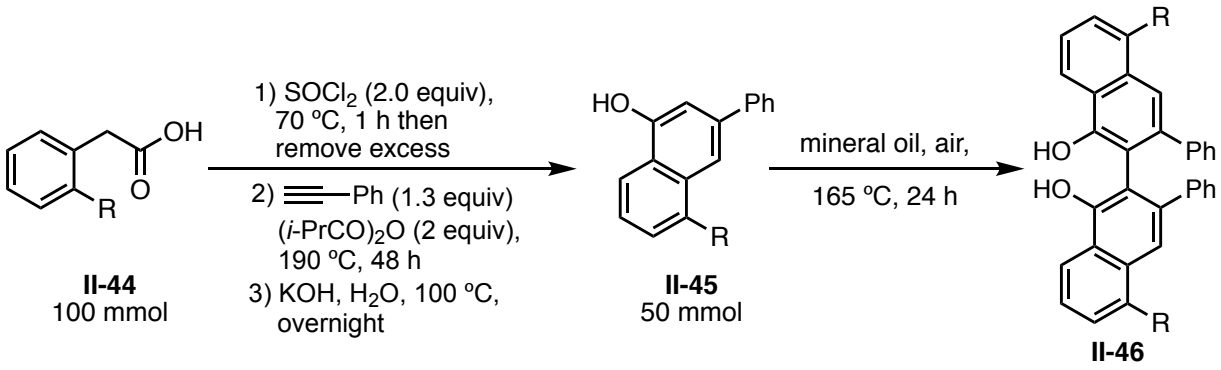
Scheme 2.22 Application of selected 7,7'-disubstituted VANOL derivatives



2.6.1 Synthesis of 5,5'-disubstituted VANOL derivatives

A series of 5,5'-disubstituted VANOL derivatives were synthesized by reported method[59, 63] as shown in *Table 2.2*. Commercially available ortho-substituted phenyl acetic acids **II-44c**–**h** were subjected to the general CAEC conditions. The corresponding 5-substituted VANOL monomers 3-phenylnaphthol **II-45c**–**g**, were obtained in good yield (52-67%) after recrystallization. For the o-nitrophenyl acetic acid **II-44h**, the reaction yielded an uncharacterizable black tar. The acid chloride (not shown) could be generated under a milder condition using oxalyl chloride $(COCl)_2$ with catalytic amount of DMF at rt. The yield of the followed CAEC reaction on **II-44c** is similar with $(COCl)_2$ as it is with $SOCl_2$ (60% vs 67%). The monomers were oxidatively dimerized under air with good yields, some of which could be further improved by increasing reaction time (96% after 36 h for **II-46c**).

Table 2.2 Synthesis of 5,5'-R_2VANOL



II-44
100 mmol

II-45
50 mmol

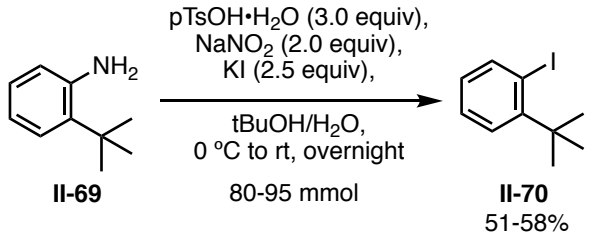
II-46

series	R	%yield of monomer **II-45**[a]	%yield of VANOL **II-46**
c	Br	67	96[b]
d	Cl	71	75
e	Me	52	72
f	OMe	52	72
g	CF_3	66	65
h	NO_2	< 5	–

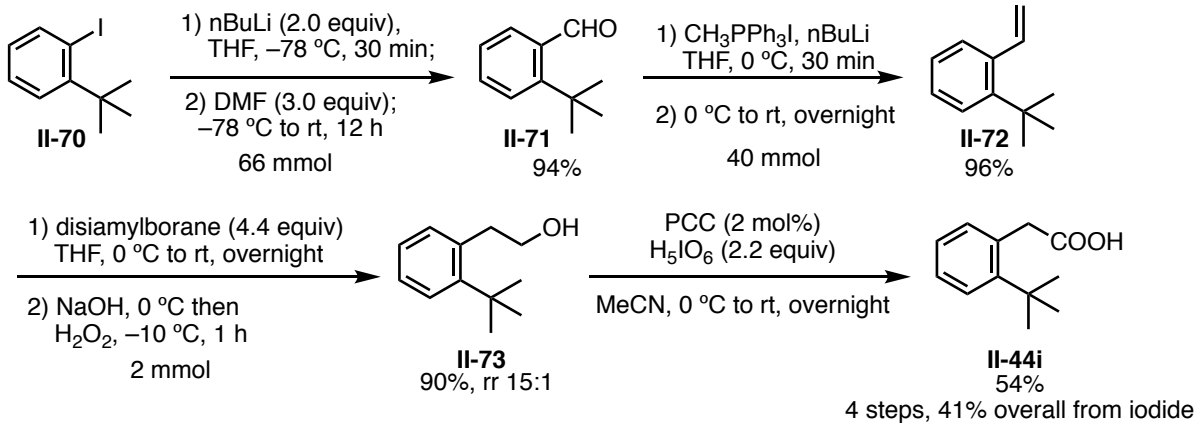
[a]combined yield from 2 crops after crystallization. [b]36 h

5,5'-*t*Bu_2VANOL **II-46i** was also successfully synthesized (**a** and **b**, *Scheme 2.21*). Rather than trying to develop an anticipated challenging synthesis from its 5,5'-dibromo analog, it was decided to prepare the ligand in a direct method that was used for related analogs (*Table 2.2*). To access its precursor *ortho*-t-butyl phenyl acetic acid **II-44i**, two routes were designed and carried out. Both routes start with the preparation of 2-tert-butyliodobenzene **II-70** via the Sandmeyer reaction of inexpensive 2-tert-butylaniline **II-69**. This reaction could be performed on 95 mmol scale in 51-58% yield. This is not as good of yield as observed on a 20 mmol scale (81%), which may be related to the cooling capacity. In the first synthesis, the iodobenzene was first converted to benzaldehyde **II-71** using an established

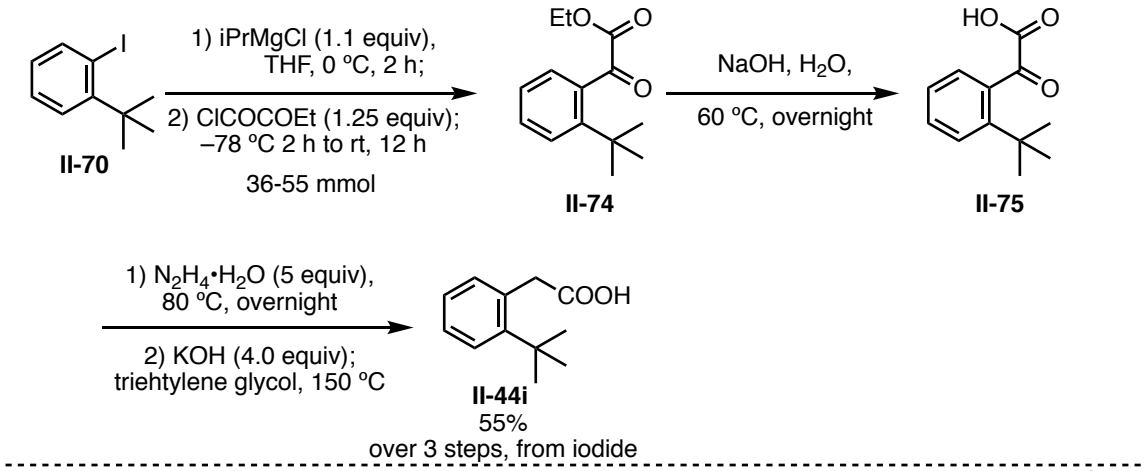
Scheme 2.23 Synthesis of 5,5'-*t*Bu_2VANOL

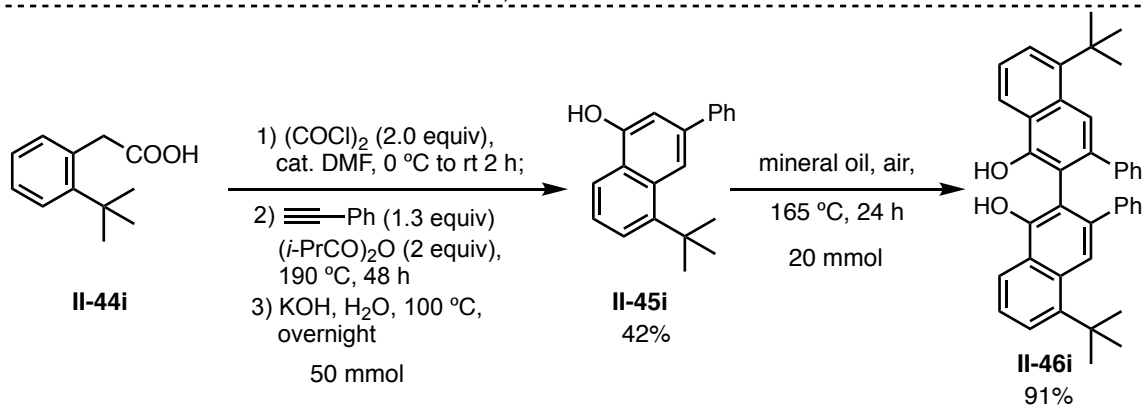


a



b



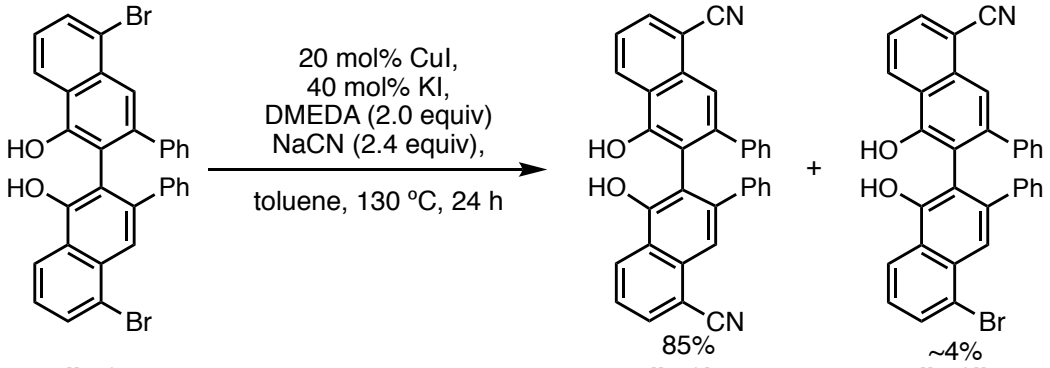


procedure[75], followed by Wittig reaction to yield the styrene **II-72**. These two transformations gave excellent yield on gram-scale. A hydroboration/oxidation sequence was then explored. Employing in-situ generated disiamylborane gave rise to the desired linear alcohol **II-73** in excellent yield and high regioselectivity, compared to 69% yield and 10:1 rr if BH_3•Me_2S was used. The chromium-catalyzed oxidation utilizing periodic acid developed[76] by process chemists at Merck successfully converted the alcohol to the desired acid **II-44i**. The moderate yield of this reaction was due to the loss of product in the work-up stage. This route was abandoned later, leaving the last two steps unoptimized for scale-up, because of its low atom economy.

The second pathway begins with iodine/magnesium exchange followed by coupling with ethyl chlorooxoacetate. After simple work up, the α-ketoester **II-74** is hydrolyzed in aqueous NaOH to give the phenylglyoxylic acid **II-75** in 93% over 2 steps. It was delightful to find that the Wolff-Kishner reduction provided the desired phenyl acetic acid **II-44i** in moderate yield. The isolated byproduct was the unreacted hydrazone intermediate, which could be subjected to another basic cleavage. The second route gives higher yield (55% vs 41%) with fewer steps, and only one column chromatography is needed. Some other coupling reactions that are more straightforward were also explored but failed (not shown). For example, the Grignard reagent generated from iodo/magnesium exchange of iodobenzene **II-70** did not couple with ethyl α-bromo acetate, nor did this coupling occur with $CoCl_2$/TMEDA as catalyst[77]. The Pd-catalyzed coupling[78] of iodobenzene **II-70** with ethyl diazoacetate and the Cu-catalyzed coupling[79] with diethyl malonate were both attempted but both failed to yield any coupled product. It

appeared that these conditions were quite sensitive to the steric hindrance of the iodobenzene component. With the o-*tert*-butylphenylacetic acid **II-44i** in hand, the CAEC reaction was carried out to give the monomer **II-45i** in 42% yield, which is lower than normal probably due to the greater steric hindrance of t-butyl group. Gratifyingly the oxidative addition gave the 5,5'-*t*Bu$_2$VANOL **II-46i** in 91% yield.

Scheme 2.24 Synthesis of 5,5'-CN$_2$VANOL



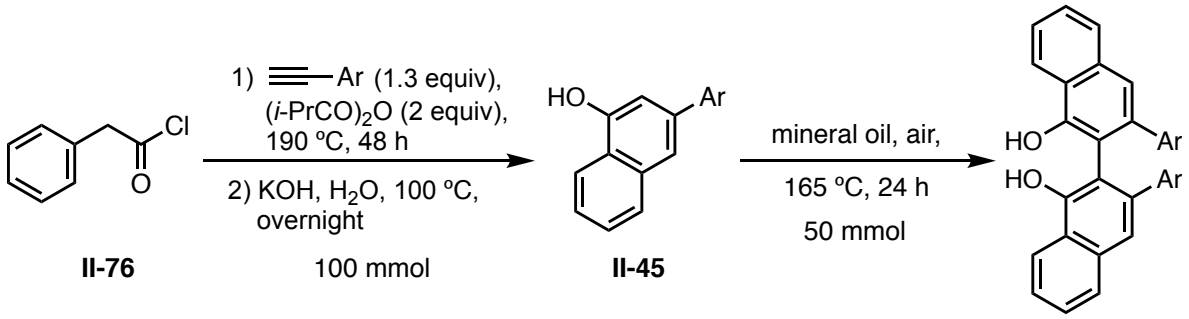
II-46c **II-46j** **II-46j'**

5,5'-CN$_2$VANOL **II-46j** was prepared by copper-catalyzed cyanation[80] of racemic 5,5'-Br$_2$VANOL **II-46c** (*Scheme 2.24*) in good yield. However, the solubility of this compound is very poor in most organic solvents, even DMSO. The purification procedure could be simply carried out by washing the solid with DCM. The cyanation from optically pure **II-46c** also produced **II-46j** in excellent yield (not shown). Unexpectedly, the resulting product, whose ee was not determined, has similar poor solubility as the racemic product.

2.6.2 Synthesis of 3,3'-disubstituted VANOL derivatives

Similarly, 3,3'-substituted VANOL derivatives were prepared from CAEC reaction using various commercially available *para*-substituted phenylacetylene and then oxidative coupling (*Table 2.3*) in moderate overall yields. The synthesis of 3,3'-dialkyl VANOL derivatives will be discussed in Chapter 3.

Table 2.3 Synthesis of 3,3'-R_2VANOL



II-76 100 mmol **II-45** **II-46**

series	Ar	%yield of monomer **II-45**[a]	%yield of VANOL **II-46**
k	4-EtC_6H_4	62	63
l	4-$CH_3OC_6H_4$	47	68
m	4-BuC_6H_4	58	49

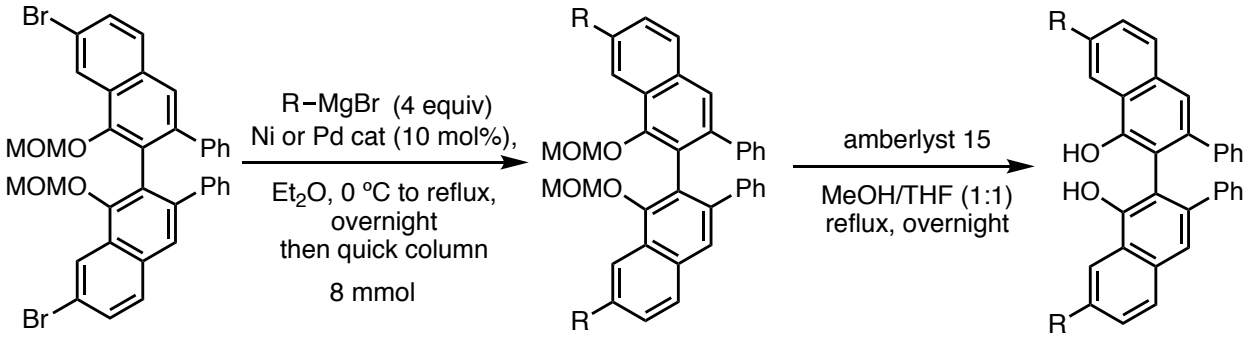
[a] combined yield from 2 crops after crystallization.

2.6.3 Synthesis of 7,7'-disubstituted VANOL

A number of 7,7'-substituted VANOL derivatives were prepared by Kumada coupling from MOM protected 7,7-Br_2VANOL (*Scheme 2.25*). 7,7-Br_2VANOL **II-46n** was prepared on large scale in good yield from acid **II-44n** via the CAEC reaction and subsequent oxidative coupling. The protection with MOMCl went well, giving **II-77** in 95% yield along with 4% of the mono-MOM protected ligand as a side-product. The Kumada coupling of **II-77** with alkyl Grignard reagents were explored and optimized. The coupling with freshly prepared 1º alkyl Grignard reagents, such as *n*-hexyl, isoamyl and 3-

phenylpropyl, can be catalyzed by 10 mol% Ni(dppp)Cl_2 giving **II-78o–q** in excellent yield. The partially deprotected products (not shown) were observed to some extent (14% isolated for II-78o) after quenching the coupling reaction. Nevertheless, the deprotection step was carried out successfully using the mixture of **II-78** and its OH/OMOM analog. Under the Ni-catalyzed conditions, the coupling with the 2º cyclohexyl Grignard reagent was sluggish. Optimization attempts by varying solvent, the method for Grignard generation and catalyst loading did not provide more than 56% yield of **II-46r**. It was thus pleasing to find that the more reactive Pd(dppf)Cl_2 was effective at rt for this substrate, giving rise to the final 7,7'-Cy_2VANOL **II-46r** in excellent yield.

Scheme 2.25 Synthesis of 7,7'-R_2VANOL



II-77 **II-78** **II-46**

series	R	catalyst	%yield of VANOL **II-46**[a]
o	hexyl	Ni(dppp)Cl_2	93
p	isoamyl	Ni(dppp)Cl_2	74
q	3-phenylpropyl	Ni(dppp)Cl_2	87
r	cyclohexyl	Ni(dppp)Cl_2	32
r	cyclohexyl	Pd(dppf)Cl_2[b]	93

[a] isolated yield after 2 steps. [b] 5 mol%, –78 ºC to rt

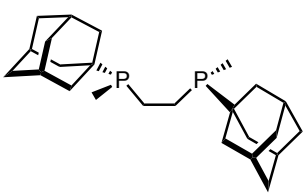
2.6.4 Synthesis of 7,7'-Ad_2VANOL

The greater enantiomeric induction often observed with *t*BuVANOL as ligand in many different asymmetric reactions led to a consideration of introducing an adamantyl (Ad) group into the 7,7'-positons of VANOL. The very rigid adamantyl group is thought to be bulkier than a *t*butyl group since it occupies a larger volume of space. A number of ligands containing an adamantyl group have been reported, many of which have found wide success in catalysis (*Scheme 2.26*).

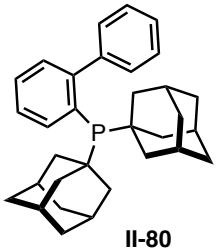
The mono-, di- and tri-adamantyl phosphine ligands **II-79–83** were developed by Imamoto[81], Buchwald[82-83], Beller[84-87], Hartwig[88], Carrow[89] and many other groups. Their superior activity in palladium or rhodium catalysis can be attributed to the steric and electronic properties of adamantyl group. First, it should be more sterically hindered than a *t*Bu group by comparison of the Charton steric parameter[90] (1.33 vs 1.24). Second, the adamantyl is more electron releasing than *t*Bu indicated by the lower calculated[89] carbonyl stretching frequency of $Ni(CO)_3(PR_3)$ (2052.1 cm^{-1} for R = adamantyl vs 2056.1 cm^{-1} for R = *t*Bu). Third, the adamantyl has better polarizability (Taft polarizability parameter σ_α –0.95 for ad compared to –0.75 for tBu)[89], which can facilitate electron donation from phosphorus to metal. These distinct characters of adamantyl are also reflected in other ligand system, such as the adamantylimido molybdenum alkylidene complex **II-84**, reported by Schrock and Hoveyda[91] and the *N*-Heterocyclic Carbene (NHC) 1,3-Bisadamantylimi-dazolin-2-ylidene **II-85a** by Herrmann[92]. Another important NHC **II-85b** was first synthesized[93] by Mol and coworkers and was applied[94] by Grubbs and Endo for *Z*-selective olefin metathesis. The steric property of adamantyl has often

been exploited in the asymmetric catalysis, as in the examples **II-86**[95], **II-87**[96] and **II-88**[97]. The adamantyl group has been incorporated into the 3,3'-positions of BINOL. In 2002, Pu and coworker reported[98] the BINOL-based catalyst for the enantioselective phenylacetylene addition to aromatic aldehydes in the presence of diethylzinc. List group reported[99] adamantyl-modified TRIP catalyst **II-90** in 2008 and it was found[100] to be the optimal catalyst in fluorination of allylic alcohols by Toste et al in 2014. Yamamoto's group also reported[101] the *N*-triflyl phosphoramide **II-91** catalyzed cycloaddition of nitrones with ethyl vinyl ether in 2008. By changing the isopropyl group to adamantyl in the para positon of aryl group at the 3,3'-positions of BINOL to give catalyst **II-91**, they obtained higher yield and greater stereoselectivity for the reaction. However, the reports of introduction of an adamantyl group into the BINOL backbone is limited[102], probably due to the lower ligand activity with the bulky group right next to the phenol OH, and the less-developed methodology for coupling of sterically hindered aryl bromides or boric acids with tertiary bromides.

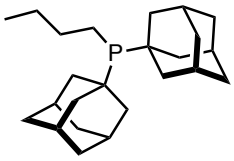
Scheme 2.26 Ligands/catalysts containing adamantyl group and their applications



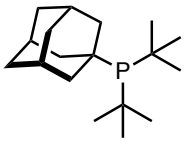
II-79
Imamoto[80], **1998**
[Rh], Asymmetric Hydrogenation



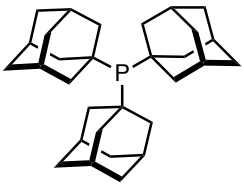
II-80
Buchwald[81-82], **1999**
[Pd], Bchwald Etherification



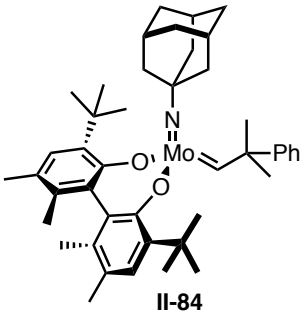
cataCXium A **II-81**
Beller[83-86], **2000**
[Pd], Suzuki-Miyaura Coupling



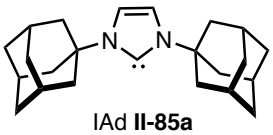
AdP*t*Bu$_2$ **II-82**
Hartwig[87], **2001**
[Pd], Heck Reaction



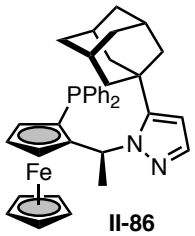
PAd$_3$ **II-83**
Carrow[88], **2016**
[Pd], Suzuki-Miyaura Coupling



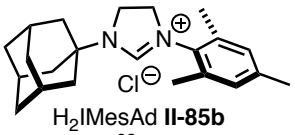
II-84
Schrock and Hoveyda[90], **2003**
Asymmetric Olefin Metathesis



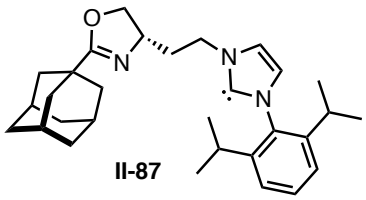
IAd **II-85a**
Herrmann[91], **2002**
[Pd], Suzuki-Miyaura Coupling



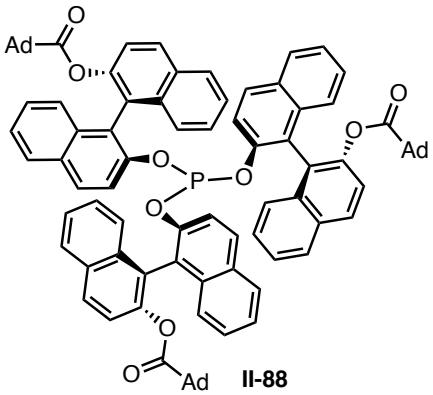
II-86
Togni[94], **2002**
[Pd], Asymmetric
Allylic Amination



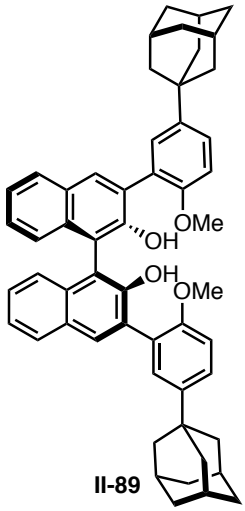
H$_2$IMesAd **II-85b**
Mol[92], **2003**
Grubbs[93], **2011**
[Ru], Z-Selective Olefin Metathesis



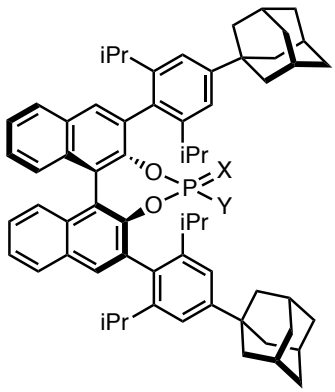
II-87
Hall and Burgess[95], **2004**
[Ir], Asymmetric hydrogenation



II-88
Reetz[96], **2009**
[Rh], Asymmetric Hydrogenation



II-89
Pu[97], **2002**
Asymmetric Alkynylzinc
Addition to Aldehydes

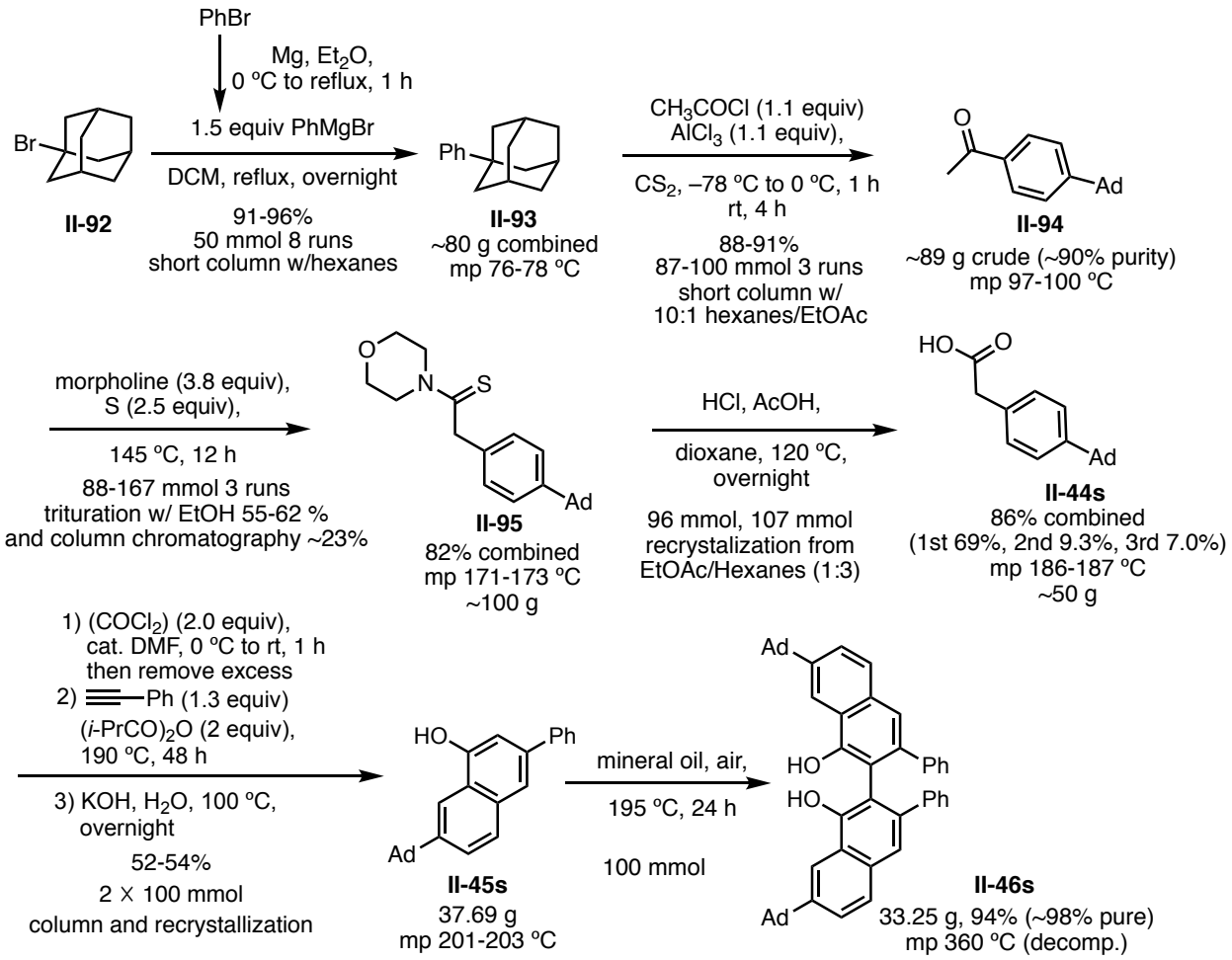


II-90, X = O, Y = OH, List[98], **2008**
Asymmetric Aminal Formation
Toste[99], **2014**
Fluorination of Allylic Alcohols

II-91, X = O, Y = NHTf, Yamamoto[100], **2008**
Enantioselective 1,3-Dipolar Cycloaddition

Introducing adamantyl into 7,7'-position of VANOL hopefully would enable unique reactivity in catalysis without adversely affect the activity because the phenol OH is much farther away than it is in 3,3'-Ad_2BINOL. Given that it would be challenging to develop a coupling reaction of 7,7'-Br_2VANOL and an adamantyl nucleophile, it was decided to explore the synthesis the *p*-adamantylphenylacetic acid — the requisite precursor for the CAEC reaction. After several failed attempts at the Friedel-Crafts reaction of methyl phenylacetate with 1-bromoadamantane **II-92** catalyzed by $AlCl_3$, $FeCl_3$[103] and $Mo(CO)_6$[104], it was delightful to find that the cross coupling reaction of **II-92** with freshly-made phenyl Grignard reagents in DCM gave 1-phenyladamantane **II-93** in excellent yield on 50 mmol scale. Converting **II-93** to the 2-(*p*-adamantylphenyl)acetic acid **II-44s** was achieved by an in-house route that had been developed for *t*BuVANOL[59]: Friedel-Crafts acylation followed by the Willgerodt-Kindler reaction and then hydrolysis. The phenyl acetic acid **II-44s** can be prepared on large scale with around 50% yield over 4 steps. Gratifyingly, the subsequent CAEC reaction and dimerization went smoothly gave the desired product in 53% and 94% yield, respectively. It is worth noting that to achieve full conversion of the oxidative coupling, it was required to elevate the temperature from 150 ºC (optimal for *t*BuVANOL) to 195 ºC which is near the melting point of **II-45s**. The reaction only reached ~50% conversion after 48 h at 170 ºC and was completely shut down at 150 ºC.

Scheme 2.27 Synthesis of 7,7'-Ad_2VANOL



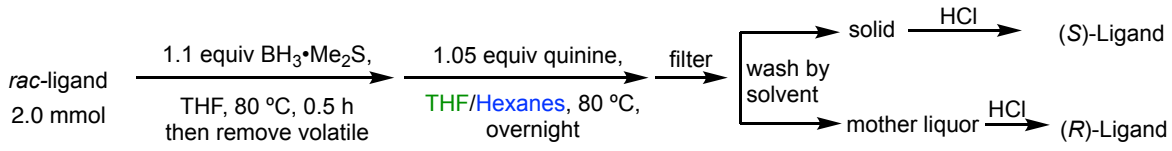
2.6.5 Resolution scope with quinine

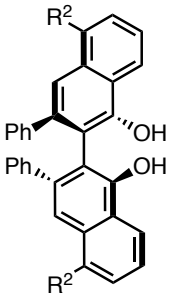
With these newly prepared 5,5'-, 7,7'- and 3,3'-disubstituded VANOL derivatives in hand, the scope of the resolution process with quinine borate (*Scheme 2.21*) was investigated. It was delightful to find that a variety of 5,5'-, 7,7'- and 3,3'-substituted VANOL derivatives could be resolved by this procedure. For 5,5'-disubstituted VANOLs, excellent yield (42-45%) and perfect ee were observed for bromo, chloro and methyl substitutents (**II-46c**–**e**, *Table 2.4*). Half of volume of hexanes was used when the quinine borates of 5,5'-$(OMe)_2$VANOL **II-46f** and 5,5'-$(CF_3)_2$VANOL **II-46g** were refluxed with THF since this was necessary to increase the yields. It is worth noting that the procedure could

be easily scaled-up to 8 mmol, giving 1.82 g (40% yield) of optically pure 5,5'-$(CF_3)_2$VANOL **II-46g**. The resolution could be applied to VANOL with branched or unbranched aliphatic substituents at the 7,7'-positions (**II-46o**, **46p**, **46r**, **46s**, *Table 2.4*), providing the optically pure ligands in moderate to good yield (10-33%, single run, unoptimized). The VANOL ligands with substituents on the 3,3'-phenyl rings are also compatible (**II-46k**–**m**, *Table 2.4*). The limitation of this resolution has also been found. The borate precipitation procedure of 7,7'-Br_2VANOL **II-46n** with quinine failed to give any diastereomeric enrichment, and refluxing of 7,7'-(3-phenylpropyl)$_2$VANOL **II-46q** and 3,3'-Cy_2VANOL **II-46t** with borane and quinine did not produce any solid even if hexanes was added.

The procedure was then applied to racemic VANOL **II-46a**, VAPOL **II-96** and isoVAPOL **II-97**[105]. It was important to find that VANOL and VAPOL could be resolved by this process with slight modifications to the volume of refluxing THF. Excellent yields (44-45%, 50% maximum) of optically pure (*S*)-enantiomer could be obtained. In the case of isoVAPOL **II-97**, the diastereomeric borate complex did not precipitated from THF alone, and the addition of hexanes was required to afford 33% of (*S*)-isoVAPOL. BINOL **II-11** was also tested in this procedure but with a smaller amount of THF than in the original report[32], giving excellent yield, albeit 91% ee. Unexpectedly, the 6,6'-Br_2BINOL **II-39** did not yield any solid borate complex even when a large amount of hexanes was added.

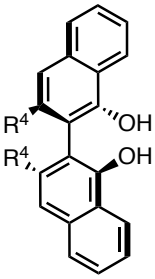
Table 2.4 Scope of resolution of VANOL derivatives with quinine borates





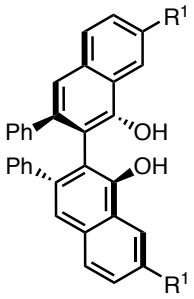
5,5'-disubstituted VANOL

II-46c, R^1 = Br, (4.5), 45%, >99% ee
II-46d, R^1 = Cl, (4.5), 44%, >99% ee
II-46e, R^1 = Me, (4.5), 42%, 99% ee
II-46f, R^1 = OMe, (4/2), 47%, >99% ee
II-46g, R^1 = CF_3, (4/2), 40%, >99% ee[a]



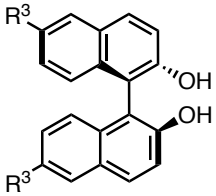
3,3'-R_2VANOL

II-46k, R^4 = *p*-EtC_6H_4, (3/3), 36%, >99% ee
II-46l, R^4 = *p*-OMeC_6H_4, (3/3), 34%, >99% ee
II-46m, R^4 = *p*-BuC_6H_4, (3/4), 17%, >99% ee
II-46t, R^4 = Cy, (3/6), trace, 10% ee



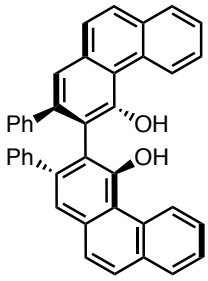
7,7'-disubstituted VANOL

II-46a, R^1 = H, (3), 45%, >99% ee
II-46b, R^1 = *t*Bu, (4), 35%, >99% ee
II-46o, R^1 = n-hexyl, (4/3),, 10%, >99% ee
II-46p, R^1 = isopentyl, (3/3), 23%, >99% ee
II-46q, R^1 = 3-phenylpropyl, (3/3), 0%
II-46r, R^1 = Cy, (4), 26%, >99% ee
II-46n, R^1 = Br, (3), 46%, 0% ee
II-46s, R^1 = Ad, (4), 33%, >99% *ee*

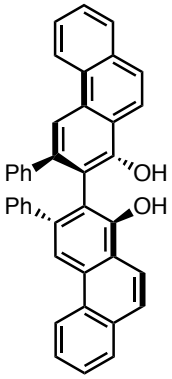


BINOL derivatives

II-11, R^3 = H, (2.5), 46%, 91% ee
II-39, R^3 = Br, (3/6), 0%



II-96, VAPOL, (3), 44%, >99% ee



II-97, isoVAPOL, (4/2), 33%, >99% ee

[a]8.0 mmol scale

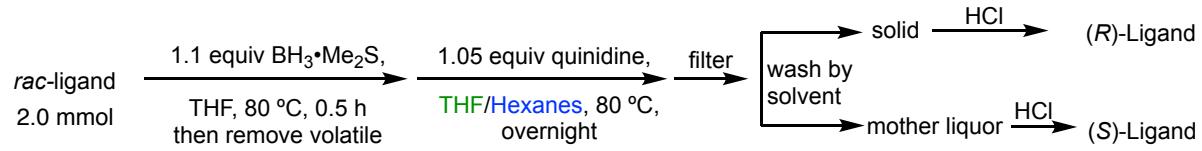
2.6.6 Resolution scope with quinidine

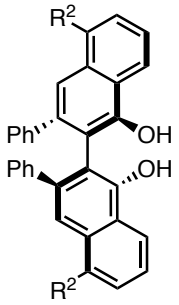
The efforts to enrich the ee of the (*R*)-enantiomer of the VANOL derivatives from the mother liquor from the quinine borate procedure were first directed to developing a procedure involving the solubilization of optically pure ligand from a scalemic mixture with hexanes (*Scheme 2.21*). However, the conditions are substrate-dependent. For example,

the optically pure 5,5'-Br_2VANOL **II-46c** was not very soluble in hexanes. Thus stirring 72% ee 5,5'-Br_2VANOL **II-46c** in hexanes and then filtering did not result in increasing ee of **II-46c** in the mother liquor (71% ee). Repeated recrystallizations were time consuming and often non-reproducible. Therefore, it was decided to develop a resolution with a borate ester with quinidine, the pseudo-enantiomer of quinine (*Table 2.5*).

Gratifyingly, the 5,5'-disubstituted VANOL derivatives **II-46c**–**g** could be resolved successfully with quinidine to afford the optically pure (*R*)-enantiomer in moderate to excellent yields (13-46%) (*Table 2.5*). In general, the quinidine process was less efficient than the quinine process for VAPOL **II-96**, VANOL **II-46a** and its 7,7'-substituted derivatives. In contrast to the quinine process, the addition of hexanes was required for some substrates to afford the precipitate with reasonable yield from the quinidine (**II-46a**, **e**, **s**, *Table 2.5*). Surprisingly, the resolution of 7,7'-Ad_2VANOL with the quinidine borate process gave the same (*S*)-enantiomer as quinine process. In contrast, BINOL and 6,6'-Br_2BINOL were resolved more effectively with quinidine (**II-11** and **II-39**, *Table 2.5*). The application of this resolution in enantioenrichment was demonstrated for **II-46l**. The scalemic mixture with 79% ee (*R*) was successfully enriched to >99% following the same procedure, leaving 89% of the (*S*)-enantiomer in 18% yield in the mother liquor. Unfortunately, refluxing of 7,7'-Br_2VANOL **II-46n** gave a precipitate containing both diastereomers in a 1:1 ratio.

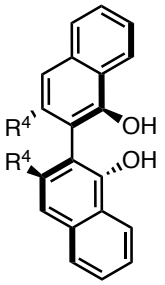
Table 2.5 Scope of resolution of VANOL derivatives with quinidine borates



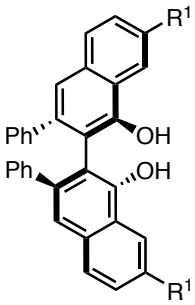


5,5'-disubstituted VANOL

II-46c, R^1 = Br, (4), 32%, >99% ee
II-46d, R^1 = Cl, (4), 41%, >99% ee
II-46e, R^1 = Me, (4/2), 39%, 99% ee
II-46f, R^1 = OMe, (4/2), 46%, >99% ee
II-46g, R^1 = CF_3, (4/2), 13%, >99% ee

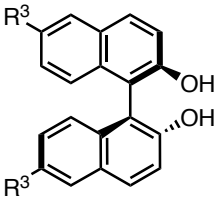


3,3'-R_2VANOL
II-46l, R^4 = *p*-$OMeC_6H_4$, (3/3), 76%, >99% ee (from 79% ee *R*)[b]

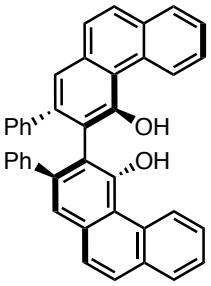


7,7'-disubstituted VANOL

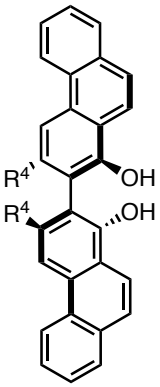
II-46a, R^1 = H, (4/4), 31%, 70% ee
II-46b, R^1 = *t*Bu, (4), 0%
II-46n, R^1 = Br, (3), 0% ee
II-46s, R^1 = Ad, (4/4), 31%, >99% ee[a]



BINOL derivatives
II-11, R^3 = H, (2.5), 39%, 94% ee
II-39, R^3 = Br, (3/1.5), 48%, >99% ee



II-96, VAPOL, (3), 28%, >99% ee



II-97, isoVAPOL, (4/2), 26%, >99% ee

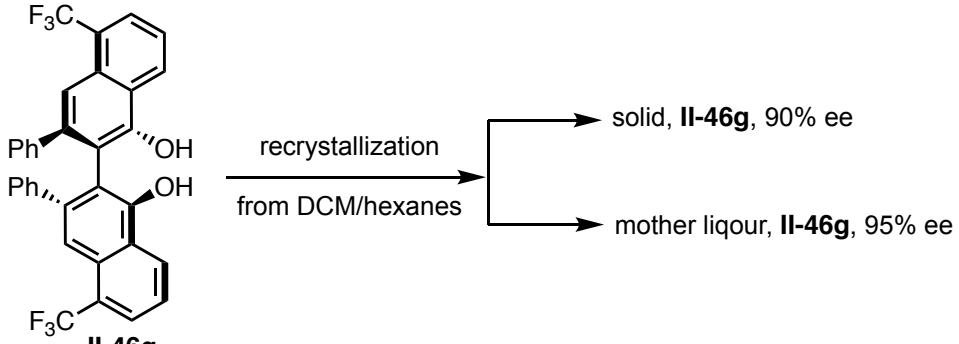
[a](S)-enantiomer was obtained from solid. [b]4.17 mmol scale.

2.7 Stability of 5,5'-substituted VANOL derivatives

During the development of the resolution of 5,5'-R_2VANOL derivatives, it was observed that the results of the resolution were inconsistent and it was suspected that this was due to a variation of the reaction times for the hydrolysis step. Moreover, the relative mass of the resulting (*R*)- and (*S*)-enantiomers has changed from 1:1. In an

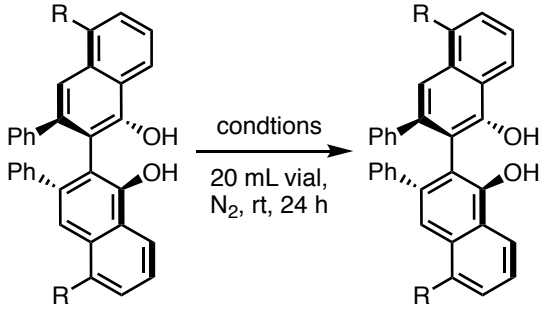
attempt to increase the enantiomeric excess of 98% ee 5,5'-$(CF_3)_2$VANOL **II-46g** by recrystallization, the ees of both the crystal and the mother liquor dropped (*Scheme 2.28*). These observations led us to investigate the racemization of ligands under various conditions (*Table 2.6*).

Scheme 2.28 Racemization of 5,5'-$(CF_3)_2$VANOL



II-46g
98% ee

Table 2.6 Racemization experiments with 5,5'-R_2VANOL



II-46 15 mg, >99% ee

II-46 15 mg, >99% ee

II-46a, R = H,
II-46c, R = Br,
II-46e, R = Me,
II-46f, R = OMe,
II-46g, R = CF_3,

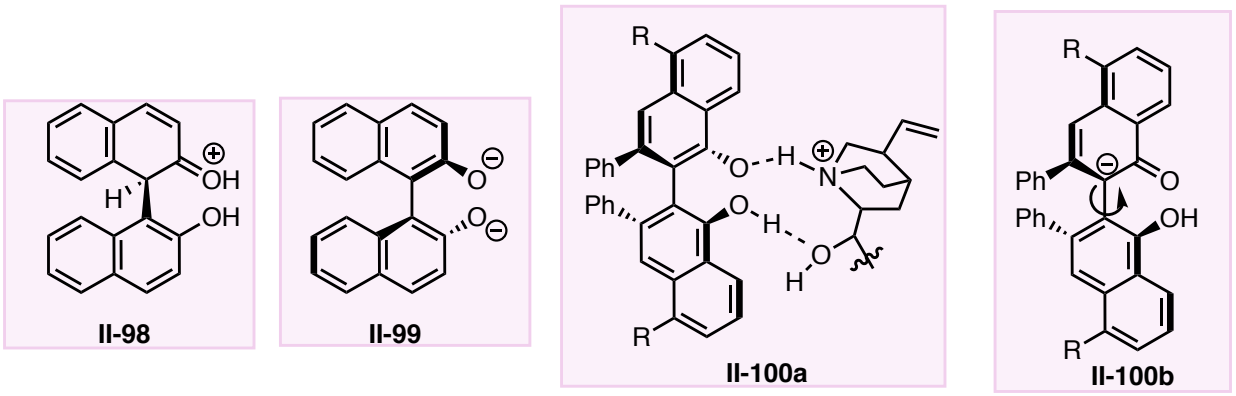
entry	R	conditions	%ee[b] (**II-46**)
1	OMe	1 mL DCM	>99
2	Me	1 mL DCM	74
3	H	1 mL DCM	>99
4	Br	1 mL DCM	>99
5	CF_3	1 mL DCM	22
6	CF_3	1 mL EtOAc	>99
7[a]	OMe	1 mL DCM, 10 mg quinine	82
8	Me	1 mL DCM, 10 mg quinine	60
9[a]	H	1 mL DCM, 10 mg quinine	>99
10[a]	Br	1 mL DCM, 10 mg quinine	80
11[a]	CF_3	1 mL DCM, 10 mg quinine	94
12	OMe	1 mL DCM, 0.5 mL 2 M HCl	>99
13	Me	1 mL DCM, 0.5 mL 2 M HCl	>99
14	H	1 mL DCM, 0.5 mL 2 M HCl	>99
15	Br	1 mL DCM, 0.5 mL 2 M HCl	>99
16	CF_3	1 mL DCM, 0.5 mL 2 M HCl	93

[a]36 h. [b]As judged by chiral HPLC.

In 20-mL vials, VANOL **II-46a** and derivatives **II-46c**, **II-46e**–**g** were dissolved separately in DCM and kept under N_2 for at least 1 day then subjected to chiral HPLC

analysis. It was surprising to find that 5,5'-$(CF_3)_2$VANOL **II-46g** and 5,5'-Me_2VANOL **II-46e** racemized readily in DCM, while the other three ligands were resistant toward racemization (entry 1-5, *Table 2.6*). The experiment in EtOAc did not result in any racemization of **II-46g** (entry 6, *Table 2.6*). In basic media with quinine, although VANOL demonstrated configurational stability after 24 h, derivatives of VANOL were more or less racemized (entry 7-11, *Table 2.6*). Oddly, **II-46g** was racemized to a lesser extent under basic conditions. It was found that VANOL ligands were less prone to epimerize under acidic conditions (entry 12-16, *Table 2.6*). No racemization was observed under acidic condition at room temperature after 24 h except for 5,5'-$(CF_3)_2$VANOL **II-46g**, to a less extent compared to neutral conditions (entry 7-11, *Table 2.6*). It was demonstrated by Cram and coworkers[106] that BINOL can racemize under basic or acidic conditions upon heating. The transition states for epimerization were proposed to involve a protonated enol **II-98**, in which the naphthyl rings can rotate about the $C(sp^2)$-$C(sp^3)$ bond, or dianion **II-99**, which has a lower rotation barrier due to the loss of intermolecular hydrogen bonding (*Scheme 2.29*). For the racemization of VANOL derivatives in the presence of quinine, a similar transition state **II-100a** could also be envisioned and is depicted in *Scheme 2.29*. After deprotonation by the quinuclidine nitrogen atom, the other phenol group in VANOL can engage in the hydrogen bonding with the hydroxyl group of the same (or another) quinine molecule, which will minimize the rotation barrier of the two naphthyl rings. An alternative pathway of racemization would be the rotation about the $C(sp^2)$-$C(sp^3)$ bond in the enolate **II-100b** of the mono deprotonated VANOL.

Scheme 2.29 Proposed pathway for racemization BINOL and VANOL



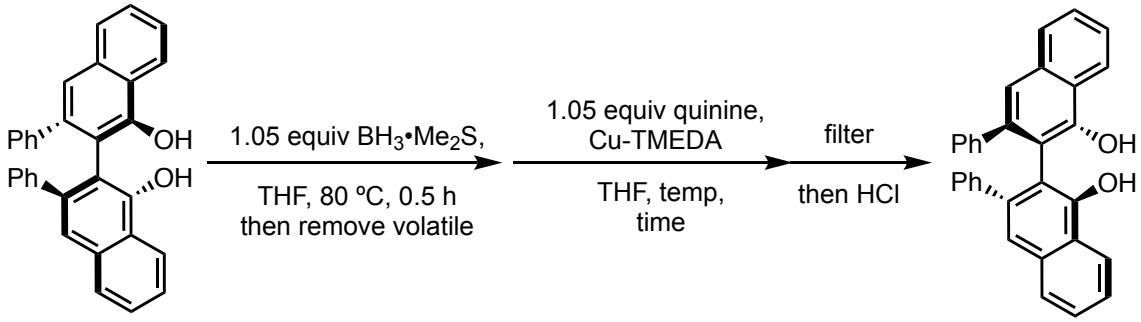
In light of the facile racemization of some VANOL derivatives, the solvent used for hydrolysis and extraction was switch from DCM to EtOAc. And the time of hydrolysis was decrease to 1 h. After the hydrolysis, a quick column chromatography was employed to remove the remaining quinine in the mixture. The process became more consistent and reproducible after these modifications.

2.8 Crystallization-induced dynamic resolution

One of the limitations for classical resolution is that a single enantiomer can only be obtained with maximum 50% yield. Dynamic resolution, on the other hand, can convert 100% of a racemic compound into an enantiopure compound. One of the keys to realize dynamic resolution is to find conditions to easily interconvert the (*R*) and (*S*) enantiomers throughout the resolution process. We envisioned that we could develop a crystallization-induced dynamic resolution (CIDR)[107] of VANOL derivatives by epimerization of their enantiomers under our resolution conditions. To the best of our knowledge, CIDR of bisphenol ligands has not been reported in literature, even though several syntheses of biaryl atropisomers by dynamic kinetic resolution process were reported[108-112] recently. It is known that a copper (II) complex with sparteine can induce deracemization of BINOL,

VANOL, VAPOL and their derivatives[59, 64-65, 113]. It was reasoned that a copper complex with an achiral amine could racemize the soluble enantiomer of a VANOL derivative and enable a CIDR process. The commercially available Cu(II)-TMEDA **II-101** catalyst has been applied to a variety of reactions, such as oxidative coupling of naphthol derivatives[114], cross coupling of aryl boronic acids with heterocycles[115-117] and coupling of terminal alkynes[118-120]. It was the catalyst of choice for initial examination of the epimerization of VANOL derivatives.

Table 2.7 Crystallization-induced dynamic resolution of VANOL

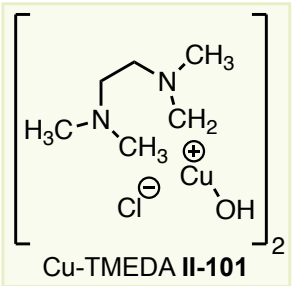


(*R*)-**II-46a**,
>99% ee, 1 mmol

(*S*)-**II-46a**
>99% ee

entry	Cu-TMEDA	THF	temp	time	(*S*)-**II-46a**[b]
1	20 mol%	3 mL	80 ºC	12 h	mixture[c]
2	10 mol%	5 mL	60 ºC	2 h	56%
3	5 mol%	5 mL	60 ºC	12 h	0
4	1 mol%	5 mL	60 ºC	24 h	0
5	—[a]	5 mL	60 ºC	12 h	0

[a]10 mol% $CuCl_2$ and 10 mol% 1,10-phenanthroline.
[b]Isolated yield after hydrolysis and column chromatography.
[c]Uncharacterized.



Cu-TMEDA **II-101**

To provide a proof of concept, the conversion of (*R*)-VANOL to (*S*)-VANOL using quinine borate resolution in the presence of Cu-TMEDA catalyst was briefly explored (*Table 2.7*). The resolution process for racemic VANOL was employed for (*R*)-VANOL

with 20 mol% Cu-TMEDA **II-101**. It was delightful to observe that a white solid precipitated from THF after 20 min reflux, which was expected to be the (*S*)-VANOL borate complex with quinine which has lower solubility than the other diastereomer. However, after reflux overnight, the mixture became a brown solution without any solid. Acidic work up gave a complex mixture with VANOL as the major spot on TLC (entry 1, *Table 2.7*). The byproduct is likely to be the dimer of VANOL which was observed in deracemization[65] by Cu-sparteine complex. To avoid decomposition, the loading of the catalyst was decreased to 10 mol%. In addition, the temperature and time of heating was reduced (60 ºC for 2 h). Pleasingly, the optically pure (*S*)-VANOL could be obtained in 56% yield, leaving 36% (*S*)-VANOL with 21% ee in the mother liquor (entry 2, *Table 2.7*). This result proved that VANOL can be epimerized by catalytic amount of Cu-TMEDA and it is feasible to develop a CIDR of VANOL. Further lower the Cu-TMEDA loading to 5 mol% or 1 mol% showed a negative effect; No solid was formed after heating for a longer period of time and the color of the solutions became darker, which indicated decomposition (entry 3 &4, *Table 2.7*). Other copper catalyst for epimerization such as 10 mol% Cu(II)-1,10-phen was tested. No solid was formed for the whole period of heating and the solution became dark brown after 12 h (entry 5, *Table 2.7*).

Nevertheless, many challenges need to be addressed in order to develop a CIDR of VANOL and derivatives. Firstly, the inclusion of copper catalyst in the borate precipitate would inhibit the racemization process, especially when the concentration of the soluble enantiomer become very dilute when the dynamic resolution reaches high conversion. Secondly, high temperature, concentration and loading of copper catalyst would effect

dimerization or other side reaction of VANOL. On the other hand, they are necessary to drive the resolution and racemization more effectively. A balance s to be reached by extensively screening the conditions of the process.

2.9 Computational Model

Attempts to grow crystallographically characterizable crystals of quinine borate complexes with VANOL and 7,7-Ad_2VANOL failed. Therefore, an effort to elucidate their structural properties was turned to computational methods. Quinine borate ester complexes of (*S*)- and (*R*)-VANOL was constructed in Spartan 08. After conformational analysis and ground state optimization in gas phase at the level of B3LYP/6-31g(d), a *spiro*borate ester with quinuclidine N–>B coordination (1.69 Å distance) was identified as the energy minimum (*Figure 2.2*).

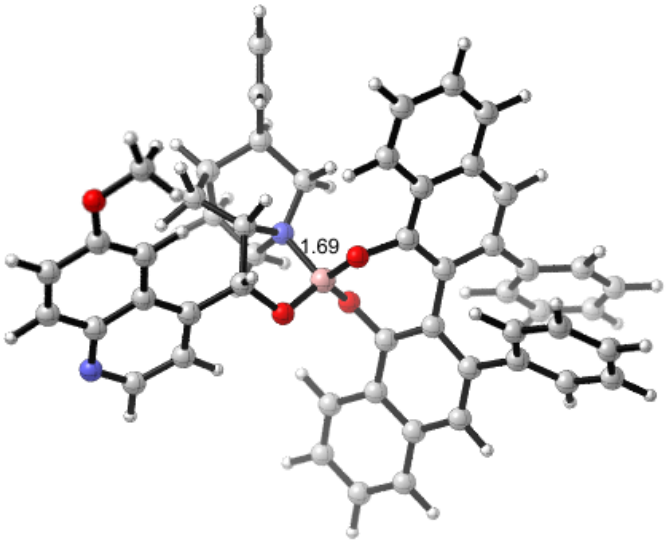
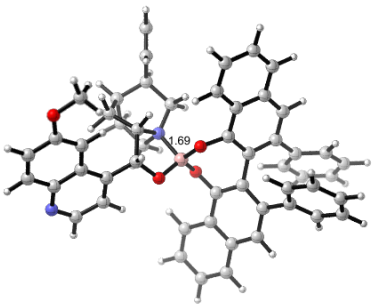
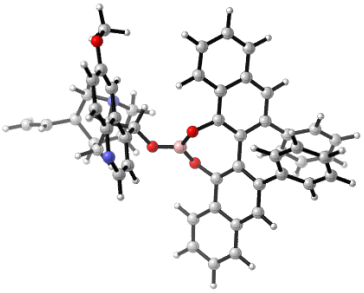
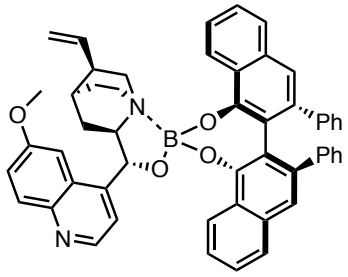


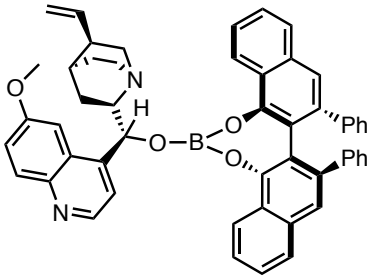
Figure 2.2 *spiro*Borate ester of (*S*)-VANOL with quinine **II-102**



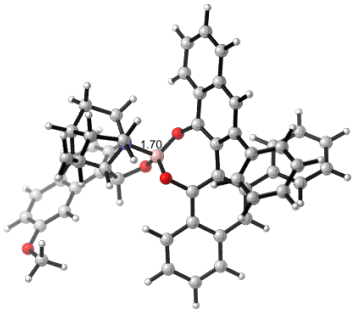


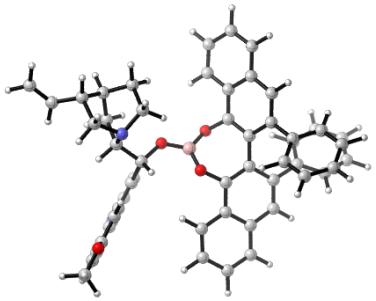


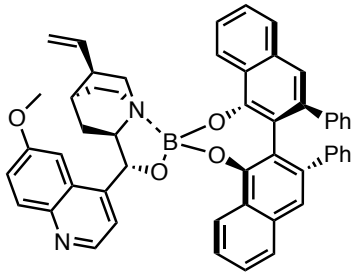
(*S*)-VANOL-QN spiroborate **II-102**
0.825 kcal/mol



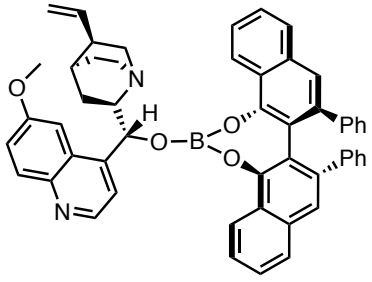
(*S*)-VANOL-QN mesoborate **II-103**
4.904 kcal/mol







(*R*)-VANOL-QN spiroborate **II-104**
0



(*R*)-VANOL-QN mesoborate **II-105**
5.938 kcal/mol

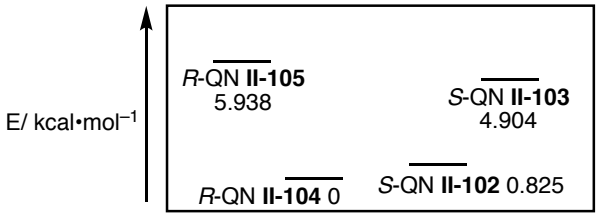


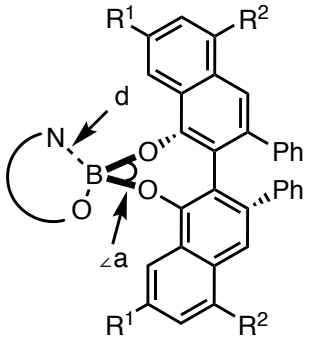
Figure 2.3 Possible geometries of VANOL quinine borates at the B3LYP/6-31G(d) level

Both (*S*)- and (*R*)-VANOL *spiro*borate esters with quinine demonstrated exceptional stabilization compared to their most stable *meso*borate isomers from DFT calculation at the B3LYP/6-31G(d) level (**II-102** vs **II-103**, **II-104** vs **II-105**, *Figure 2.3*). The less THF-soluble (*S*)-VANOL *spiro*borate is slightly less stable at gas phase compared to (*R*)-VANOL *spiro*borate probably due to the unfavorable steric interaction of quinuclidine with naphthyl ring. It is worth noting that similar borate esters with O_3BN framework have been synthesized[35, 121-127] and applied in BINOL resolution[35], asymmetric ketone reduction[121, 124-125, 127] and aldol reaction[123] by the Shan, Ortiz-Marciales and Krzemiński groups.

In order to probe the correlation between the efficiency of resolution and DFT structural properties, 5,5-Br_2VANOL **II-46c**, 7,7-Br_2VANOL **II-46n** and 7,7-Ad_2VANOL **II-46s** were constructed based on the optimized structure of the VANOL *spiro*borate of quinine/quinidine and then further optimized at the B3LYP/6-31G(d) level. The distance of N–B coordination and the angle of ligand O–B–O were measured. The results are shown in *Table 2.8*. The O–B–O bond angles of *spiro*borates (114.1~116.0) clearly indicated the boron is pyramidalized. It is interesting that the smaller angle difference between their (*R*)- and (*S*)-diastereomers, the higher efficiency of the resolution in THF. For example, for VANOL **II-46a** and **II-46c**, quinine resolution is more efficient than quinidine (angle difference 0.2 vs 0.6, 0.1 vs 0.5). Resolution of VANOL **II-46n** did not yield any diastereomeric excess, and the angle differences between diastereomeric borates were larger than the other 3 ligands (1.0 for QN and 0.5 for QD). The distances of N–B did not vary much (1.68~1.72) and no correlation was found between them and

the efficiency of the resolution. A similar trend was observed for the energy difference between the (*R*)- and (*S*)-diastereomers and efficiency of the resolution of **II-46a**, **II-46c** and **II-46s**: the energy difference of the pair of quinidine is larger, and the efficiency is lower for quinidine than quinine. The abnormality of 7,7-Ad_2VANOL **II-46s** was also demonstrated in the computational structures. In contrast to ligand **II-46a** and **II-46c**, the quinine borate with (*R*)-**II-46s** is more pyramidalized and higher in energy, than the diastereomer with (*S*)-**II-46s**. Nevertheless, the solubility of the borate diastereomers could not be correlated to these properties. The details of the crystal packing were not available from DFT calculation.

Table 2.8 Structural properties of optimized DFT structures of quinine/quinidine borates with VANOL derivatives



II-46a, R^1, R^2 = H
II-46c, R^1 = H, R^2 = Br
II-46n, R^1 = Br, R^2 = H
II-46s, R^1 = Ad, R^2 = H

entry	ligand	QN/QD	∠a(°)	d(Å)	ΔE (kcal/mol)[a]
1	**II-46a**	(*S*)-QN	115.6	1.69	0.825
2	**II-46a**	(*R*)-QN	115.8	1.70	0
3	**II-46a**	(*S*)-QD	114.9	1.70	0
4	**II-46a**	(*R*)-QD	115.5	1.72	0.951
5	**II-46c**	(*S*)-QN	115.4	1.69	0.851
6	**II-46c**	(*R*)-QN	115.5	1.70	0
7	**II-46c**	(*S*)-QD	114.7	1.69	0
8	**II-46c**	(*R*)-QD	115.2	1.72	1.030
9	**II-46n**	(*S*)-QN	114.1	1.68	1.195
10	**II-46n**	(*R*)-QN	115.1	1.69	0
11	**II-46n**	(*S*)-QD	114.1	1.69	0
12	**II-46n**	(*R*)-QD	114.6	1.72	0.673
13	**II-46s**	(*S*)-QN	116.0	1.69	0
14	**II-46s**	(*R*)-QN	115.9	1.70	0.236
15	**II-46s**	(*S*)-QD	115.1	1.69	0
16	**II-46s**	(*R*)-QD	115.6	1.72	1.331

[a]Energy difference between the borate diastereomers of (*S*)- and (*R*)-ligand.

2.10 Conclusion and outlook

In summary, a general resolution of VANOL, VAPOL and BINOL and their derivatives via borates with quinine or quinidine was developed. A variety of optically pure VANOL derivatives could be readily accessible by this method. The procedure is time efficient and can be easily scaled up. Quinine and quinidine used in the resolution could be recycled by simple manipulations. The borate esters of the ligands with quinine or quinidine were proposed to consist of *spiro*borates with N–>B coordination based on DFT calculations. The potential of developing a CIDR in the presence of Cu-TMEDA was demonstrated. In order to resolve those ligands that did not yield any solid or gave solid without significant diastereomeric excess from THF, other ether solvents such as Et_2O and methyl *tert*-butyl ether, could be tested.

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CHAPTER THREE

DEVELOPMENT OF OTHER STRATEGIES FOR THE SYNTHESIS OF VANOL MONOMER

"VAPOL doesn't grow on trees."

– William D. Wulff

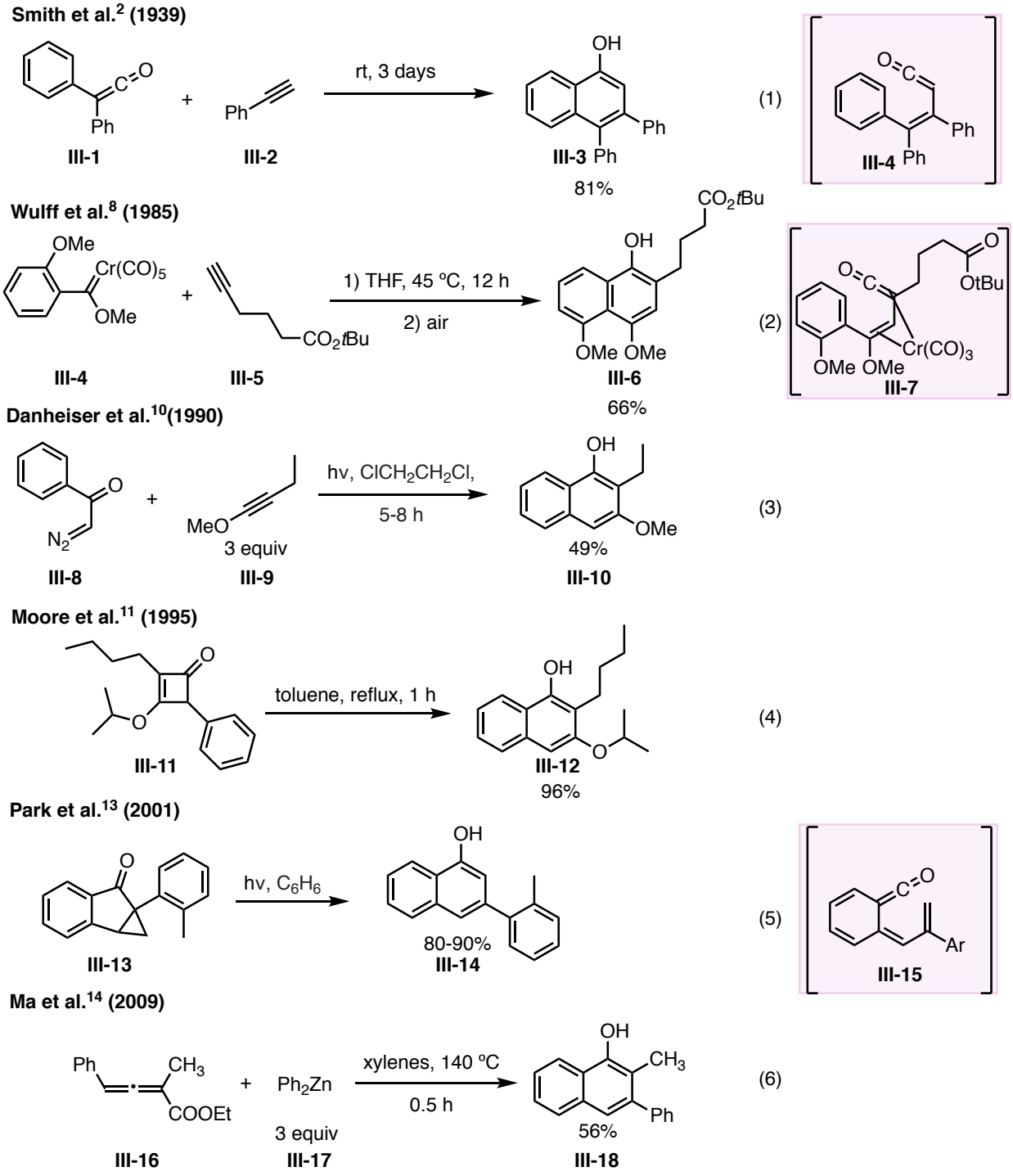
3.1 Strategies of 1-naphthol synthesis

1-Naphthols are important building blocks for organic synthesis. There is nonetheless a need for developing convenient and efficient methodologies for the synthesis of 1-naphthols especially because they are precursors to the VANOL ligands[1]. A variety of methods for 1-naphthol synthesis have been developed. They can be classified into five categories in terms of their reaction pathways.

The benzannulation reaction of diphenylketene and phenyl acetylene was reported[2] by Smith et al. in 1939 (eq 1, *Scheme 3.1*). Interestingly, the addition product is 1-naphthol **III-3** instead of a 2-naphthol, which would have been the product if the reaction occurs by a [4+2] cycloadditon. The mechanism was studied and proposed[3] by Smith and Hoehn in 1941. It involves a [2+2] cycloaddition with phenyl acetylene and ketene to form a cyclobutenone (not shown). The cyclobutenone ruptures readily to give the vinylketene intermediate **III-4** which undergoes a 6 electron electrocyclic ring closure to give naphthalen-1-one and then, upon tautomerization, generates the 1-naphthol. This process has been recently modified by Wulff and coworkers and is now one of the most

widely used method for the synthesis of VANOL and VAPOL derivatives[4-5]. Another important benzannulation reaction involving Fischer carbine complexes was first discovered[6] by Dötz in 1975. Recognizing the synthetic potential of the Dötz reaction, the Wulff group started developing and applying this benzannulation reaction in the syntheses of phenols and quinones[7-9]. Subsequently, this reaction has become known as Wulff–Dötz reaction. The intermediacy of vinylketene complex **III-7** was supported by DFT studies[7]. The product 1-napthol **III-6** could be oxidatively liberated from the chromium by exposure its complex to air (eq 2, *Scheme 3.1*). Danheiser and coworkers reported[10] that the vinylketene could be generated from a Wolff rearrangement by irradiation (or thermolysis) of diazo ketones such as **III-8** (eq 3, *Scheme 3.1*). Moore and coworkers synthesized 1-naphthols from the relatively stable substituted cyclobutenone **III-11**[11-12] (eq 4, *Scheme 3.1*). Upon heating, an electrocyclic ring opening occurred to give a vinylketene intermediate similar to **III-4**. Vinylketene **III-15** could also be formed by photoinduced rearrangement of cyclopropane **III-13**[13] (eq 5, *Scheme 3.1*). Ma and coworkers reported[14] a Michael addition/cyclization cascade of allenoates **III-16** with organo zinc compounds **III-17** (eq 5, *Scheme 3.1*). The mechanism likely involves a vinylketene intermediate.

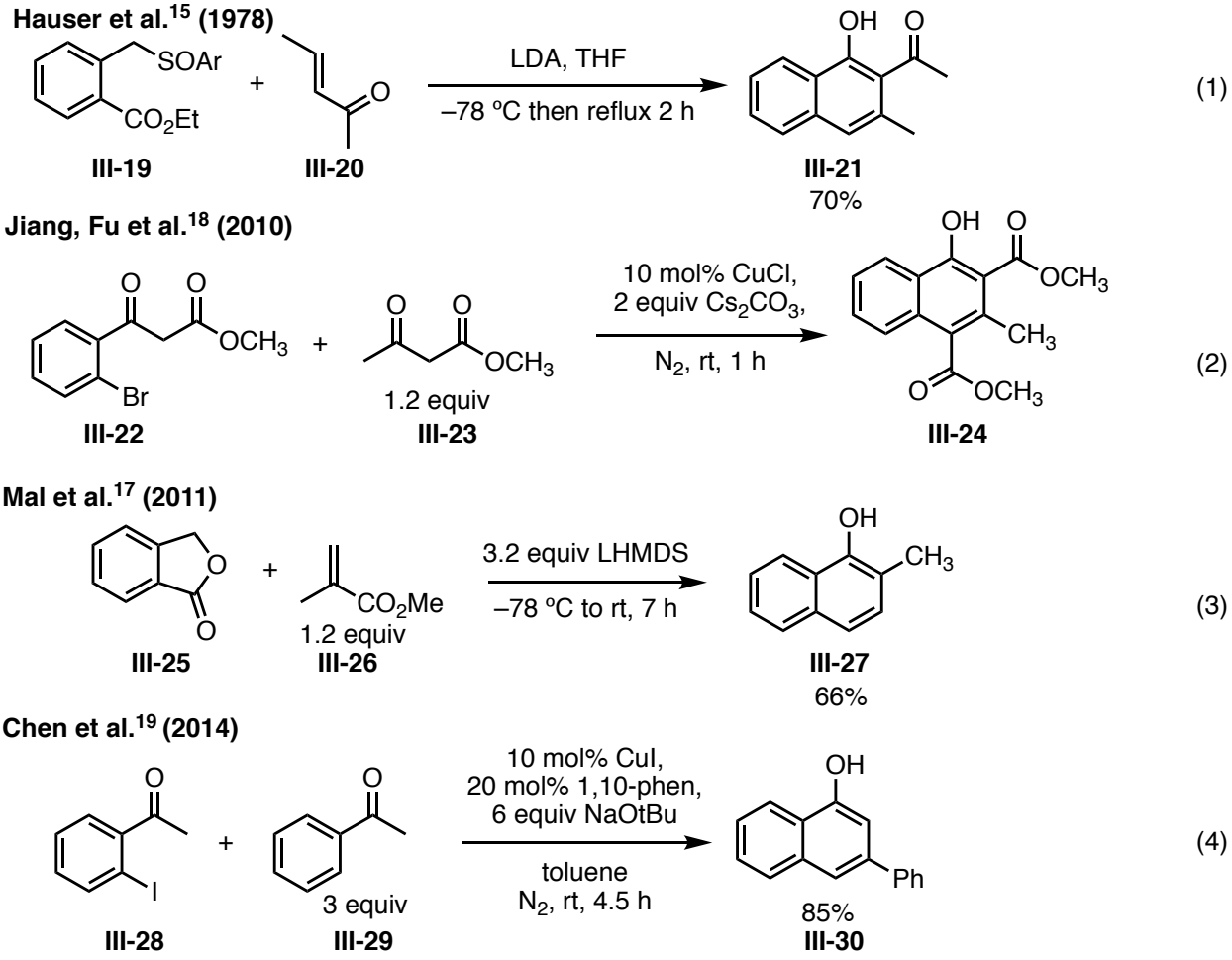
Scheme 3.1 Benzannulation via a vinylketene intermediate



Hauser first described[15] the annulation of stabilized phthalide derivative such as **III-19** with Michael acceptor **III-20** in 1978 (eq 1, *Scheme 3.2*). The phenylsulfonyl group

functioned as a leaving group to allow aromatization following annulation. The same annelation strategy was studied and applied in the total synthesis of (–)-Hongconin by Swenton and coworkers[16]. A similar reaction using the anion of phthalide **III-25** was developed[17] by Mal (eq 3, *Scheme 3.2*). The proposed mechanism involves Michael addition, followed by Dieckmann cyclization, then intramolecular nucleophilic attack to form carbonate and finally fragmentation to give **III-27** with loss of CO_2 and MeO^-. With the advance in the transition-metal catalyzed coupling reactions, cross-coupling/condensation strategy has been used to make 1-naphthols. Jiang and coworkers developed[18] the synthesis of 1-naphthols containing multifunctional groups catalyzed by CuCl under mild condition (eq 2, *Scheme 3.2*). Arylation of methyl 3-(2-bromophenyl)-3-oxopropanoate **III-22** with a variety of β-keto esters, ketones and nitriles, followed by aldol condensation provided a desired 1-naphthol such as **III-24** with good yield. In 2014, Chen and coworkers reported an arylation/cyclization cascade of o-iodoacetophenones and methyl ketones catalyzed by CuI/1,10-phen in the presence of NaO*t*Bu condition (eq 4, *Scheme 3.2*). This gave 1-naphthols with aryl or alkyl substituent on the 3-position in good to excellent yields under mild conditions[19]. In 2016, Yu, Bao and coworkers demonstrated[20] a similar CuI catalyzed NaO*t*Bu promoted S_NAr reactions between two molecules of o-haloacetophenones (I, Br, Cl) to provide 3-(2-halophenyl)-naphthalen-1-ol derivatives in moderate to good yield (22-76%) (not shown).

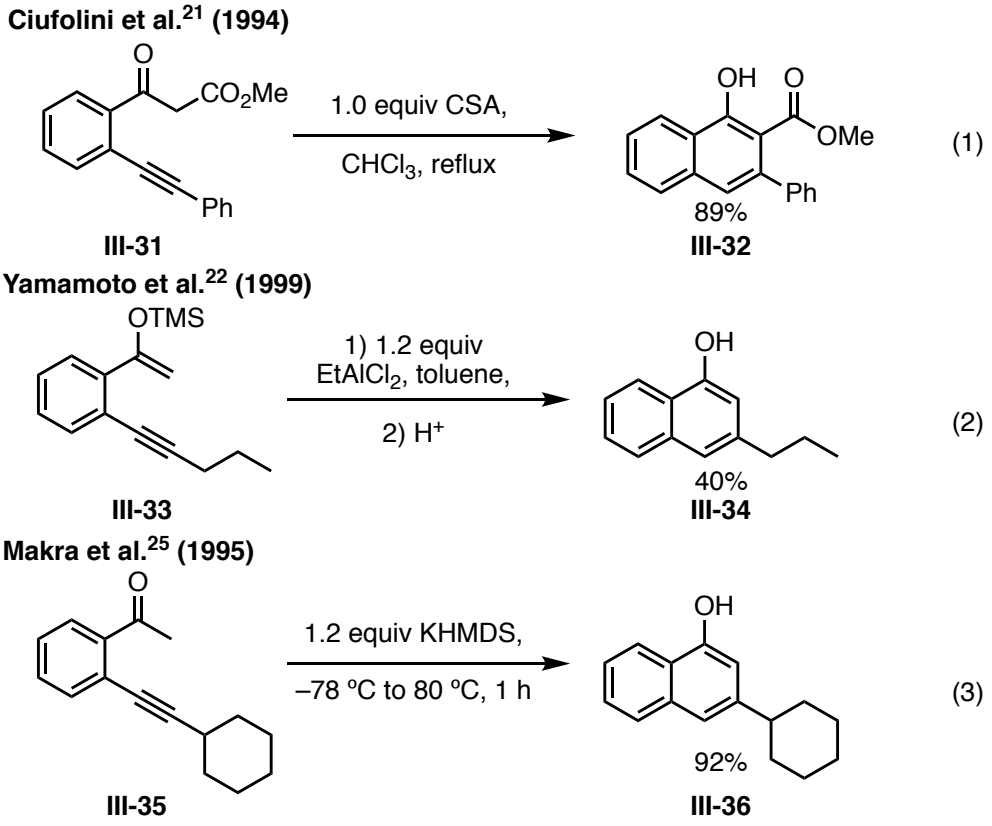
Scheme 3.2 Synthesis of 1-naphthols via addition/condensation cascade



The higher energy π-system of alkynes have also been employed in the formation of naphthol rings. The cycloaromatization could be promoted by Lewis and Brønsted acids or bases. Ciufolini and Weiss described[21] the use of camphorsulfonic acid (CSA) as a trigger for cyclization of *ortho*-alkynylphenyl-β-ketoesters **III-31** to form 2,3-disubstituted 1-naphthols in excellent yields (eq 1, *Scheme 3.3*). Yamamoto and coworkers reported[22] one preliminary example of the benzannulation of silyl enol ether **III-33** promoted by the Lewis acid $EtAlCl_2$ (eq 2, *Scheme 3.3*). Similar reactions of silyl enol ethers have been reported using transition metal catalysts such as $AgSbF_4$[23] and

$[Rh(CO)_2Cl]_2$[24]. In 1995, Makra and coworkers reported the syntheses of a variety of 3-alkyl-1-naphthols by treating the *ortho*-alkynylalkyl acetophenone substrates such as **III-35** with potassium bases (e.g. KOtBu, KHMDS or KOH) (eq 3, *Scheme 3.3*). They proposed[25] a mechanism involving acetylene to allene isomerization, followed by rapid allenyldiene electrocyclization. A similar strategy has been developed[26] for the syntheses of a series of multi-substituted-1-naphthols.

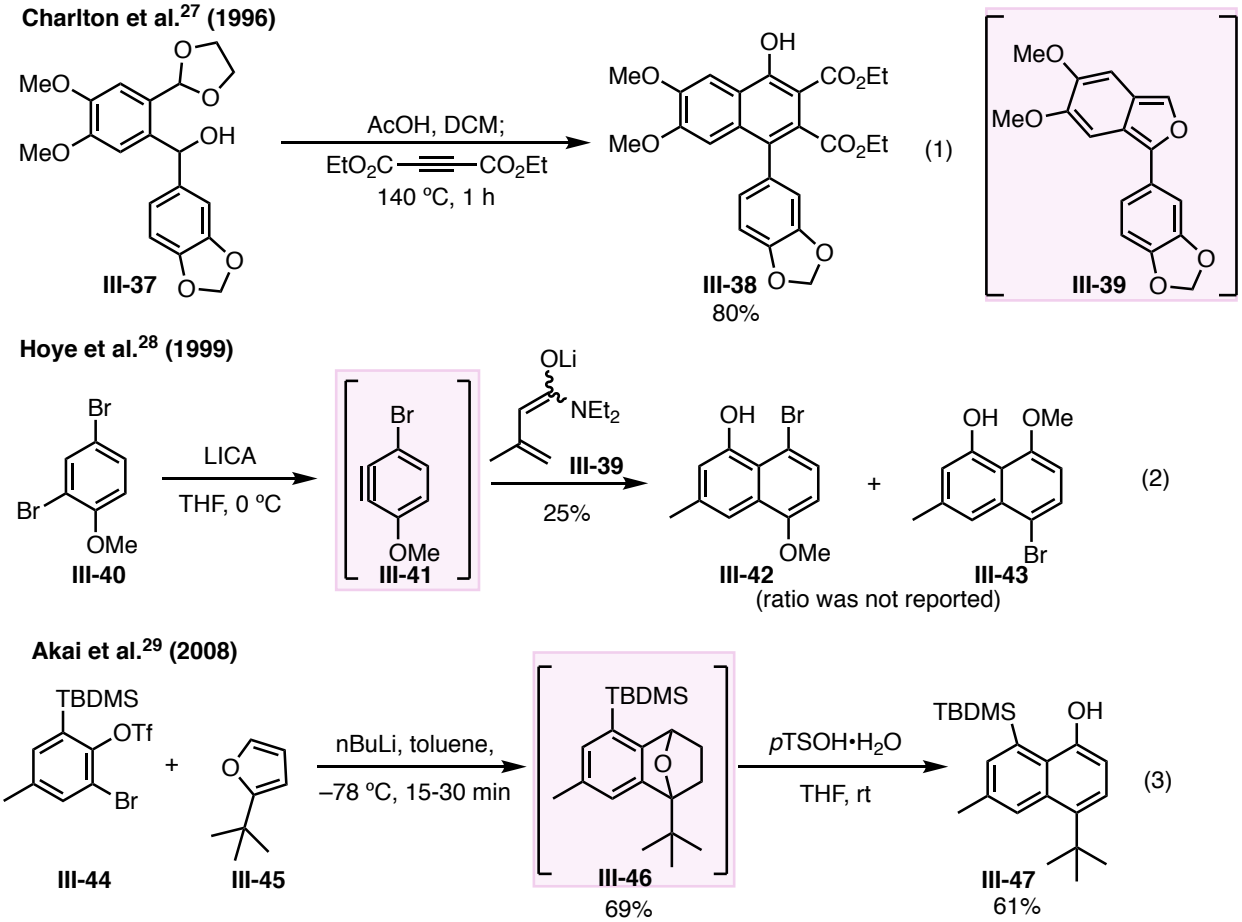
Scheme 3.3 Acid/base-promoted cycloaromatization



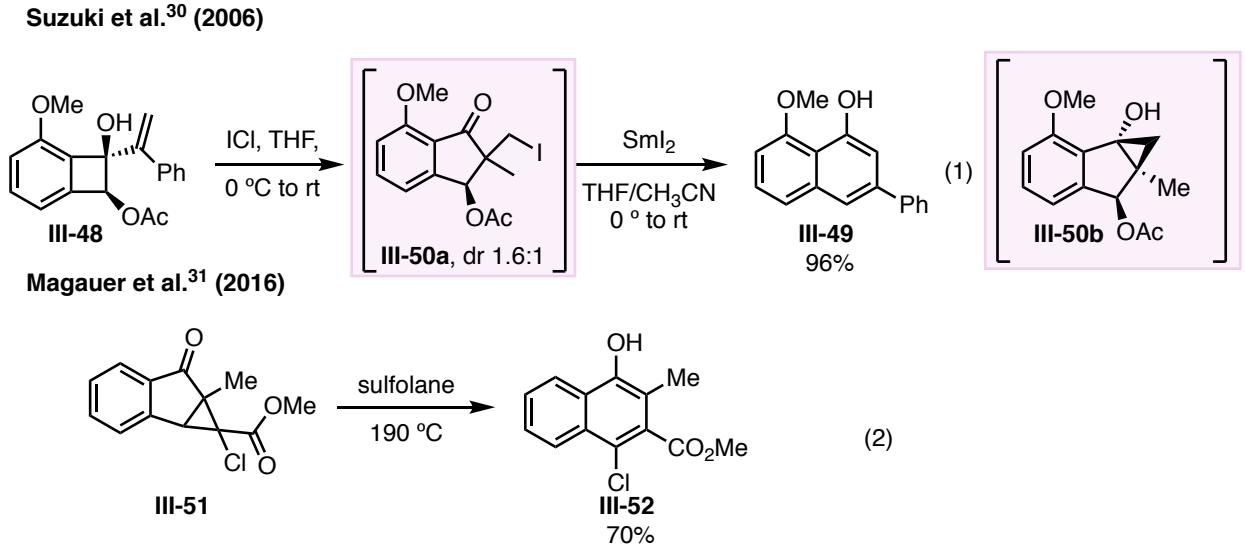
Another way to make substituted 1-naphthols that has been used frequently is via Diels Alder reactions of alkynes or benzynes. Charlton and coworkers have utilized[27] hydroxyl acetals, such as **III-37**, as precursors to isobenzofurans **III-39** which can react with acetylenes to make the multi-substituted 1-naphthol **III-38** in 80% yield (eq 1,

Scheme 3.4). Hoye and coworkers reported[28] a DA reaction of the transient benzyne **III-41** with preformed dienolate anion **III-39** to form naphthol **III-42** and **III-43** as a mixture in only 25% yield despite considerable attempts at optimization (eq 2, *Scheme 3.4*). They had to developed an alternative, multistep synthesis in order to get access to their desired product **III-43**. Akai and coworkers utilized[29] a 3-TBDMS-substitutedbenzyne, generated in situ by treatment of **III-44** with nBuLi, to react with 2-*t*butylfuran **III-45** to afford the DA adduct **III-46** with high regioselectivity. The isomerization to 1-naphthol **III-47** was achieved by treatment with *p*TsOH•H_2O in good yield (eq 3, *Scheme 3.4*).

Scheme 3.4 Synthesis of 1-naphthols via Diels Alder [4+2] cycloaddition



Scheme 3.5 Synthesis of 1-naphthols via ring expansion



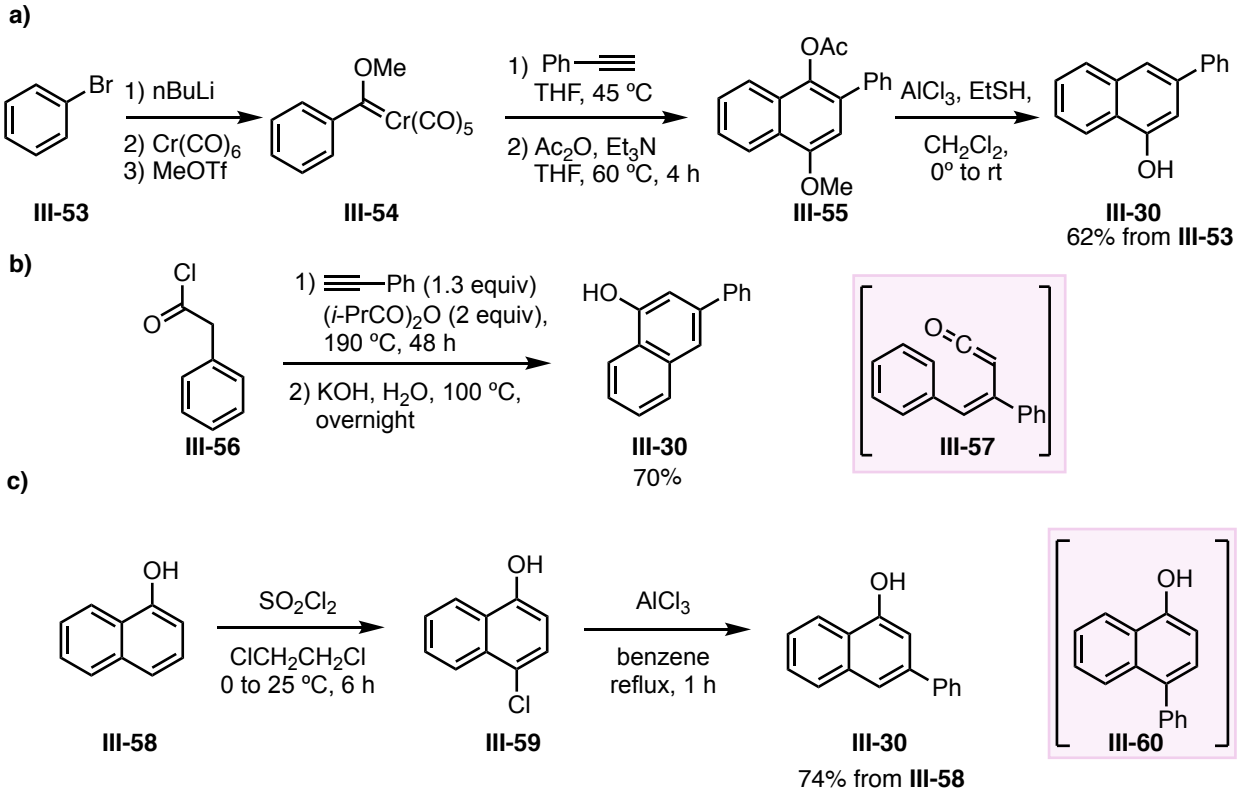
Ring expansion strategies have not yet been employed extensively in the synthesis 1-naphthols. Suzuki and coworkers reported[30] a 4–>5–>6 tandem ring expansion process to generate 1-naphthol derivatives (eq 1, *Scheme 3.5*). After the first reaction with ICl, **III-48** was converted into the iodomethyl indanone **III-50a** in excellent yield, which will generate intermediate **III-50b** upon treatment of SmI_2 in one pot. Subsequent Grob fragmentation of cyclopropanol intermediate **III-50b** gave **III-49** in excellent yield. More recently, Magauer demonstrated[31] a thermally induced electrocyclic ring opening with simultaneous 1,2-chlroride migration of indanone-cyclopropane **III-51**, which is readily available from indanones via oxidation and cyclopropanation (eq 2, *Scheme 3.5*). The usefulness of their methodology was demonstrated in the total synthesis of chartarin.

3.2 Syntheses of 3-phenyl-1-naphthol

The original route[1] to the VANOL monomer 3-phenyl-1-naphthol **III-30** developed by Wulff and coworkers involved a benzannulation reaction of vinylketene intermediates generated either from the reaction of alkyne with carbene complex (a, *Scheme 3.6*) or

from the reaction of alkyne with an aryl ketene. The large-scale of cycloaddition/electrocyclization cascade (CAEC) of the latter has also been developed by the Wulff group[4] (b, *Scheme 3.6*). This route proved to be effective for the syntheses of a large number of VANOL derivatives[5].

Scheme 3.6 Synthesis of VANOL monomer **III-30**



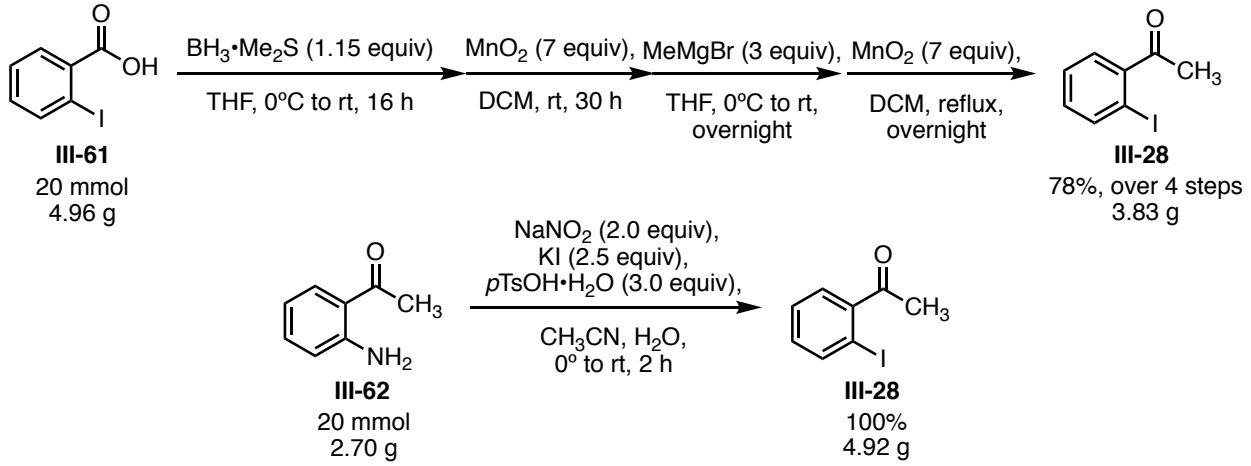
Several alternative routes were examined[32] in an effort to identify a more cost-efficient process for the VANOL monomer. It was found that the most efficient approach involves a $AlCl_3$-assisted tautomerization and a 1,2-migration of the phenyl group in 4-phenyl-1-naphthol **III-60**, which is generated in situ from the reaction of 4-chloro-1-naphthol **III-59** with $AlCl_3$ and benzene (c, *Scheme 3.6*). However, the substrate scope of this process is limited. Therefore, the CAEC process is the route of choice when it comes to the synthesis of VANOL and VAPOL derivatives.

Even though the CAEC process has a broad scope in constructing VANOL ligands with substituents on the 5,5'- and 7,7'- positions with good yields, it suffers from several drawbacks. First, the process requires heating at a high temperature over a long period of time (48 h). Second, large amounts of sensitive reagents (acid chloride, $SOCl_2$ or $(COCl)_2$ and KOH) that need special handling are used in the process. Third, various substituted phenyl acetylenes are not commercially available or are costly. In an effort to develop an alternative synthesis of substituted VANOL monomers, the recent method developed by Chen and coworkers (eq 4, *Scheme 3.2*) seemed to have practical potentials. This procedure starts from commercially available o-iodoacetophenones and methyl ketones, many of which are inexpensive compared with phenylacetylene derivatives. A large amount of base (6 equiv) was employed but the reaction time is relatively short at room temperature. Attempts to reproduce their method and to utilize it in the synthesis of VANOL monomers were undertaken.

Although 2'-iodoacetophenone **III-28** is commercially available, the relative high cost ($95/25 g, combi-blocks) prompted an exploration of alternative synthetic routes from cheap aromatic precursors. Two starting materials were identified: 2'-aminoacetophenone **III-62** ($55/100 g, combi-blocks) and 2-iodobenzoic acid **III-61** ($40/100 g, combi-blocks). The syntheses were planned and carried out as shown in *Scheme 3.7*. The optimized synthesis from **III-61** involves reduction to (2-iodophenyl)methanol by $BH_3 \cdot Me_2S$, followed by oxidation to aldehydes and then reacting with methyl Grignard reagent. Finally, oxidation of the secondary alcohol with MnO_2 afforded desired **III-28**. The whole process required only one flash column

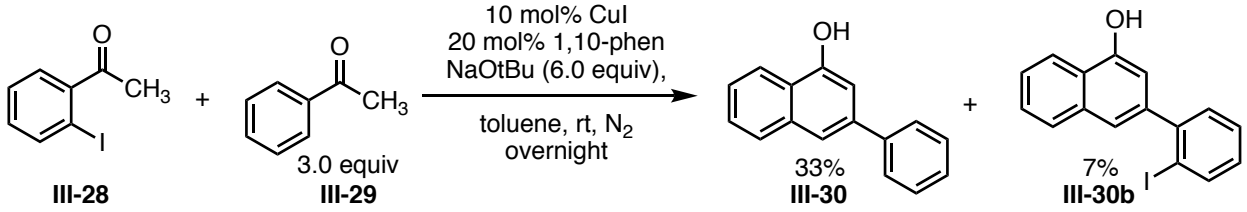
chromatography and gave 78% overall yield. Shorter routes such as direct reaction[33] of benzoic acid with 3 equiv of MeMgBr or a Weinreb ketone synthesis were attempted but did not gave clean conversions. The Sandmeyer reaction[34] with **III-62** as starting material on the same scale proved to be more effective and provided ketone **III-28** in quantitative yield.

Scheme 3.7 Synthesis of 2'-iodoacetophenone **III-28**



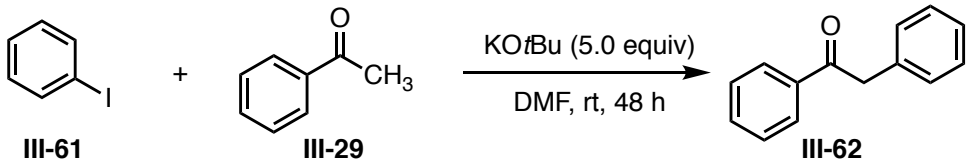
With the 2'-iodoacetophenone in hand, an attempt was made to repeat the reaction by Chen et al. (eq 4, *Scheme 3.2*) under the reported conditions except that the reaction was carried out in a round bottom flask instead of in a sealed tube (*Scheme 3.8*). The yield of desired product **III-30** was significantly lower than the 85% yield reported and was formed along with a 7% yield (NMR analysis) of the major side product **III-70b** from self-coupling/cyclization. It should be noted that the CuI catalyst used was not freshly purified (purified ~ 4 weeks ago), which might be one of the sources of the inconsistency.

Scheme 3.8 Copper-catalyzed coupling/cycloaromatization reaction



III-28 **III-29** **III-30** **III-30b**

Scheme 3.9 Base-promoted arylation of acetophenone **III-29** with iodobenzene



III-61 **III-29** 2.0 equiv **III-62** 92%

Nevertheless, it was still deemed worthwhile to develop the reaction into a more reliable and efficient process that could be applied to the synthesis of VANOL ligands. Attention was quickly drawn to a transition-metal-free α-arylation of enolizable aryl ketones with aryl iodides using KO*t*Bu in DMF as reported[35] by Taillefer et al (*Scheme 3.9*). The mechanistic studies and DFT calculations suggested a radical process. A plausible arylation/aldol condensation/rearromatization process was envisioned and attempted. 2'-iodoacetophenone **III-28** was added to a mixture of 2 equiv acetophenone and KO*t*Bu solution in DMF. Pleasingly, the desired 3-aryl-1-naphthol **III-30** was isolated in 57% yield after stirring for 12 h. The side product **III-30b** resulted from self-coupling of **III-28** was difficult to isolated from the major product **III-30** by column chromatography but could be observed in the ^{1}H NMR spectrum.

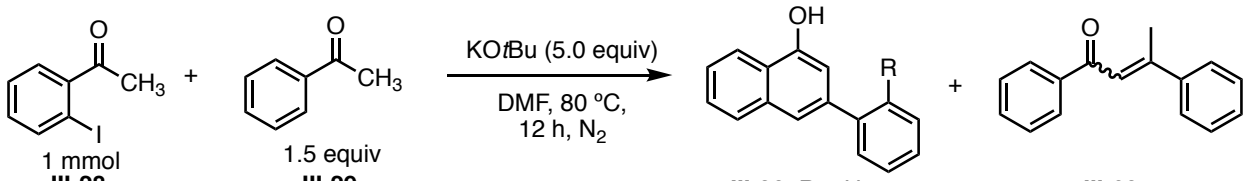
The combined yield of **III-30** and **III-30b** is reported for the initial optimizations (*Table 3.1- Table 3.5*) without taking a ^{1}H NMR analysis. This was done because when the ratio of **III-30** and **III-30b** was large (>10:1), as in the cases of the reactions with

KO*t*Bu, they can be partially separated with some efforts by silica gel column chromatography. However, later findings (Scheme 3. 11, *Table 3.5- Table 3.6*) indicated that when the ratio became closer (<5:1), these two compounds were indistinguishable by flash column chromatography (silica gel) or TLC analysis, which casted a shadow on the results of the initial optimizations.

Not surprisingly, the aldol condensation product of acetophenone **III-63** could be isolated (5-18%) as a major side product in the reactions (entry 1-3, *Table 3.1*). For the development later, it was isolated out and its amount was not determined. Decreasing the equivalent of acetophenone from 2.0 to 1.5 increase the yield slightly (entry 1 vs 2, *Table 3.1*). Further decrease to 1.2 equiv did not show a positive effect (entry 7, *Table 3.1*). The temperature effect was studied (entry 3 and 4, *Table 3.1*). Significant increase of side reaction (18% **III-63**) was observed from the reaction at 60 ºC, and yield of 1-naphthol dropped to 33%. Higher temperature did not increase the yield for the reaction. Amount of the base was also screened. Both the reaction with higher or lower equiv of KO*t*Bu afford the desired 1-naphthol in lower yield (entry 5 and 6, *Table 3.1*). In agreement of the original report[35], the reaction proved to be sensitive to the effect of solvent: yield of product dropped to 26% in DMSO and only trace amount of 1-naphthol is produced in toluene (entry 8 and 9, *Table 3.1*). Elongation of the reaction time decreased the yield, presumably due to the decomposition of the product (entry 10, *Table 3.1*). And lastly, the concentration effect was not significant (entry 11 and 12, *Table 3.1*). Therefore, it was decided to quench the reaction early to avoid decomposition. The reaction with 1.1 equiv **III-29** in a more concentrated (0.67 M) DMF solution was quenched after 3 h and afford the 1-naphthol in

57% yield (entry 13, *Table 3.1*). Sticking with 1.1 equiv of acetophenone, more solvent and less reaction time gave only 30% yield, expectedly (entry 14, *Table 3.1*). The yield can be improved by increasing the reaction time (entry 15 vs 14, *Table 3.1*), increasing the amount of base (entry 16, *Table 3.1*) or increasing the reaction temperature (entry 17, *Table 3.1*). The sodium base NaO*t*Bu gave poor conversion, which is also consistent with the original report[35].

Table 3.1 Initial optimization of the arylation/cycloaromatization reaction

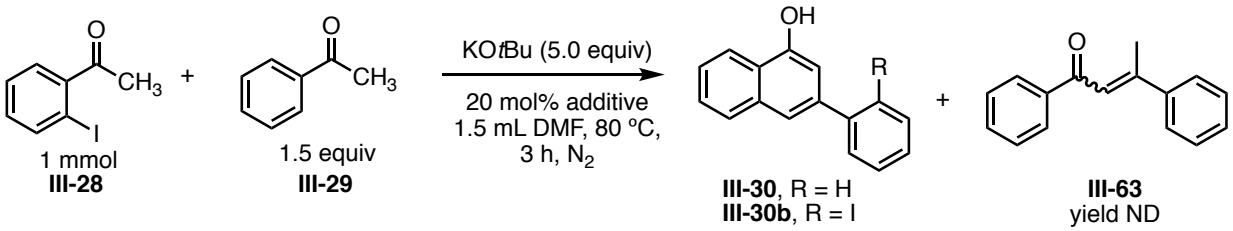


entry	variation from "standard conditions[a]"	%yield[b] (**III-30**+**III-30b**)
1	none	61[c]
2	2.0 equiv **III-29**	57[d]
3	2.0 equiv **III-29**, 60 °C	33[e]
4	2.0 equiv **III-29**, 100 °C	59
5	4.0 equiv KO*t*Bu, 15 h	39
6	8.0 equiv KO*t*Bu	44
7	1.2 equiv **III-29**	59
8	toluene instead of DMF	trace
9	DMSO instead of DMF	26
10	24 h	55
11	1.5 mL DMF	60
12	6.0 mL DMF	56
13	1.5 mL DMF, 1.1 equiv **III-29**, 3 h	**57**
14	1.1 equiv **III-29**, 1 h	30
15	1.1 equiv **III-29**, 3 h	53
16	1.1 equiv **III-29**, 7.0 equiv KO*t*Bu, 1 h	48
17	1.1 equiv **III-29**, 100 °C, 1 h	52
18	entry 15, NaO*t*Bu instead of KO*t*Bu	14

[a]Reaction was carried out in Schlenk Flask. [b]Isolated yield of mixuture of **III-30/III-30b** after chromatography on silica gel. [c]6% of **III-63** was isolated. [d]5% of **III-63** was isolated. [e]18% of **III-63** was isolated.

In order to increase the yield of the desired 1-naphthol product, the effects of additives were extensively studied. The conditions in entry 13 *Table 3.1* was selected as optimal condition for the additive study (*Table 3.2*). Inorganic potassium salts did not have a positive effect on the yield (entry 2-4 vs 1, *Table 3.2*). Amine bases, such as Et_3N and iPr_2NEt, showed slightly positive to no effect on the yield (entry 5-6 vs 1, *Table 3.2*). Coordinating N-containing heteroaromatics as well as PPh_3 decreased the yield slightly (entry 7-11 vs 1, *Table 3.2*). Surprisingly, the yield decreased significantly with 5 mol% $Pd(OAc)_2$ (entry 12 vs 1, *Table 3.2*). Common Lewis acids, such as $AlCl_3$, $ZnCl_2$ and $B(OPh)_3$, as well as nickel complexes and silver nitrate decreased the yield considerably (entry 16-21 vs 1, *Table 3.2*). It was delightful to observed that almost all of the copper salts tested (except Cu-TMEDA) showed positive effects on the yield of the 1-naphthol (**III-30** and **III-30b)** (entry 13-15, 22-28 vs 1, *Table 3.2*). The reaction with Cu(II) additive gave slightly higher yield than Cu(I) salt (entry 24-28 vs 13-15 & 22, *Table 3.2*). In the presence of TEMPO additive, the reaction did not shut down but became less effective (entry 29, *Table 3.2*)., which suggested that a closed-shell mechanism might be operative alongside the radical pathway. $CuCl_2$ was identified as the optimal additive and the reaction with 20 mol% $CuCl_2$ was subjected to further optimizations.

Table 3.2 Additive effect study of the arylation/cycloaromatization reaction[a]



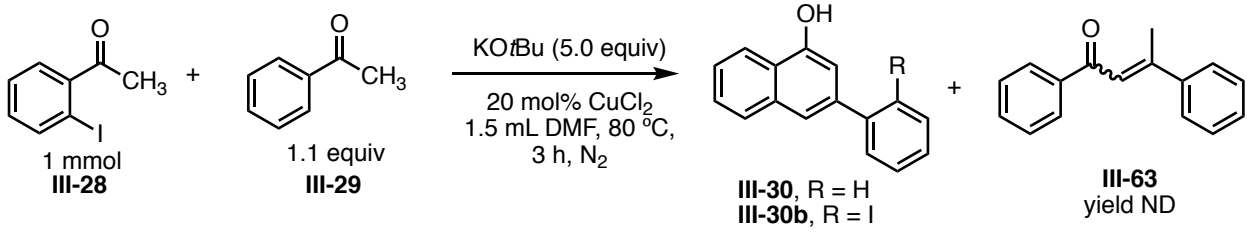
entry	additive	%yield[b] (**III-30**+**III-30b**)	entry	additive	%yield[b] (**III-30**+**III-30b**)
1	none	57	16	$AlCl_3$	42
2	KI	50	17	$ZnCl_2$	48
3	KOAc	56	18	$B(OPh)_3$	34
4	K_3PO_4	52	19	$AgNO_3$	25
5	Et_3N	59	20	$Ni(acac)_2$	31
6	DIPEA	57	21	$dppeNiCl_2$	26
7	PPh_3	53	22	CuCN	65
8	imidazole	53	23	Cu-TMEDA	53
9	pyridine	54	24	$Cu(acac)_2$	64
10	pyrrolidine	55	25	$CuBr_2$	66
11	phenanthroline	38	**26**	**$CuCl_2$**	**71**
12	5 mol% $Pd(OAc)_2$	29	27	$CuSO_4$	67
13	CuI	61	28	$Cu(OTf)_2$	68
14	CuBr	58	29	TEMPO	21
15	CuCl	59			

[a]Reaction were carried out in a Schlenk Flask. [b]Isolated yield of mixuture of **III-30/III-30b** after chromatography on silica gel.

The additive and solvent screening for $CuCl_2$-catalyzed reaction was carried out (*Table 3.3*). It was indicated that the reaction was not relatively sensitive to the water residue in the acetophenone and solvent (entry 2 vs 1, *Table 3.3*). Addition of common ligand for coppers such as 1,10-phenanthroline, BINAP and DMEDA did not increase the yield of the 1-naphthol product (entry 3-6 vs 1, *Table 3.3*). Interestingly, the $CuCl_2$ catalyzed reaction still gave 59% of 1-naphthol (**III-30** and **III-30b**) in the presence of 20 mol% TEMPO, indicating the major pathway should be a two-electron process (entry 7, *Table 3.3*). Reactions in other common solvents did not gave better results, and no **III-30** was isolated from the reactions in Et_3N or hexanes, probably due to the unfavorable coordination and solubility, respectively (entry 8-15 vs 1, *Table 3.3*). In contrast to the

reaction without $CuCl_2$ (entry 18 vs 1, *Table 3.1*), other strong sodium base such as NaO*t*Bu or NaH gave comparable results under the $CuCl_2$-catalyzed conditions (entry 16-17 vs 1, *Table 3.3*). Finally, the catalyst loading study showed that 10 mol% catalyst was sufficient to provide III-30 in 72% yield (entry 18-20 vs 1, *Table 3.3*).

Table 3.3 Optimization of $CuCl_2$-catalyzed arylation/cycloaromatization reaction



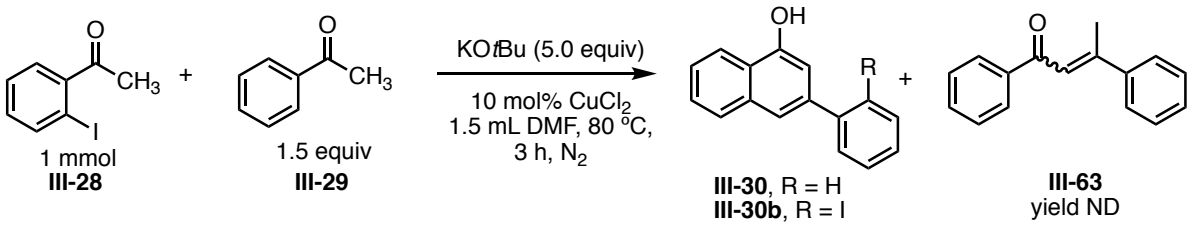
entry	variation from "standard conditions[a]"	%yield[b] (**III-30**+**III-30b**)
1	none	73
2	**III-29** and DMF used without distillation	71
3	with 20 mol% Phen	67
4	with 20 mol% BINAP	69
5	with 20 mol% Et_3N	72
6	with 20 mol% DMEDA	70
7	with 20 mol% TEMPO	59
8	DMA instead of DMF	59
9	Et_3N instead of DMF	0
10	*t*BuOH instead of DMF	49
11	THF instead of DMF	32
12	dioxane instead of DMF	55
13	HMPA instead of DMF	15
14	DMSO instead of DMF	14
15	hexanes instead of DMF	0
16	NaO*t*Bu instead of KO*t*Bu	73
17	NaH instead of KO*t*Bu	74
18	100 mol% $CuCl_2$	53
19	5 mol% $CuCl_2$	62
20	10 mol% $CuCl_2$	72

[a]Reaction was carried out in Schlenk Flask. [b]Isolated yield of mixuture of **III-30/III-30b** after chromatography on silica gel.

The conditions with 10 mol% $CuCl_2$ were further optimized (*Table 3.4*). It was found that the yield of (**III-30** and **III-30b**) increased when 1.5 equiv acetophenone was employed (entry 2 vs 1, *Table 3.4*). However, a further increase in the amount of

acetophenone to 2.0 equiv led to a decreased yield, presumably due to the side aldol reaction (yield not determined) that consumed the KO*t*Bu (entry 3 vs 2, *Table 3.4*). Modifications to the temperature, concentration, catalyst loading and reaction time did not give higher yield (entry 4-7 vs 2, *Table 3.4*). The reaction with 50 mg 3 Å MS gave the same result, whereas the 4 Å and 5 Å MS gave lower yield (entry 8-10 vs 2, *Table 3.4*). Expectedly, using NaH and NaO*t*Bu instead of KO*t*Bu gave comparable results (entry 11-12 vs 2, *Table 3.4*). In contrast to the experiment with 20 mol% $CuCl_2$ (entry 18 vs 1, *Table 3.3*). the reaction in dimethylacetamide (DMA) provide the 1-naphthol in slightly higher yield (entry 13 vs 2, *Table 3.4*). It was found that the reaction with 5 mol% loading of $CuCl_2$ in 3 mL DMF provided the highest yield with either KO*t*Bu or NaH (entry 14 & 17 vs 2, *Table 3.4*). Under these new conditions, using DMA as solvent instead of DMF with NaO*t*Bu as base were found to be less effective (entry 15 & 16 vs 14, *Table 3.4*). The reaction with 5 equiv NaH and 2 mol% $CuCl_2$ at rt afforded the 3-aryl-1-naphthol in 92% yield but a longer reaction time was needed (entry 19, *Table 3.4*). The reactions using NaH as base can be reproduced in a round bottom flask and can be scaled up to 5 mmol with comparable yield.

Table 3.4 Further optimization of $CuCl_2$-catalyzed arylation/cycloaromatization reaction

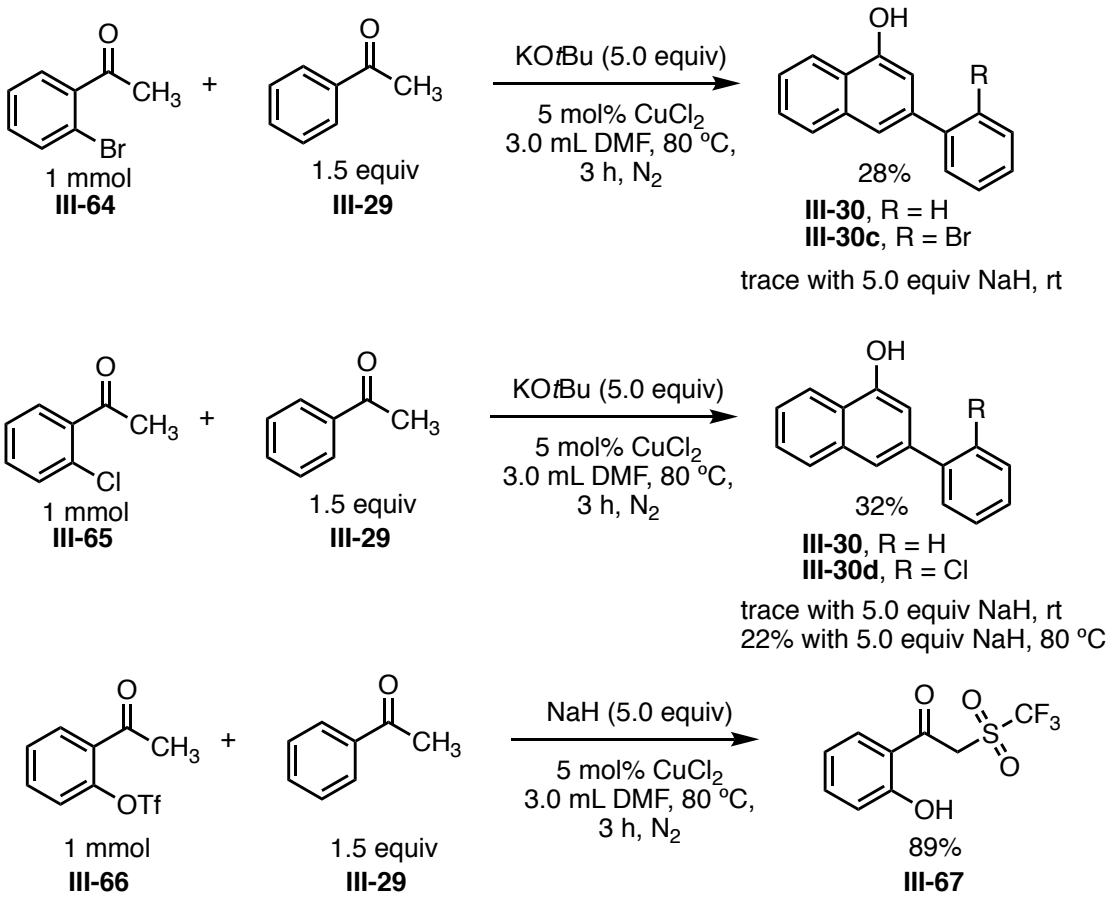


entry	variation from "standard conditions[a]"	%yield[b] (**III-30**+**III-30b**)
1	1.1 equiv **III-29**	72
2	none	85
3	2.0 equiv **III-29**	64
4	100 °C	81
5	3 mL DMF, 5 h	71
6	5 mol% $CuCl_2$, 5 h	81
7	12 h	79
8	with 50 mg 3 A MS	85
9	with 50 mg 4 A MS	71
10	with 50 mg 5 A MS	48
11	NaH instead of KO*t*Bu	78
12	NaO*t*Bu instead of KO*t*Bu	80
13	DMA instead of DMF	87
14	**5 mol% $CuCl_2$, 3 mL DMF**	**88**
15	entry 14, NaO*t*Bu instead of KO*t*Bu	68
16	entry 14, DMA instead of DMF, 1.5 h	65
17	entry 14, NaH instead of KO*t*Bu	91
18	entry 17, 1 h	84
19	entry 17, 2 mol% $CuCl_2$, 15 h, rt	92
20	entry 17, in RBF	87
21	entry 17, 5 mmol scale	88

[a]Reactions were carried out in a Schlenk Flask. [b]Isolated yield of mixuture of **III-30/III-30b** after chromatography on silica gel.

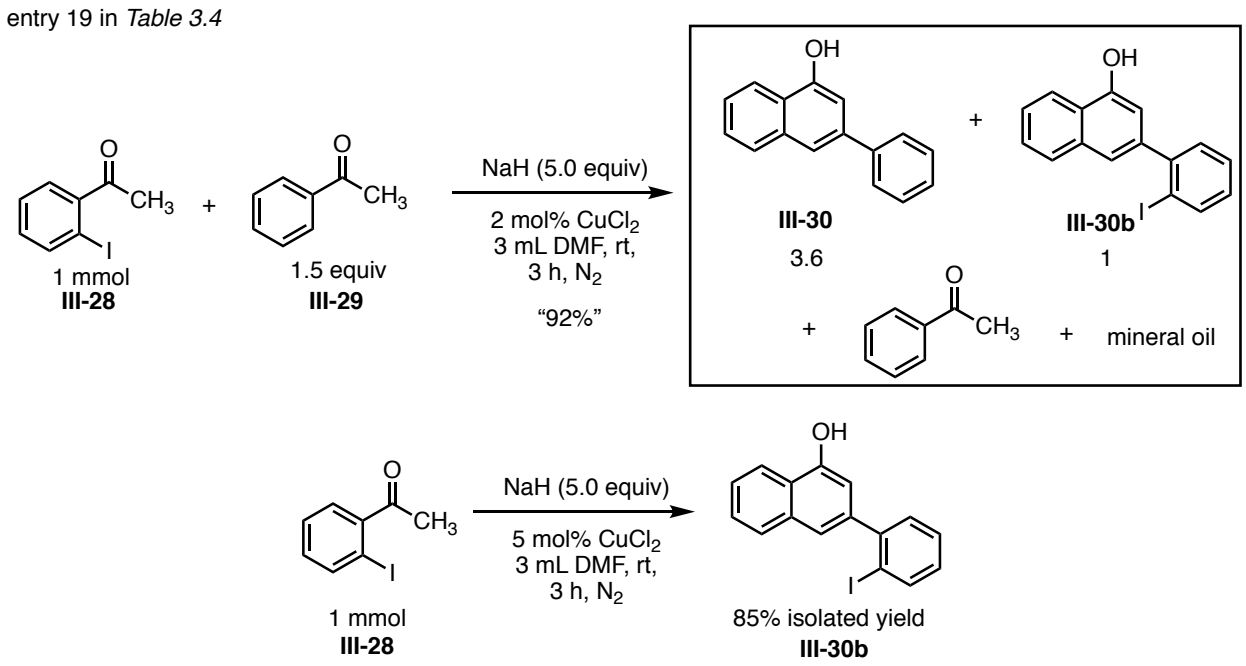
The reactions with other ortho-haloacetophenones were explored (*Scheme 3.10*). For the *ortho*-bromoacetophenone **III-64** and *ortho*-chloroacetophenone **III-65**, the reactions with KO*t*Bu at 80 °C only provide the 3-aryl-1-naphthol in low yields. The reactions were less effective with NaH at 80 °C and only a trace amount of 3-aryl-1-naphthol was observed at rt. Interestingly, migration of sulfur group to the methyl occurred to give the sulfone **III-67** when 2'-OTf acetophenone **III-66** was subjected to the conditions with NaH.

Scheme 3.10 $CuCl_2$-catalyzed arylation/cycloaromatization reaction with other o-haloacetophenone substrates



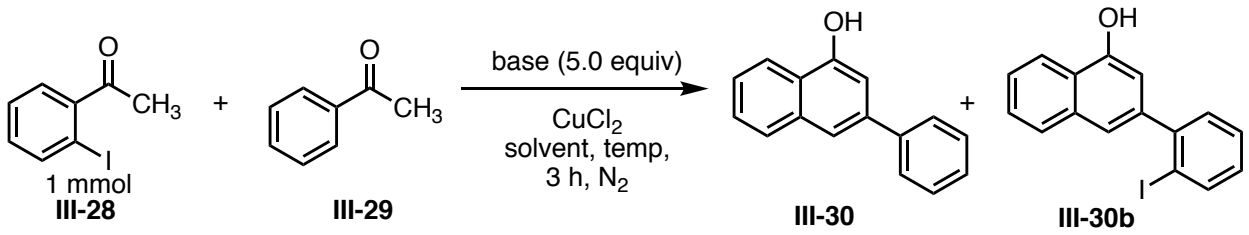
It was a disappointment to find out from the ^1H NMR spectrum that the isolated product obtained consist of a 3.6 : 1 ratio of desired product **III-30** and **III-30b** under the optimal conditions with NaH, together with a small amount of unreacted **III-29** and mineral oil (from NaH). To confirm the structure of **III-30b**, arylation/cycloaromatization was carried out without acetophenone. The 3-(2-iodophenyl)-1-naphthol **III-30b** was obtained in 85% isolated yield.

Scheme 3.11 ^{1}H NMR analysis of the mixtures of 3-aryl-1-naphthols



In order to reduce the amount of **III-30b**, further optimization was performed where the yield and ratio of **III-30**/**III-30b** was monitored by ^{1}H NMR analysis (*Table 3.5*). It was found that KO*t*Bu is the best base in terms of yield and selectivity of the reaction (entry 1 vs 2 & 4, *Table 3.5*). The effectiveness of NaH in the synthesis of **III-30** judged by the previous optimization was not very accurate because of the larger weight of the **III-30b** in the inseparable mixture. The reaction in DMA gave **III-30** in lower yield and selectivity than that in DMF (entry 3 vs 1, *Table 3.5*). The yield and selectivity went down when the $CuCl_2$ loading was reduced to 5 mol% (entry 5 vs 4, *Table 3.5*). Portionwise addition of the base only provide negligible improvement (entry 6 vs 5, *Table 3.5*). For the reactions with KO*t*Bu as base, increasing the equivalents of **III-29** did not increase the selectivity in spite of the minimal increase in yield (entry 8 vs 7, *Table 3.5*). Addition of KO*t*Bu at 0 ºC did not have a positive effect on the result of the reaction (entry 9 vs 10, *Table 3.5*).

Table 3.5 Optimization of conditions for $CuCl_2$-catalyzed arylation/cycloaromatization reaction[a]



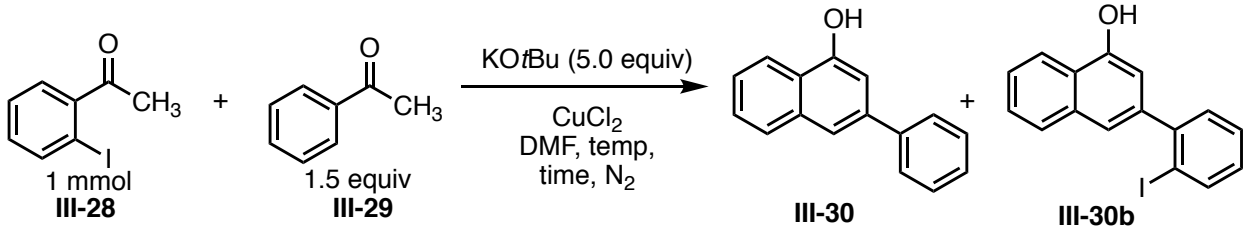
entry	equiv (**III-29**)	base	mol% ($CuCl_2$)	solvent	temp (ºC)	%yield[b] (**III-30**)	ratio[b] (**III-30/III-30b**)
1	1.5	KO*t*Bu	10	1.5 mL DMF	80	62	12.6
2	1.5	NaO*t*Bu	10	1.5 mL DMF	80	51	11.9
3	1.5	KO*t*Bu	10	1.5 mL DMA	80	56	6.9
4	1.5	NaH	10	1.5 mL DMF	rt	42	3.0
5	1.5	NaH	5	1.5 mL DMF	rt	30	1.7
6[c]	1.5	NaH	5	1.5 mL DMF	rt	32	1.9
7	2.0	KO*t*Bu	5	3.0 mL DMF	rt	61	7.5
8	2.5	KO*t*Bu	5	3.0 mL DMF	rt	63	7.6
9	1.5	KO*t*Bu	5	3.0 mL DMF	0 to 40	53	7.1
10	1.5	KO*t*Bu	5	3.0 mL DMF	rt to 40	54	8.4

[a]Reactions were carried out in a round bottom flask. Yield of aldol adduct was not determined. [b]Determined by NMR analysis of the mixture of **III-30** and **III-30b** after chromatography on silica gel with Ph_3CH added as standard. [c]III-29 was added in 3 portions within 1.5 h.

More procedural optimization was performed with 5 equiv KO*t*Bu in DMF (*Table 3.6*). The yield and ratio of **III-30**/**III-30b** increased when the volume of DMF increased from 1.5 mL to 5 mL (entry 1-3, *Table 3.6*). However, increasing the $CuCl_2$ loading decreased the yield and selectivity (entry 4-5 vs 1, *Table 3.6*). On the other hand, both the yield and selectivity for **III-30** increased as the reaction temperature increased (entry 6-7 vs 1, *Table 3.6*). The effect of method for the addition of **III-28** was studied. It was found that a longer waiting time after the addition of **III-29** led to lower selectivities (entry 8-9 vs 6, *Table 3.6*). Not surprisingly, slower addition was found to increase the selectivity (entry 10 vs 11, *Table 3.6*). Further reducing the loading of $CuCl_2$ did not increase the

ratio of **III-30/III-30b** and it was found that the reaction time could be reduced to 30 min (entry 12 & 13, *Table 3.6*). And finally, it was found that under the optimal conditions, the $CuCl_2$-catalyzed arylation/cycloaromatization reaction was complete after 30 min to give the desire product **III-30** in 63% yield with 3% yield of the side product **III-30b** (entry 14, *Table 3.6*, *Scheme 3.12*). Additionally, when 10 mol% 1,10-phen[19] was added, the reaction was less effective (entry 15 vs 14, *Table 3.6*).

Table 3.6 Further optimazation of conditions for $CuCl_2$-catalyzed arylation/cycloaromatization reaction[a]

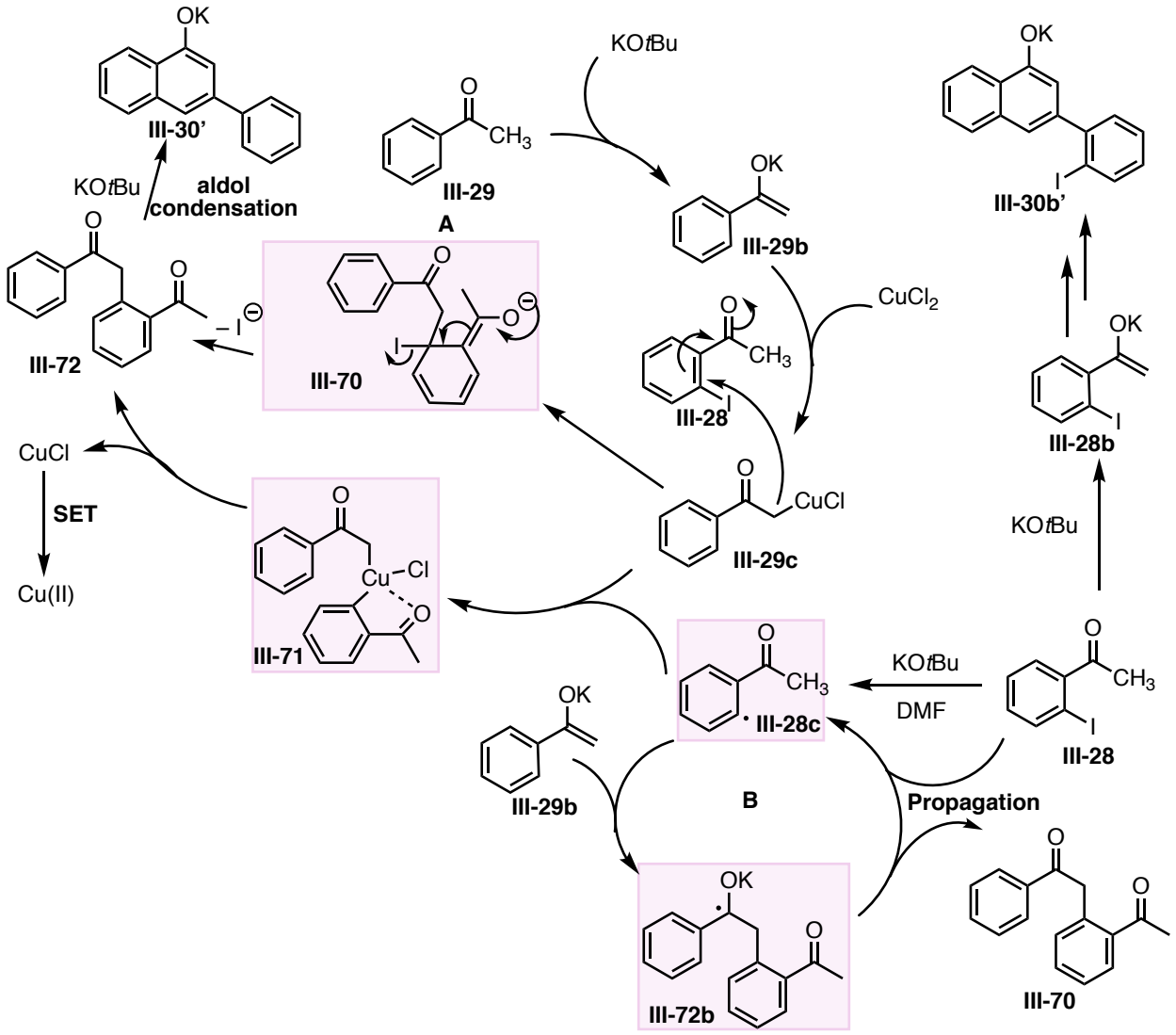


entry	addition sequence (**III-28**)	mol% ($CuCl_2$)	DMF (mL)	time (h)	temp (°C)	%yield[b] (**III-30**)	ratio[b] (**III-30/III-30b**)
1	after 1 min, within 1 min	5	3.0	3	40	53	4.9
2	after 1 min, within 1 min	5	1.5	3	40	32	1.4
3	after 1 min, within 1 min	5	5.0	3	40	55	5.2
4	after 1 min, within 1 min	10	3.0	3	40	50	4.3
5	after 1 min, within 1 min	20	3.0	3	40	45	3.7
6	after 1 min, within 1 min	5	3.0	3	60	55	10.6
7	after 1 min, within 1 min	5	3.0	3	80	63	37.3
8	after 10 min, within 1 min	5	3.0	3	60	56	8.4
9	after 20 min, within 1 min	5	3.0	3	60	60	7.7
10	after 5 min, within 5 min	5	3.0	2	80	58	10.6
11	after 5 min, within 2.5 min	5	3.0	0.5	80	55	6.9
12	after 5 min, within 5 min	2.5	3.0	1	80	60	9.4
13	after 5 min, within 5 min	2.5	3.0	0.5	80	60	8.5
14	**after 1 min, within 5 min**	**5**	**3.0**	**0.5**	**80**	**63**	**22.6**
15[c]	after 1 min, within 5 min	5	3.0	0.5	80	52	13.2

[a]Reactions were carried out in a round bottom flask. o-Iodocetophenone **III-28** was added to the mixure of KO*t*Bu, acetophenone **III-29** and CuCl2 in DMF under the indicated temperature. Yield of aldol adduct was not determined. [b]Determined by NMR analysis of the mixture of **III-30** and **III-30b** after chromatography on silica gel with Ph_3CH added as standard.
[c]10 mol% 1,10-phen was added.

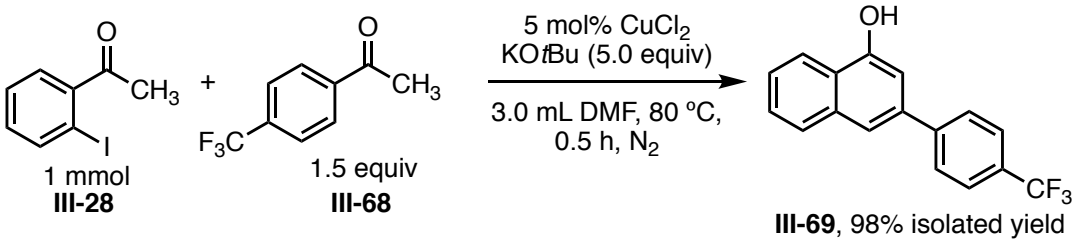
The mechanism of the $CuCl_2$-catalyzed arylation/cycloaromatization reaction is proposed (*Scheme 3.12*) base on literature reports. Two catalytic cycles are thought to be operational: **A** $S_{RN}1$ and **B** S_NAr. In catalytic cycle **B**, in the absence of $CuCl_2$ the radical **III-28c** can be formed[35] with DMF and KO*t*Bu. Nucleophilic attack by enolate **III-29b** generated from acetophenone **III-29** and KO*t*Bu affords radical anion **III-72b**. A final SET from **III-72b** to another molecule of **III-28** releases the diketone **III-72**. In the presence of $CuCl_2$, copper enolate **III-29c** can be generated by transmetallation. Copper enolate **III-29c** can undergo addition-elimination with **III-28** to generate diketone **III-72**. A crossover pathway might occur: the radical **III-28c** react with copper enolate **III-29c** to generate a copper (III) species. Reductive elimination give rise to diketone **III-72**. The Cu(II) could be regenerate by SET process with **III-28.** Diketone **III-72** subsequently undergo aldol condensation to form the potassium base of the desire product **III-30'**. The side product **III-30b'** came from a similar process of the enolate **III-28b**. The higher ratio of **III-30/III-30b** for the reaction with the bulky KO*t*Bu than NaH is thought to due to the higher selectivity in generating **III-29b** vs the more hindered **III-28b**.

Scheme 3.12 Proposed mechanism for $CuCl_2$-catalyzed arylation/cycloaromatization reaction



Based on this proposed mechanism, it was reasoned that if the acetophenone forms an enolate more thermodynamically favorable than **III-28b**, the side product formation would be slowed down. Therefore, electron deficient 4'-(trifluoromethyl)acetophenone **III-68** was subjected to the reaction conditions, the desired product **III-69** could be isolated in excellent yield, no self-coupling side-product was observed.

Scheme 3.13 Synthesis of 3-(4-(trifluoromethyl)phenyl)-1-naphthol



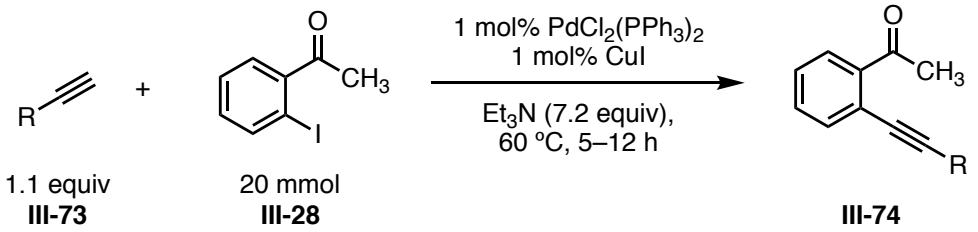
In summary, the $CuCl_2$-catalyzed arylation/cycloaromatization reaction of ortho-iodoacetophenone **III-28** with acetophenone has been developed. Under the optimal conditions, the VANOL monomer can be afforded in good yield within 0.5 h. Compared with the methodology developed by Chen, the conditions are more tolerant with catalyst purity and reaction vessel (entry 14, *table 3.3* vs *Scheme 3.8*). Even though the scope of this methodology was not explored, it was thought be preferable for the synthesis of VANOL monomers with an electron-poor aryl ring at 3-positions.

3.3 Syntheses of 3,3'-dialkyl-VANOL

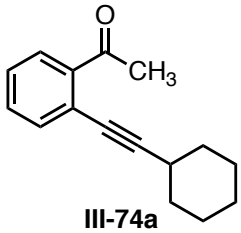
A variety VANOL derivatives have been prepared[5, 36] in the Wullf Group with alkyl or aryl substituents at 4,4'-, 5,5'-, 6,6'-, 7,7'- and 8,8'-postitions either by oxidative coupling of monomers or derivatization by coupling reactions. However, the synthesis of VANOL derivatives with alkyl groups at the 3,3'-position has not been established. The synthesis of 3,3'-didecylVANOL was reported[37] using the CAEC process by Schuster and Redic. Attempt to synthesize 3,3'-Bu_2VANOL by Raney-Ni reduction of 3,3'-dithiophen-2-yl-VANOL was made[38] by Guan. However, no yield was reported. In order to investigate the substituent effect of alkyl groups on the 3,3'-positions of VANOL, an effort was made to synthesize 3,3'-dialkyl VANOLs by employing the base-promoted cycloaromatization reported by Makra (eq 3, *Scheme 3.3*)[25].

The substrates *o*-alkynylacetophenone **III-74a-f** were prepared by the Sonogashira coupling reaction of o-iodoacetophenone **III-28** with the terminal alkynes **III-73a-f**. After a brief optimization of reaction temperature, equivalence of Et_3N and catalyst loading, the optimal conditions with 1mol% $PdCl_2(PPh_3)_2$ and 1 mol% CuI (purified) delivered the desired coupling products **III-74a-f** in excellent yield (67%-100%) on 20 mmol scale (*Scheme 3.14*). The diminished yield of the coupling product from the benzylacetylene was thought to be caused by allene formation by prototropic rearrangement[39].

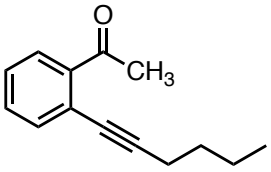
Scheme 3.14 Syntheses of o-alkynylacetophenones **III-74** via the Sonogashira Coupling



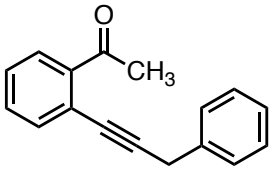
1.1 equiv **III-73** | 20 mmol **III-28** | **III-74**



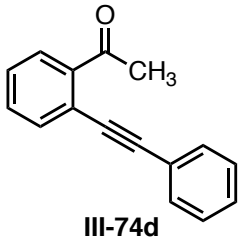
III-74a
100%



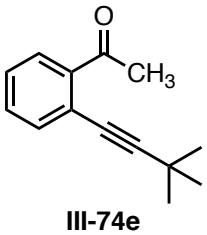
III-74b
97%



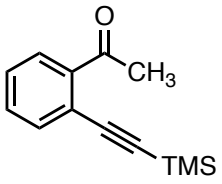
III-74c
67%



III-74d
92%



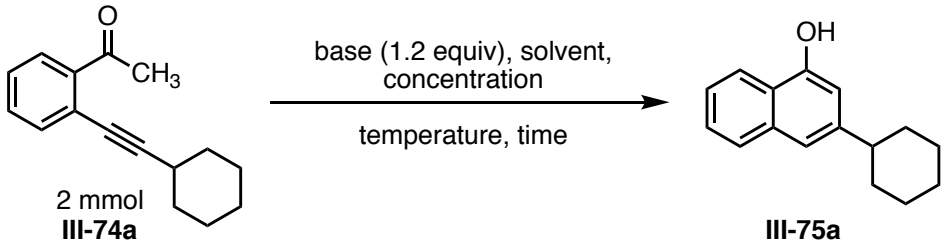
III-74e
97%



III-74f
100%

o-Alkynylacetophenone **III-74a** was chosen as the model substrate for the optimization of the cycloaromatization reaction (*Table 3.7*). It was found that the 3-cyclohexyl-1-naphthol was obtained in 60% yield under the reported procedure[25] (entry 1, *Table 3.7*). It was worth noting that the yield is affected by the quality of the KHMDS solution that was purchased and directly used from bottle. It was delightful to find that the reaction provided **III-75a** in a higher yield with KO*t*Bu in THF (entry 2, *Table 3.7*). The solid base KO*t*Bu was easier to handle and the addition at low temperature (–78 ºC) was not necessary. The weaker base KOH and sodium base NaO*t*Bu did not promote the cycloaromatization, in support of the original finding by Makra and coworkers[25](entry 3 & 4, *Table 3.7*). An unexpected solvent evaporation caused the reduced yield of the product (entry 5 vs 2, *Table 3.7*)., which led us to investigate the concentration effect. Gratifyingly, the reaction performed at a lower concentration gave **III-75a** in higher yield (entry 6 vs 2, *Table 3.7*). The yield increased when the reaction was run for 2 h (entry 7 vs 6, *Table 3.7*). The reaction at 70 ºC only gave 1-naphthol in 53% yield after 4.5 h (entry 8, *Table 3.7*). However, the yield could not be increased by running at a higher temperature (entry 9 vs 7, *Table 3.7*). Finally, the reaction could be carried out on a 10 mmol scale under the optimal conditions to afford the desired product **III-75a** in excellent yield (entry 10, *Table 3.7*).

Table 3.7 Optimization of base-promoted cycloaromatization



2 mmol
III-74a

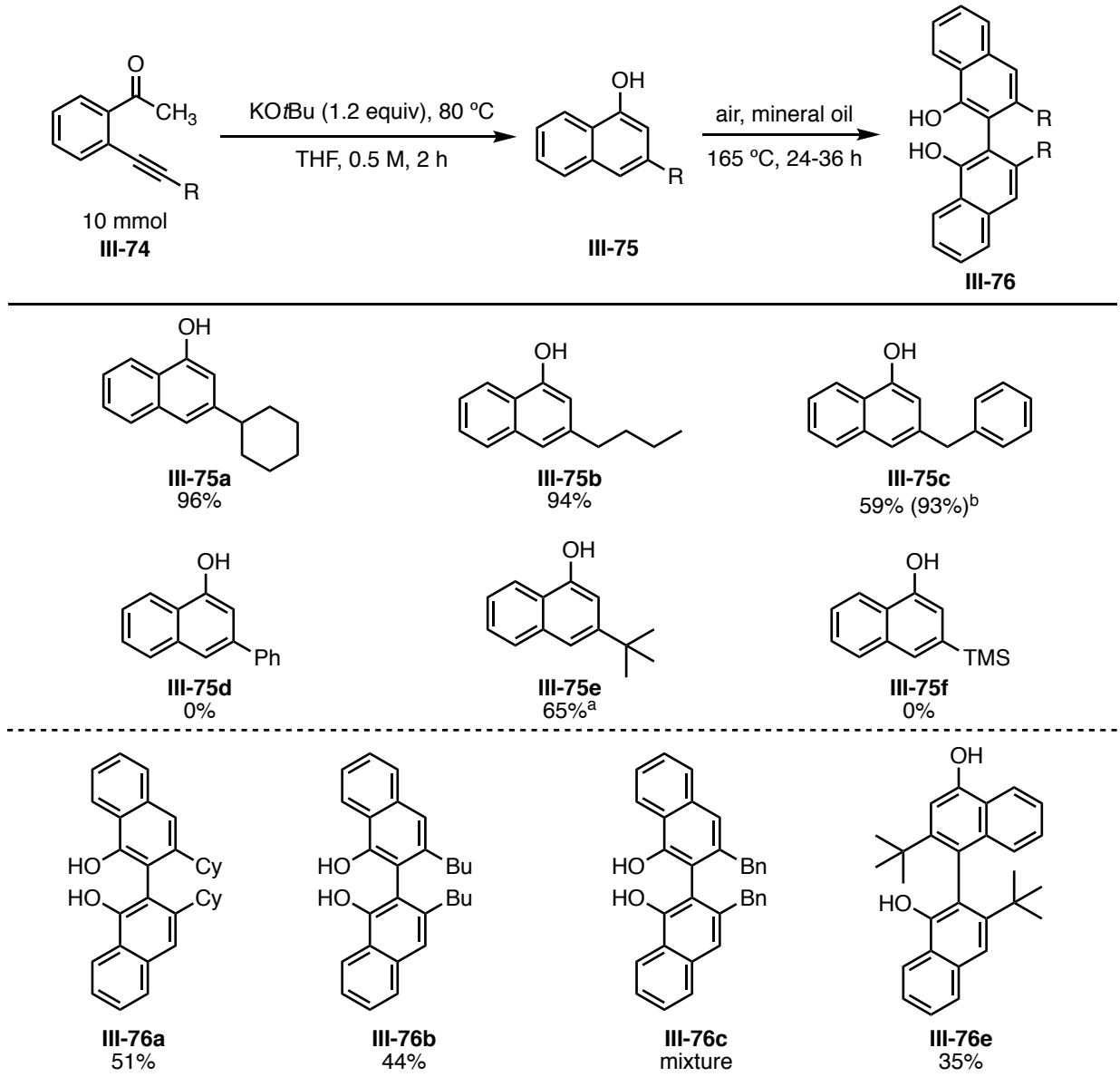
III-75a

entry	base	solvent	conc. (M)	time (h)	temp (ºC)	%yield[a] (**III-75a**)
1	KHMDS	toluene	1.0	1	–78 to 75	60 (92)
2	KO*t*Bu	THF	1.0	1	80	76
3	KOH	THF	1.0	1	80	trace
4	NaO*t*Bu	THF	1.0	1	80	trace
5	KO*t*Bu	THF	>1.0	1	80	65
6	KO*t*Bu	THF	0.5	1	80	85
7	KO*t*Bu	THF	0.5	2	80	94
8	KO*t*Bu	THF	0.5	4.5	70	53
9	KO*t*Bu	THF	0.5	2	90	94
10[b]	KO*t*Bu	THF	0.5	2	80	96[c]

[a]Isolated yield after column chromatography. Yield in parenthesis was reported in the literature.
[b]10 mmol scale. [c]Average of 3 trials

Other acetophenone substrates **III-74b-f** were next examined. The cycloaromatization reaction only works for o-alkynylacetophenones **III-74** with R is an aliphatic group. The reaction delivered the 1-naphthol with 1º (**III-75b**), 2º (**III-75a**), 3º (**III-75e**), or a benzyl group (**III-75c**), at the 3-position in moderate to excellent yield (51-96%). Substrate **III-75d** (R = phenyl) did not cyclized under the same conditions while the **III-75f** gave complex mixtures. The subsequent oxidative coupling reactions for **III-75a-c** and **III-75e** were carried out under the general procedure. It was a delight to find that 3,3'-Cy_2VANOL and 3,3'-nBu_2VANOL were obtained in moderate yield. The reaction with **III-75c** gave multiple products (isolation was not attempted). Interestingly the oxidation coupling of **III-75e** gave 2,4 coupling product as the major product, no 3,3'-*t*Bu_2VANOL was obtained probably due to the steric hindrance of the *t*-butyl group.

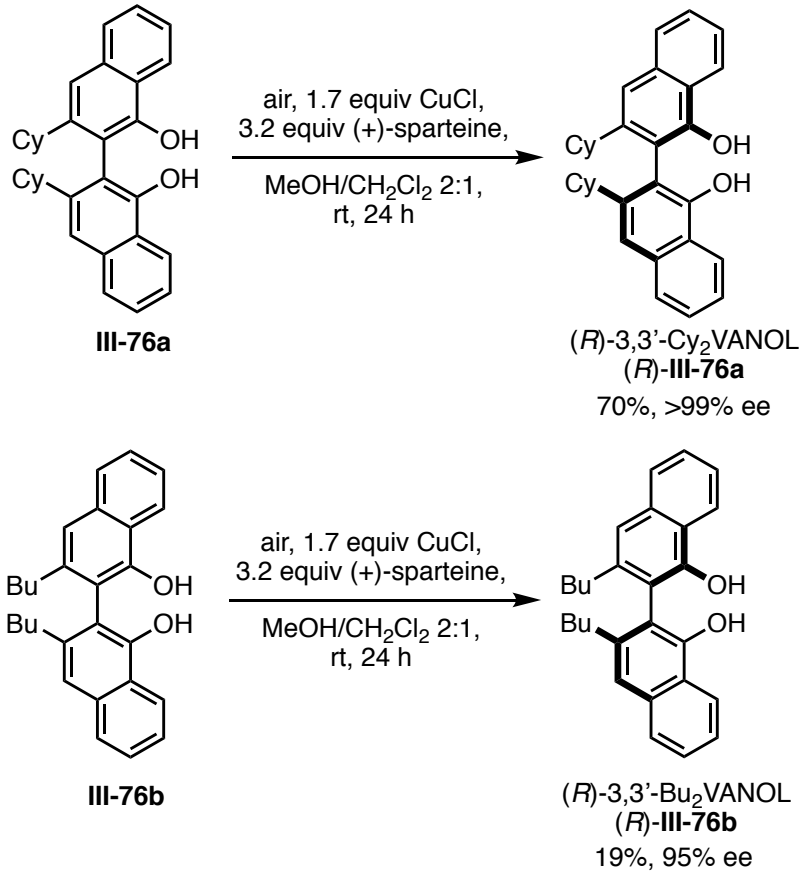
Scheme 3.15 Syntheses of 3,3'-dialkylVANOL



[a]KHMDS instead of KO*t*Bu, reflux in toluene for 110 °C, 20 mmol scale. [b]Addition of KO*t*Bu at 0 °C.

With 3,3'-Cy_2VANOL and 3,3'-*n*Bu_2VANOL in hand, efforts to obtain optically pure ligand turned to resolution with quinine borate and deracemization. Resolution by making borate with quinine or quinidine did not form precipitates from THF and hexanes (*Table 2.4*). Nevertheless, the deracemization with Cu(II)-sparteine did provided optically pure **III-76a** and 95% ee **III-76b** in 70% and 19% yield, respectively (*Scheme 3.16*).

Scheme 3.16 Deracemization of 3,3'-dialkylVANOL



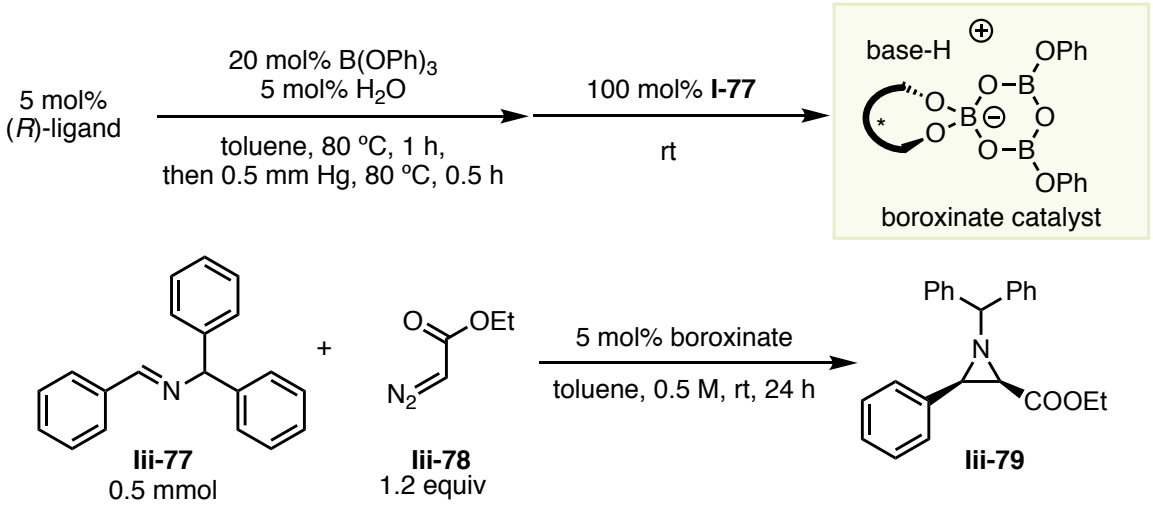
III-76a

(*R*)-3,3'-Cy_2VANOL
(*R*)-**III-76a**
70%, >99% ee

III-76b

(*R*)-3,3'-Bu_2VANOL
(*R*)-**III-76b**
19%, 95% ee

Scheme 3.17 Aziridination catalyzed by boroxinate of 3,3'-dialkylVANOL



Ligand	*cis*:*trans*[a] (**lii-79**)	%yield[b] (**lii-79**)	%ee[c] (**lii-79**)
(*R*)-3,3'-Cy_2VANOL	28:1	72	11
(*R*)-3,3'-Bu_2VANOL[d]	32:1	74	–7
(*S*)-VANOL (10%)[e]	>50:1	84	93

[a]As judged by ^{1}H NMR of crude product. [b]Isolated yield after chromatography on silica gel. [c]As judged by chiral HPLC. [d]95 % ee. [e]Prepared by VANOL, BH_3•Me_2S, PhOH and H_2O (see Table 1.22 method D for details)

The boroxinate-catalyzed aziridination reactions of imine **III-77** and EDA **III-78** was examined with the 3,3'-dialkylVANOL (*Scheme 3.17*). It was disappointing to find that the reaction with boroxinate prepared from 3,3'-Cy_2VANOL (>99% ee) and 3,3'-*n*Bu_2VANOL (95% ee) gave rise to the *cis*-aziridine **III-79** in good yields but with poor enantioselectivities. These results suggest that the phenyl group, with the ability to form a π-π interaction outside of the catalytic pocket, might play an important role leading an asymmetric induction in the aziridination reactions.

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REFERENCES

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CHAPTER FOUR

EXPERIMENTAL SECTION

"If you want to have good ideas you must have many ideas. Most of them will be wrong, and what you have to learn is which ones to throw away."

– Linus Pauling

4.1 General Experimental

All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen unless otherwise indicated. Unless otherwise specified, all solvents were strictly dried before use: dichloromethane were distilled over calcium hydride under nitrogen; tetrahydrofuran, and ether were distilled from sodium and benzophenone; toluene was distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Formations of water-sensitive precatalyst were carried out in the home-made Schlenk flask (*Figure 4. 1*) equipped with a stir bar under nitrogen unless otherwise noted.

Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in KBr matrix (for solids) and on NaCl disc (for liquids) on a Nicolet IR/42 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 300 MHz or Varian Unity Plus 500 MHz or Varian Inova 600 MHz spectrometer using $CDCl_3$ as solvent (unless otherwise noted). The residual peak of $CDCl_3$ or TMS was used as the internal standard for both ^{1}H NMR (δ = 7.24 ppm for $CDCl_3$ or δ = 0 ppm for TMS) and ^{13}C NMR (δ = 77.0 ppm). The ^{11}B NMR

spectra were recorded on a Varian 500 MHz instrument spectrometer in $CDCl_3$ unless otherwise noted. The ^{11}B NMR spectra were done in a Norell® quartz NMR tube and referenced to external standard $BF_3 \cdot Et_2O$ (δ = 0 ppm). Chemical shifts were reported in parts per million (ppm). High Resolution Mass Spectrometry was performed in the Department of Chemistry at Michigan State University Mass Facility.

Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with potassium permanganate. Column chromatography was performed with silica gel 60 (230 – 450 mesh). HPLC analyses were performed using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation.

Optical rotations were obtained at a wavelength of 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C and the concentrations are given in gram per 100 mL in DCM unless otherwise noted.

All reagents were purified by simple distillation or crystallization with simple solvents unless otherwise indicated. Triphenylborate was obtained from Aldrich Chemical Co., Inc. and used as received. VAPOL and VANOL were made according to published procedure. Unless otherwise noted, all NMR analysis has been carried out using Ph_3CH as the internal standard.

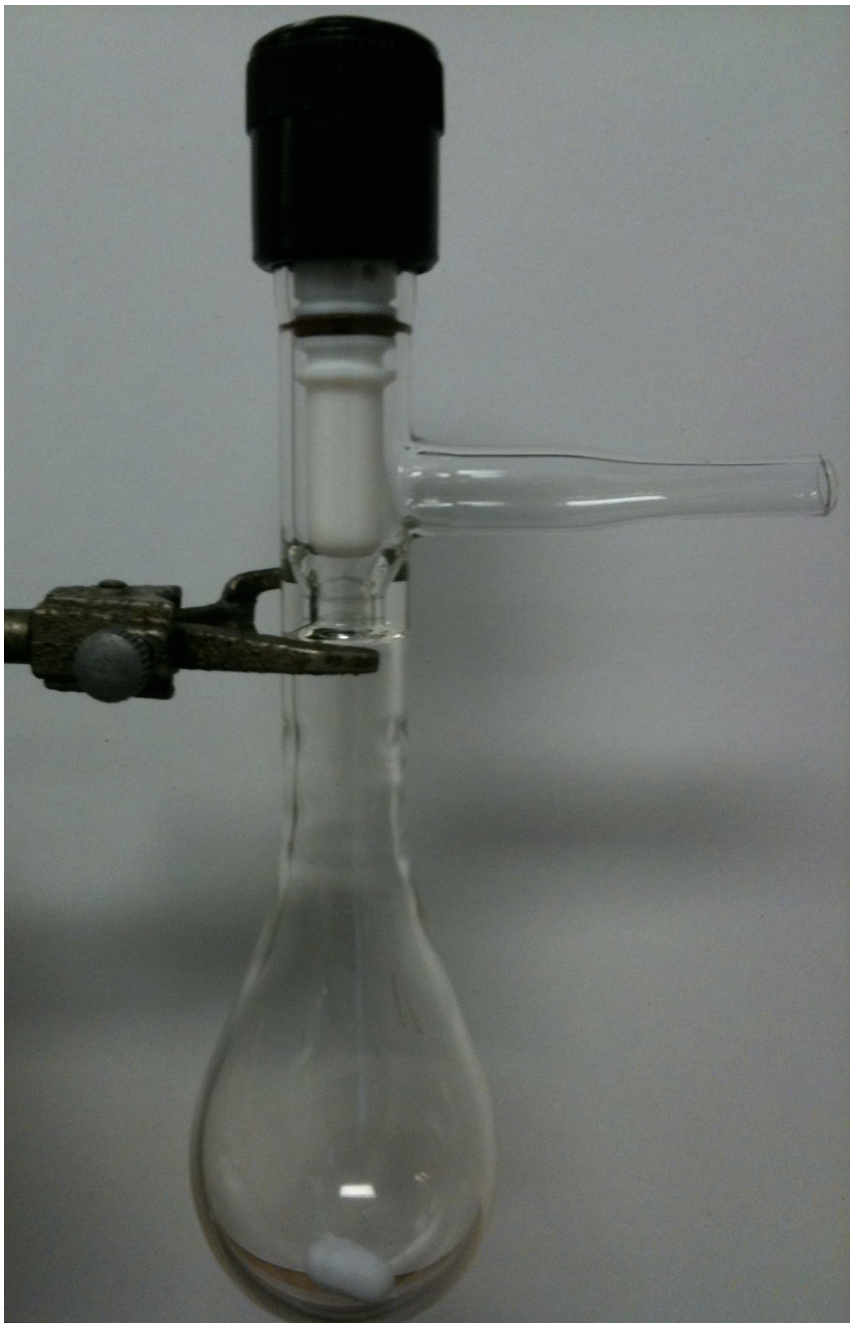
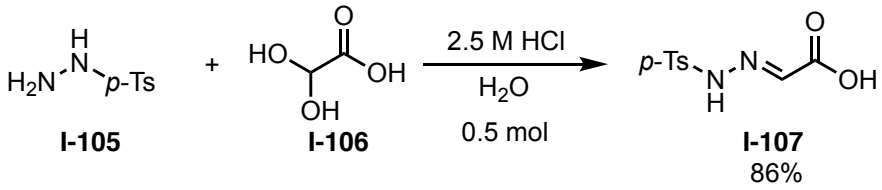


Figure 4. 1 Home-made 50 mL Schlenk flask

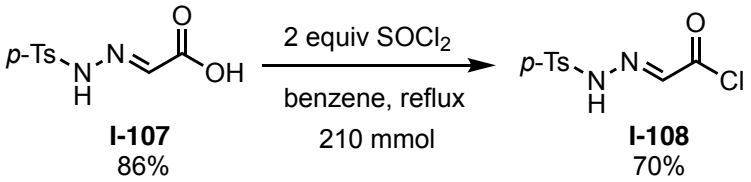
4.2 Experimental for Chapter One

4.2.1 Preparations of diazo compounds



*2-(2-tosylhydrazono) acetic acid **I-107**:* To a 1 L single-necked round bottom flask was added glyoxylic acid monohydrate **I-106** (46.3 g, 500 mmol) and water (500 mL). The mixture was stirred at 65 ºC (oil bath) until **I-106** dissolved completely. To this solution was then added a warm suspension (at approximately 65 ºC) of *p*-toluenesulfonylhydrazide **I-105** (93.1 g, 500 mmol) in 2.5 M aqueous hydrochloric acid (300 mL). The reaction mixture was stirred at 65 °C for 15 min, then allowed to cool to room temperature gradually until all of the oil solidified and then the flask was kept in a refrigerator overnight. The crude product was collected on filter paper using a Büchner funnel (8 cm diameter), washed with cold water (70 mL), and dried for 2 days in open air followed by exposure to high vacuum overnight. To a 1 L single-necked round bottom flask containing acid **I-107** and equipped with a stir bar and with a condenser was added boiling EtOAc until all of the solids dissolved. Hexanes were added until the solution became cloudy. Thereafter, hot EtOAc was added until it just became clear again. The solution was then allowed to cool to room temperature and then allowed to set in a freezer overnight (–20 ºC). The solid was filtered and washed with ice-cold 1:2 EtOAc/hexanes to afford **I-107** as a white solid (mp 150-152 ºC) in 86% isolated yield (105 g, 432 mmol).

Spectral data for **I-107**: R_f = 0.45 (1:1, EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.46 (s, 3H), 3.40 (br, 2H), 7.34 (s, 1H), 7.47 (d, 2H, J = 8.0 Hz), 7.85 (d, 2H, J = 8.0 Hz); ^{13}C NMR (CD_3COCD_3, 126 MHz) δ 21.89, 128.94, 131.07, 137.42, 137.85, 145.77, 163.23. These spectral data match those previously reported for this compound except for the exchanging protons.[1]



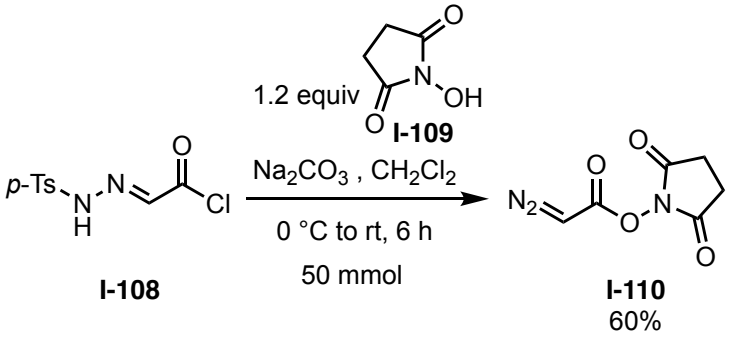
I-107
86%

I-108
70%

*2-(2-tosylhydrazono)acetyl chloride **I-108**:* To a suspension of acid **I-107** (50.2 g, 210 mmol) in benzene (250 mL) was added $SOCl_2$ (30 mL, 420 mmol, freshly distilled). The reaction mixture was heated to reflux (90 ºC oil bath) until vigorous gas evolution ceased and most of the suspended solid dissolved (~2 h). The reaction mixture then was cooled under nitrogen and filtered through a Celite® pad on a sintered-glass funnel. The filtrate was then concentrated to dryness under reduced pressure. The residual solid was mixed with anhydrous benzene (50 mL, warmed to ~40 to 50 ºC), and the solid mass was broken up to give a fine suspension. The suspension was cooled and filtered quickly using a Büchner funnel (8 cm diameter) and then the solid was washed quickly with cold benzene (30 mL × 2) to remove most of the residual colored impurities. The combined filtrates were stripped of solvent on the rotary evaporator and the residue was washed quickly with cold benzene (30 mL × 2) to give a second crop of the crude product. Purification by crystallization was achieved by dissolving the crude product in boiling benzene (~100 mL), followed by the addition of hexanes (~100 mL, bp. 60-90 ºC). The mixture was allowed to cool down to room temperature, and stand overnight. The acid

chloride **I-108** was collected as a white solid (mp. 100-103 ºC) in 70% isolated yield (38.3 g, 147 mmol).

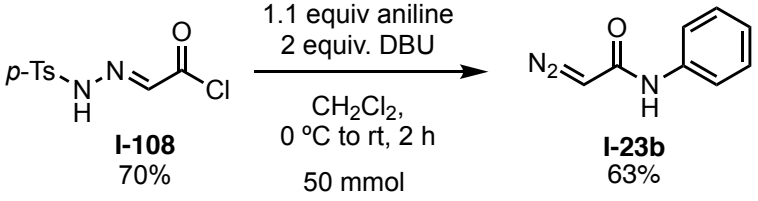
Spectral data for **I-108**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.46 (s, 3H), 7.25 (d, 1H, J = 0.9 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.86 (d, 2H, J = 8.4 Hz), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.70, 128.10, 130.14, 133.78, 136.05, 145.81, 165.01.



2,5-dioxopyrrolidin-1-yl 2-diazoacetate ***I-110****:* To a flame dried 500 mL single-necked round bottom flask was added *N*-hydroxysuccinimide **I-110** (6.33 g, 55.0 mmol) and Na_2CO_3 (7.95 g, 75.0 mmol) and anhydrous CH_2Cl_2 (75 mL). The flask was then brought to 0 ºC using a chiller over a period of 30 min. Meanwhile, to another flame-dried 250 mL single-necked round-bottom flask was added acid chloride **I-108** (13.04 g, 50.00 mmol) and dry CH_2Cl_2 (100 mL). This solution was added to the suspension of succinimide **I-109** at 0 ºC over a period of 2 h utilizing two syringe pumps. The resulting mixture was stirred for an additional hour at 0 ºC. After 1 h, the solution was warmed to room temperature and then stirred for 3 h at room temperature. The reaction mixture was then filtered using a Büchner funnel (8 cm diameter) with filter paper and the filtrate was collected in a 500 mL round-bottom flask. The residue was then washed with EtOAc (200 mL × 2). A small amount of solid was observed in the filtrate. The solid impurities remaining in the filtrate were removed by passing through a short plug (35 mm × 60 mm)

of silica gel. The filtrate was collected in a 500 mL round-bottom flask. The silica plug was then washed with EtOAc (150 mL × 2). The washing was monitored by TLC. The combined EtOAc layer was then concentrated under reduced pressure to provide crude succinimidyl diazoacetate as a light yellow solid (~6.36 g). The crude diazo compound was kept under vacuum for a period of 1 h. Recrystallization from CH_2Cl_2/ hexanes (55 mL, 4:1) gave diazo **I-110** (mp 113.5-115.0 ºC) as light yellow solid crystals in 29% yield (2.68 g, 14.5 mmol, first crop). Successive crystallization yielded the diazo compound **I-110** in a combined yield of 60% (29%, 2.68 g, mp 113.5-115.0 ºC, first crop; 15%, 1.40 g, mp 115.0-118.0 °C, second crop; 16%, 1.43 g, mp 115.0-118.0 °C, third crop). The amounts of solvent (CH_2Cl_2/ hexanes, 4:1) used for second and third crystallizations are 29 mL and 19 mL respectively. The amounts of the solid residue from the mother liquor after the first and second crystallizations are 3.57 g and 2.15 g respectively.

Spectral data for **I-110**: R_f = 0.13 (3:1 ether/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.81 (s, 4H), 5.10 (brs, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 25.44, 45.11, 162.24, 169.36; IR (thin film) 3105w, 2135s, 1736vs, 1375s, 1206s, 1105s cm^{-1}; These spectral data match those previously reported for this compound.[2]

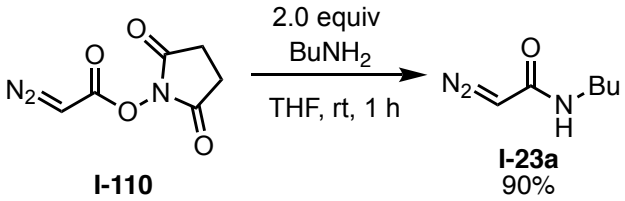


*2-diazo-N-phenylacetamide **I-23b**:* To a flame-dried 500 mL round bottom flask equipped with a magnetic stir bar and flushed with argon was added acid chloride **I-108** (14.4 g, 55.2 mmol, 1.00 equiv) and dry CH_2Cl_2 (120 mL). The flask was then fitted with

a rubber septum and an Argon balloon and cooled to 0 °C in an ice-bath. The reaction mixture was stirred at 0 ºC for 15 min. Aniline (5.60 mL, 60.8 mmol, 1.10 equiv) and DBU (16.6 mL, 110 mmol, 2.00 equiv) were then added sequentially to the reaction flask at 0 ºC via plastic syringe. The reaction mixture was stirred at 0 ºC for 2 h, and then warmed up to room temperature. The mixture was then added to sat. NH_4Cl (~120 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 once, the organic layers combined, washed with brine once, dried over Na_2SO_4, and filtered. The product solution thereafter was transferred to a 500 mL round bottom flask and enough silica gel was added for subsequent column chromatography ("dry load"). This solid was then subjected to rotary evaporation to dryness, and directly loaded onto a silica gel column (30 mm × 270 mm). An eluent mixture of 3:1 hexanes:EtOAc was used for the flash chromatography, all yellow colored fractions were collected, and subjected to rotary evaporation until dry and finally high vacuum to afford the impure product **I-23b** as a yellow solid. This solid was then washed with ether (1-4 times) until all impurities had been removed as indicated by TLC (3:1 hexanes/EtOAc), this afforded pure diazoacetamide **I-23b** (mp. 147-149 ºC) as a bright yellow solid in 63% yield (5.59 g, 34.7 mmol).

Spectral data for **I-23b**: R_f = 0.18 (1:50 MeOH:CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.16 (s, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$,126 MHz) δ 47.60, 118.96, 122.73, 128.36, 138.87, 163.86. The spectral data of **I-23b** match those previously reported for this compound.[3]

General Procedure **A** for synthesis of *N*-alkyl diazoacetamides -- illustrated for synthesis of *N*-butyl-2-diazoacetamide **I-23a**

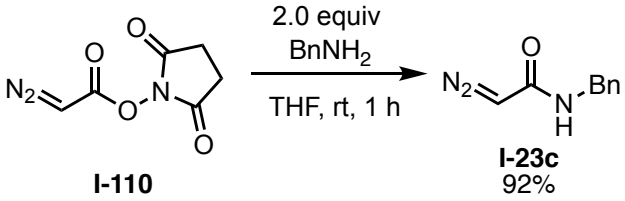


I-110 **I-23a** 90%

*N-butyl-2-diazoacetamide **I-23a**:* To a flame dried 500 mL single-necked round-bottom flask was added succinimidyl diazoacetate **I-110** (7.33 g, 40.0 mmol) and THF (330 mL). To the solution was added *N*-butylamine (8 mL, 80 mmol, freshly distilled) in one portion. Appearance of a yellow solid was observed after 1-2 min. The reaction mixture was stirred for 1 h at room temperature. The reaction was complete and the solvent was removed under reduced pressure. Purification of the crude diazo compound by silica gel chromatography (30 mm × 300 mm column, 1:3 hexanes/EtOAc) afforded pure diazoacetamide **I-23a** as a yellow solid (mp 75-76 ºC) in 90-93% isolated yield (5.10-5.25 g, 35-37.2 mmol). Alternatively, the crude product, after the evaporation of the solvent, was directly loaded to a short plug (35 mm × 60 mm) of silica gel. The silica plug was then washed with 1:3 hexanes/EtOAc (100 mL). The washing was continued until the yellow eluent stopped coming down the plug. All yellow fractions can be collected in a flask and the solvent was evaporated to afford pure diazoacetamide **I-23a** as a yellow solid (mp 75-76 ºC). No difference in the yield was observed when the purification was performed in this way compared to column chromatography.

Spectral data for **I-23a**: R_f = 0.33 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.3 Hz, 3H), 1.32 (dq, J = 14.7, 7.3 Hz, 2H), 1.46 (p, J = 7.3 Hz, 2H), 3.25

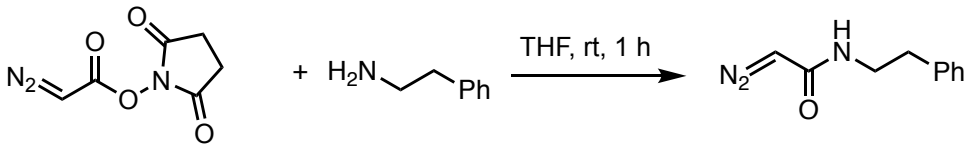
(brs, 2H), 4.73 (brs, 1H), 5.38 (brs, 1H); ^{13}C NMR ($CDCl_3$,126 MHz) δ 13.69, 19.97, 32.03, 39.83, 46.92, 165.32. These spectral data match those previously reported for this compound.[3]



I-110 **I-23c** 92%

*N-benzyl-2-diazoacetamide **I-23c**:* Diazoacetamide **I-23c** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (1.83 g, 10.0 mmol) and benzylamine (2.2 mL, 20 mmol, freshly distilled) to afford pure diazoacetamide **I-23c** as a yellow solid (mp 100-103 ºC) in 92% isolated yield (1.62 g, 9.24 mmol).

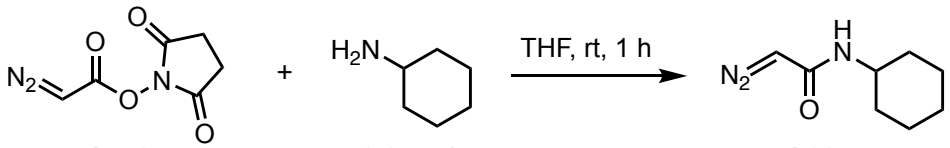
Spectral data for **I-23c**: R_f = 0.15 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.39 (d, J = 5.0 Hz, 2H), 4.68 (s, 1H), 5.44 (brs, 1H), 7.19-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$,126 MHz) δ 43.95, 47.20, 127.55, 127.67, 128.70, 138.25, 165.40. These spectral data match those previously reported for this compound.[3]



I-110 2.0 equiv **I-23d** 93%

*N-phenethyl-2-diazoacetamide **I-23d**:* Diazoacetamide **I-23d** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and 2-phenylethan-1-amine (1.26 mL, 10.0 mmol, freshly distilled) to afford pure diazoacetamide **I-23d** as a yellow solid in 93% isolated yield (883 mg, 4.65 mmol).

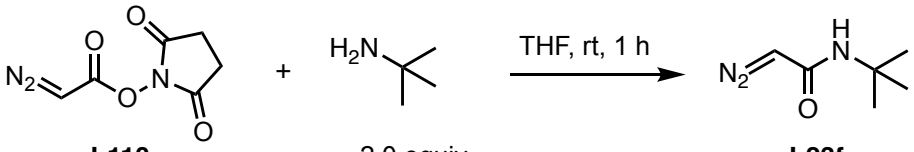
Spectral data for **I-23d**: R_f = 0.38 (3:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81 (t, *J* = 7.2 Hz, 2H), 3.51 (q, *J* = 7.6, 7.1 Hz, 2H), 4.85 (s, 1H), 6.17 (s, 1H), 7.03 – 7.43 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.08, 41.22, 47.06, 126.50, 128.60, 128.72, 138.85, 165.97.



I-110 2.0 equiv **I-23e** 82%

*N-cyclohexyl-2-diazoacetamide **I-23e**:* Diazoacetamide **I-23e** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and cyclohexanamine (1.15 mL, 10.0 mmol, freshly distilled) to afford pure diazoacetamide **I-23e** as a yellow solid in 82% isolated yield (683 mg, 4.09 mmol).

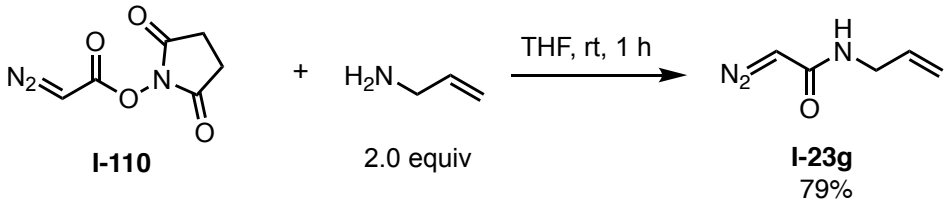
Spectral data for **I-23e**: R_f = 0.33 (3:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 – 1.32 (m, 6H), 1.19 – 1.98 (m, 5H), 4.80 (s, 1H), 6.30 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.83, 25.43, 33.27, 46.56, 48.51, 164.79.



I-110 2.0 equiv **I-23f** 84%

*N-tert-butyl-2-diazoacetamide **I-23f**:* Diazoacetamide **I-23f** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and *tert*-butylamine (1.05 mL, 10.0 mmol, freshly distilled) to afford pure diazoacetamide **I-23f** as a yellow solid in 84% isolated yield (591 mg, 4.19 mmol).

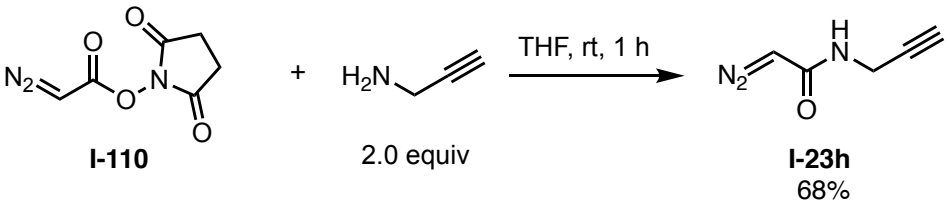
Spectral data for **I-23f**: R_f = 0.5 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H), 4.69 (s, 1H), 5.24 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.16, 47.48, 51.85, 164.94.



I-110 2.0 equiv **I-23g** 79%

*N-allyl-2-diazoacetamide **I-23g**:* Diazoacetamide **I-23g** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and allylamine (0.75 mL, 10.0 mmol, freshly distilled) to afford pure diazoacetamide **I-23g** as a yellow semisolid in 79% isolated yield (494 mg, 3.95 mmol).

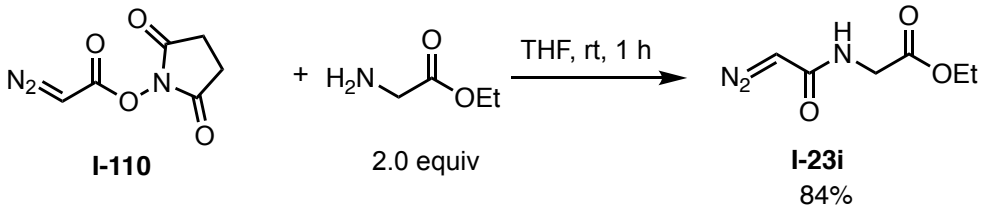
Spectral data for **I-23g**: R_f = 0.27 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 – 3.94 (s, 2H), 4.98 (s, 1H), 5.04 – 5.21 (m, 2H), 5.79 (ddt, J = 17.0, 10.6, 5.4 Hz, 1H), 6.46 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 42.21, 47.02, 116.01, 134.34, 166.12.



I-110 2.0 equiv **I-23h** 68%

*N-propargyl-2-diazoacetamide **I-23h**:* Diazoacetamide **I-23h** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and propargylamine (0.64 mL, 10.0 mmol, freshly distilled) to afford pure diazoacetamide **I-23h** as a yellow semisolid in 68% isolated yield (417 mg, 3.39 mmol).

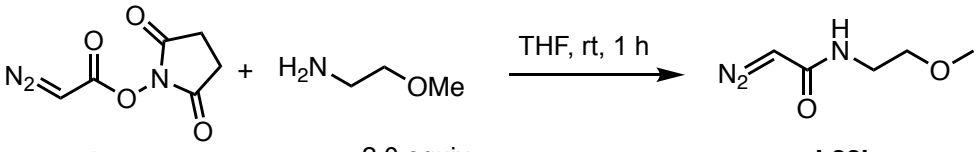
Spectral data for **I-23h**: R_f = 0.26 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (t, *J* = 2.6 Hz, 1H), 3.91 (dd, *J* = 5.5, 2.6 Hz, 2H), 4.94 (s, 1H), 7.22 (d, *J* = 50.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.05, 46.83, 71.06, 80.20, 165.90.



I-110 2.0 equiv **I-23i** 84%

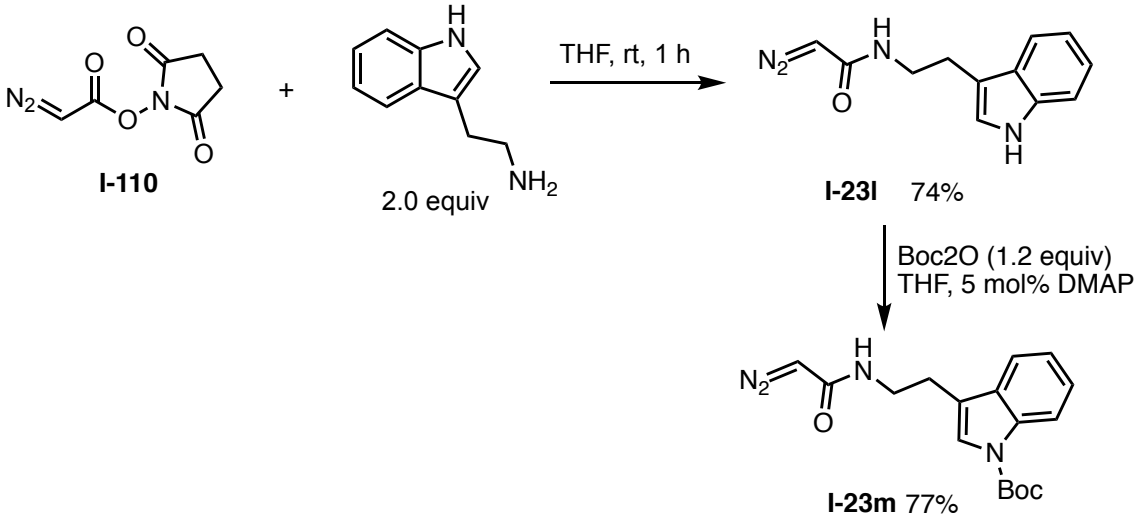
*ethyl (2-diazoacetyl)glycinate **I-23i**:* Diazoacetamide **I-23i** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and ethyl glycinate (1.031 g, 10.0 mmol) to afford pure diazoacetamide **I-23i** as a yellow semisolid in 84% isolated yield (417 mg, 4.19 mmol).

Spectral data for **I-23i**: R_f = 0.28 (3:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3H), 3.98 (d, *J* = 5.7 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.02 (s, 1H), 6.70 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.04, 41.57, 47.17, 61.44, 166.57, 170.46.



I-110 2.0 equiv **I-23j** 80%

*N-methoxyethyl-2-diazoacetamide **I-23j**:* Diazoacetamide **I-23j** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and 2-methoxyethylamine (0.87 mL, 10.0 mmol, freshly distilled) to afford pure diazoacetamide **I-23j** as a yellow semisolid in 80% isolated yield (517 mg, 3.99 mmol). R_f = 0.34 (1:1 EtOAc/hexanes);



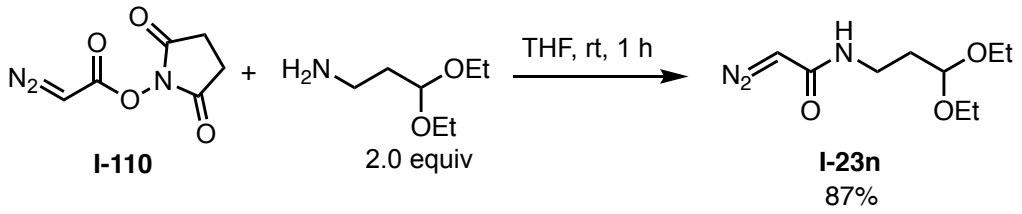
N-(2-(1H-indol-3-yl)ethyl)-2-diazoacetamide ***I-23l****:* Diazoacetamide **I-23l** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (915.6 mg, 5.000 mmol) and tryptamine (1.602 g, 10.0 mmol) to afford pure diazoacetamide **I-23l** as a pale yellow solid in 74% isolated yield (849 mg, 3.72 mmol).

Spectral data for **I-23l**: R_f = 0.13 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (t, *J* = 6.9 Hz, 2H), 3.49 (q, *J* = 6.4 Hz, 2H), 4.75 (s, 1H), 6.35 (s, 1H), 6.77 – 7.12 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.69, 40.22, 46.75, 111.42, 112.37, 118.51, 118.91, 121.59, 122.41, 127.29, 136.47, 165.82.

tert-butyl 3-(2-(2-diazoacetamido)ethyl)-1H-indole-1-carboxylate ***I-23m***: To a 25 mL round bottomed flask was added diazoacetamide **I-23l** (537 mg, 2.35 mmol), di-*tert*-butyl dicarbonate (617 mg, 2.82 mmol, 1.20 equiv), DMAP (14.4 mg, 0.118 mmol) and THF (15 mL). The reaction mixture was stirred at rt for 1 h. When the reaction was complete, the reaction mixture was concentrated and purified by column chromatography

(EtOAc/hexanes 1:1, silica gel) to afford **I-23m** (594 mg, 1.81 mmol) as a pale-yellow solid in isolated 77% yield.

Spectral data for **I-23m**: R_f = 0.20 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 9H), 2.92 (t, J = 6.9 Hz, 2H), 3.61 (d, J = 7.3 Hz, 2H), 4.69 (s, 1H), 5.35 (d, J = 51.6 Hz, 1H), 7.17 – 7.63 (m, 4H), 8.13 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.55, 28.22, 39.58, 47.19, 83.70, 115.32, 117.57, 118.92, 122.58, 123.23, 124.56, 130.31, 135.54, 149.70, 165.55.

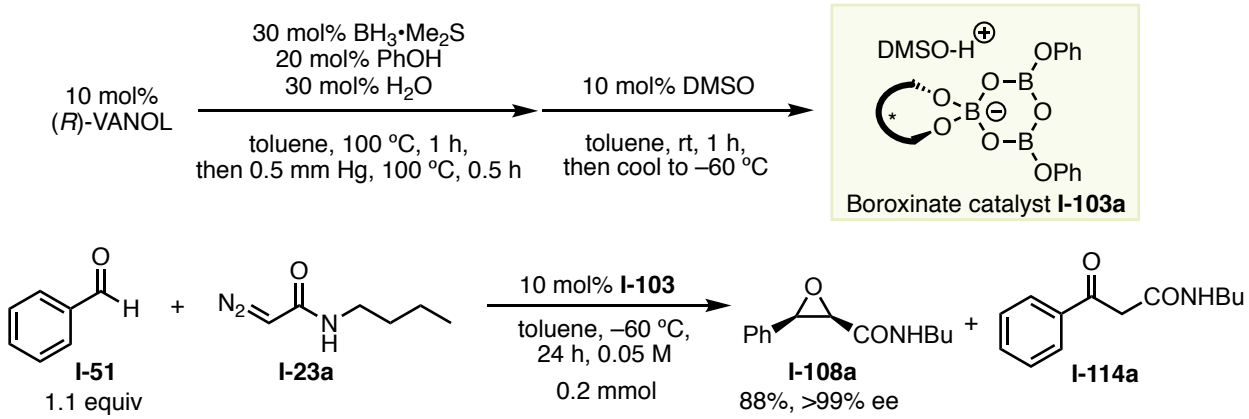


I-110 2.0 equiv **I-23n** 87%

*N-(3,3-diethoxypropyl) diazoacetamide **I-23n**:* Diazoacetamide **I-23n** was prepared by the General Procedure **A** with succinimidyl diazoacetate **I-110** (1.831 g, 10.00 mmol) and 3,3-diethoxypropan-1-amine (3.3 mL, 20 mmol) to afford pure diazoacetamide **I-23n** as a yellow liquid in 87% isolated yield (1.882 g, 8.74 mmol).

Spectral data for **I-23n**: R_f = 0.30 (3:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, J = 7.1 Hz, 6H), 1.62 (q, J = 6.5 Hz, 2H), 3.14 (d, J = 7.2 Hz, 2H), 3.25 – 3.38 (m, 2H), 3.45 (dd, J = 9.2, 6.8 Hz, 2H), 4.35 (t, J = 5.5 Hz, 1H), 4.85 (s, 1H), 6.80 (t, J = 5.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.08, 33.51, 35.74, 46.58, 61.53, 101.37, 165.90.

4.2.2 General Procedure **B** for symmetric epoxidation catalyzed by Boroxinate **I-103a** (*Table 1.2*) -- illustrated for benzaldehyde **I-51a** and *N*-butyl-2-diazoacetamide **I-23a**



*Preparation of the catalyst stock solution **I-103a***: To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-VANOL (26.3 mg, 0.0600 mmol) and PhOH (11.3 mg, 0.120 mmol, freshly sublimed). Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to effect dissolution. After the addition of the toluene, BH_3•Me_2S (90 µL, 0.18 mmol, 2 M in toluene) and water (3.2 µL, 0.18 mmol) were added. The flask was sealed by closing the Teflon valve, and then placed in a 100 ºC oil bath for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 100 ºC (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk

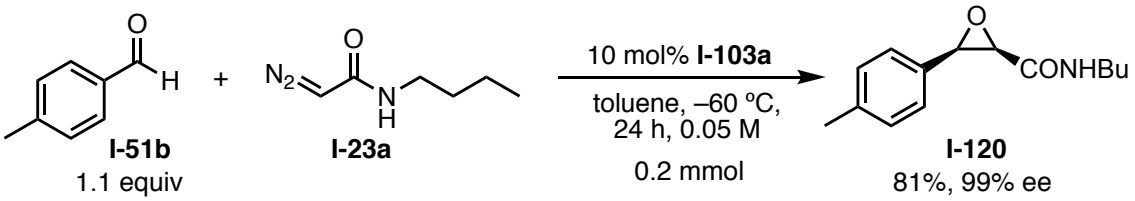
flask. This residue was then completely dissolved in dry toluene (3 mL) under a nitrogen flow through side-arm of the Schlenk flask. An aliquot of 1 mL (0.020 mmol) of the pre-catalyst was then transferred to a 10 mL flame-dried home-made Schlenk flask equipped with a stir bar and flushed with argon. To the flask containing the pre-catalyst (1 mL aliquot from 0.02 M stock solution) was added the dimethyl sulfoxide (1.4 µL, 0.020 mmol) under a nitrogen flow through side-arm of the Schlenk flask. The resulting mixture was stirred for 1 h at room temperature to afford the solution of the catalyst.

Asymmetric epoxidation protocol: The flask containing the catalyst ***I-103a*** (0.020 mmol) was cooled to –60 °C for 10 min. To this solution was added a solution of diazoacetamide **I-23a** (28.2 mg, 0.200 mmol in 2.5 mL toluene). The flask containing the diazoacetamide **I-23a** was then rinsed with toluene (0.5 mL) and the rinse was then transferred to the flask containing the catalyst at –60 °C. Then the Teflon valve was closed and the resulting mixture was stirred for 10 min at –60 °C. To the mixture containing diazoacetamide **I-23a** and the catalyst was added neat benzaldehyde **I-51a** (22 µL, 0.22 mmol) dropwise using a microsyringe and the resulting mixture was stirred for 24 h at –60 °C. The reaction was quenched by the addition of Et_3N (0.5 mL) and then was warmed to room temperature. The reaction mixture was then transferred to a 50 mL round bottom flask. The reaction flask was rinsed with EtOAc (3 mL × 2) and the rinse was added to the 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.5 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid.

The *cis/trans* ratio was determined by comparing the ^{1}H NMR integration of the ring methine protons (δ 3.77 for *cis*, δ 3.60 for *trans*) for each epoxide in the crude reaction mixture. The yield of the acyclic β-ketoamide side product was determined by ^{1}H NMR analysis of the crude reaction mixture by integration of the methylene protons (δ 3.94) relative to the internal standard (Ph_3CH). Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 2:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-108a** as a white solid (mp 52-53 ºC on 99% *ee* material) in 88% isolated yield (38.6 mg, 0.176 mmol); *cis/trans*: 100:1. β-ketoamide side product: <1% yield. The optical purity of **I-108a** was determined to be 99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times; R_t = 13.8 min (minor enantiomer, *ent*-**I-108a**) and R_t = 24.6 min (major enantiomer, **I-108a**). Each enantiomer was obtained and confirmed by a separate reaction using (*R*)-VANOL as ligand. Side product β-ketoamide **I-114a** was isolated in a separate experiment and characterized by NMR.

Spectral data for **I-108a**: R_f = 0.61 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (t, J = 7.2 Hz, 3H), 0.89-1.04 (m, 4H), 2.82-2.88 (m, 1H), 3.08 (dq, J = 13.6, 6.9 Hz, 1H), 3.77 (d, J = 4.8 Hz, 1H), 4.31 (d, J = 4.8 Hz, 1H), 5.84 (s, 1H), 7.35–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.53, 19.62, 31.17, 38.21, 56.27, 58.08, 126.49, 128.31, 128.38, 133.19, 165.95; IR (thin film) 3316 br, 2959 vs, 2932 vs, 1651 vs, 1545 s, 1454 s cm^{-1}; HRMS (ESI-TOF) *m/z* 220.1334 [(M+H$^+$); calcd. for $C_{13}H_{18}NO_2$: 220.1338]; $[\alpha]_D^{20}$ +18.6 (*c* 1.0, EtOAc) on 99.3% *ee* material (HPLC).

Spectral data for **I-114a**: R_f = 0.40 (1:3 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.33-1.39 (m, 2H), 1.49-1.55 (m, 2H), 3.30 (td, J= 7.1, 5.7 Hz, 2H), 3.94 (s, 2H), 7.07-7.15 (m, 1H), 7.47-7.51 (m, 2H), 7.61 (ddt, J = 8.4, 6.5, 1.6 Hz, 1H), 8.00 (dt, J = 8.4, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.69, 20.04, 31.43, 39.40, 45.26, 128.56, 128.85, 134.04, 136.23, 165.55, 196.37. These spectral data match those previously reported for this compound.[10]



I-51b
1.1 equiv

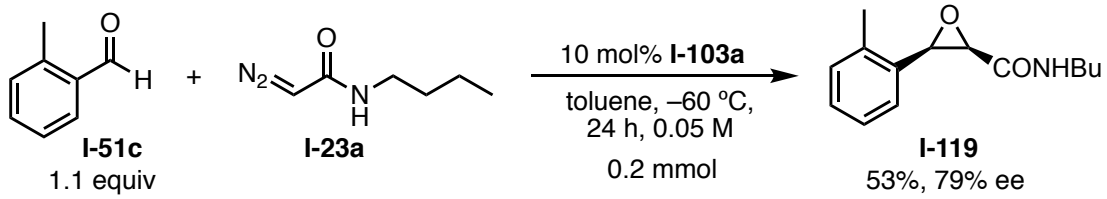
I-23a

I-120
81%, 99% ee

(2R,3R)-N-butyl-3-(p-tolyl)oxirane-2-carboxamide ***I-120***: Aldehyde **I-51b** was reacted according to the General Procedure **B** with (*R*)-VANOL as ligand. Purification of the crude epoxide by silica gel chromatography (17 mm × 300 mm column, 2:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-120** as a white solid (mp 58-59 ºC on 99% *ee* material) in 81% isolated yield (37.9 mg, 0.162 mmol); *cis/trans*: >100:1. β-ketoamide side product: <1% yield. The optical purity of **I-120** was determined to be 99% *ee* by HPLC analysis (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times; R_t = 23.76 min (minor enantiomer, *ent*-**I-120**) and R_t = 35.09 min (major enantiomer, **I-120**).

Spectral data for **I-120**: R_f = 0.56 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (t, J = 7.2 Hz, 3H), 0.88-0.96 (m, 2H), 1.00-1.06 (m, 2H), 2.32 (s, 3H), 2.83-2.89 (m, 1H), 3.11 (dq, J = 13.6, 6.9 Hz, 1H), 3.74 (d, J = 4.8 Hz, 1H), 4.27 (d, J = 4.7 Hz, 1H), 5.83 (s, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz)

δ 13.58, 19.66, 21.15, 31.28, 38.26, 56.32, 58.09, 126.45, 128.99, 130.21, 138.21, 166.12; IR (thin film) 3310 br, 2961 s, 2932 s, 1653 vs, 1547 vs, 1433 s cm^{-1}; HRMS (ESI-TOF) *m/z* 234.1504 [(M+H^+); calcd. For $C_{14}H_{20}NO_2$: 234.1494]; $[\alpha]_D^{20}$ +22.0 (*c* 1.0, EtOAc) on 99% *ee* material (HPLC).



I-51c
1.1 equiv

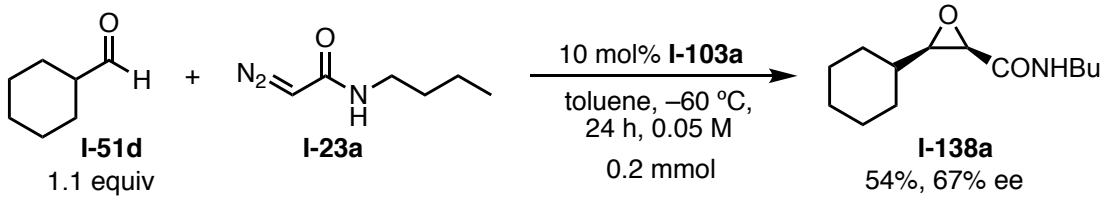
I-23a

I-119
53%, 79% ee

(2R,3R)-N-butyl-3-(o-tolyl)oxirane-2-carboxamide ***I-119****:* Aldehyde **I-51c** was reacted according to the General Procedure **B** with (*R*)-VANOL as ligand. Purification of the crude epoxide by silica gel chromatography (17 mm × 300 mm column, 2:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-119** as a white solid (mp 41-43 ºC on 79% *ee* material) in 53% isolated yield (24.1 mg, 0.106 mmol); *cis/trans*: >100:1. *β*-ketoamide side product: <1% yield. The optical purity of **I-119** was determined to be 79% *ee* by HPLC analysis (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times; R_t = 17.11 min (minor enantiomer, *ent*-**I-119**) and R_t = 20.61 min (major enantiomer, **I-119**).

Spectral data for **I-119**: R_f = 0.58 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (t, *J* = 7.1 Hz, 3H), 0.87-0.96 (m, 4H), 2.36 (s, 3H), 2.78-2.83 (m, 1H), 3.07 (dq, *J* = 13.7, 6.9 Hz, 1H), 3.84 (d, *J* = 4.7 Hz, 1H), 4.25 (d, *J* = 4.7 Hz, 1H), 5.72 (s, 1H), 7.15 (dd, *J* = 11.6, 7.5 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.56, 18.69, 19.59, 31.20, 38.20, 56.13, 57.69, 125.46, 126.15, 128.31, 130.02, 131.77, 136.73, 166.11; IR (thin film) 3330 br, 2959 s, 2930 s, 1666 vs,

1539 vs, 1458 m cm^{-1}; HRMS (ESI-TOF) *m/z* 234.1503 [(M+H^+); calcd. for $C_{14}H_{20}NO_2$: 234.1494]; $[\alpha]_D^{20}$ +39.8 (*c* 1.0, EtOAc) on 80% *ee* material (HPLC).



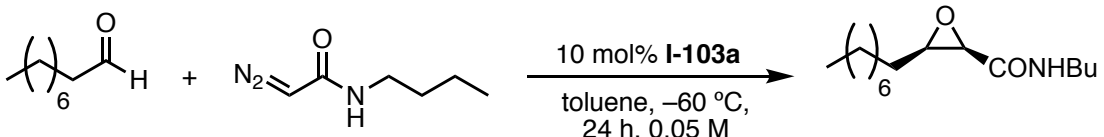
I-51d
1.1 equiv

I-23a

I-138a
54%, 67% ee

*(2R,3R)-N-butyl-3-cyclohexyloxirane-2-carboxamide **I-138a**:* Aldehyde **I-51d** was reacted according to the General Procedure **B** with (*R*)-VANOL as ligand. Purification of the crude epoxide by silica gel chromatography (17 mm × 300 mm column, 2:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-138a** as a colorless oil in 54% isolated yield (24.1 mg, 0.107 mmol); *cis/trans*: >100:1. *β*-ketoamide side product: <1% yield. The optical purity of **I-138a** was determined to be 67% *ee* by HPLC analysis (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times; R_t = 6.72 min (minor enantiomer, *ent*-**I-119**) and R_t = 10.61 min (major enantiomer, **I-119**).

Spectral data for **I-138a**: R_f = 0.23 (1:2 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, *J* = 7.1 Hz, 3H), 1.00-1.20 (m, 6H), 1.24-1.32 (m, 2H), 1.40–1.46 (m, 2H), 1.56-1.76 (m, 4H), 1.84 (br, 1H), 2.82 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.14 (dt, *J* = 13.0, 7.5 Hz, 1H), 3.32 (dt, *J* = 14.0, 7.0 Hz, 1H), 3.43 (d, *J* = 4.5 Hz, 1H), 6.11 (s, 1H); ^{13}C ($CDCl_3$, 125 MHz) δ 13.62, 20.01, 25.28, 25.29, 25.98, 28.37, 30.44, 31.62, 36.81, 38.44, 55.30, 62.54, 167.32; HRMS (ESI-TOF) *m/z* 226.1812 [(M+H^+); calcd. for $C_{13}H_{24}NO_2$: 226.1807].



I-51d
1.1 equiv

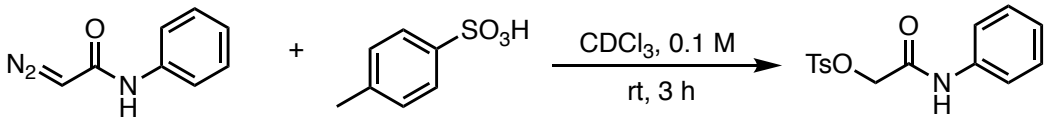
I-23a

I-137a
81%, 79% ee

*(2R,3R)-N-butyl-3-octyloxirane-2-carboxamide **I-137a**:* Aldehyde **35** was reacted according to the General Procedure **B** with (*R*)-VANOL as ligand. Purification of the crude epoxide by silica gel chromatography (17 mm × 300 mm column, 3:1 to 1:1 hexanes/ ethyl acetate as eluent) afforded pure *cis*-epoxide **I-137a** as a white semi-solid in 81% isolated yield (41.3 mg, 0.162 mmol); *cis/trans*: nd. *β*-ketoamide side product: 6% yield. The optical purity of **I-137a** was determined to be 79% *ee* by HPLC analysis (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 97:3 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times; R_t = 22.64 min (minor enantiomer, *ent*-**I-137a**) and R_t = 27.43 min (major enantiomer, **I-137a**).

Spectral data for **I-137a**: R_f = 0.32 (1:2 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.85 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 1.21-1.27 (m, 8H), 1.28-1.35 (m, 4H), 1.40-1.53 (m, 6H), 3.11-3.14 (m, 1H), 3.21 (dq, J = 13.2, 6.6 Hz, 1H), 3.30 (dq, J = 13.5, 6.7 Hz, 1H), 3.46 (d, J = 4.8 Hz, 1H), 6.11 (s, 1H); ^{13}C NMR($CDCl_3$, 126 MHz) δ 13.63, 14.04, 20.05, 22.61, 26.01, 27.64, 29.12, 29.30, 29.33, 31.63, 31.80, 38.55, 55.36, 58.57, 167.26; IR (thin film) 3312 br, 2957 s, 2938 s, 2857 m, 1661 vs, 1539 vs, 1458 m, cm^{-1}; HRMS (ESI-TOF) *m/z* 256.2271 [(M+H$^+$); calcd. for $C_{15}H_{30}NO_2$: 256.2277]; $[\alpha]_D^{20}$ +2.1 (*c* 1.0, EtOAc) on 79% *ee* material (HPLC).

4.2.3 Protonation/nucleophilic addition to **I-23b**

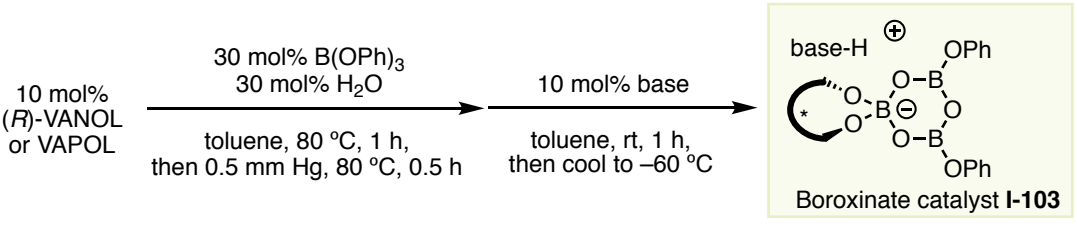


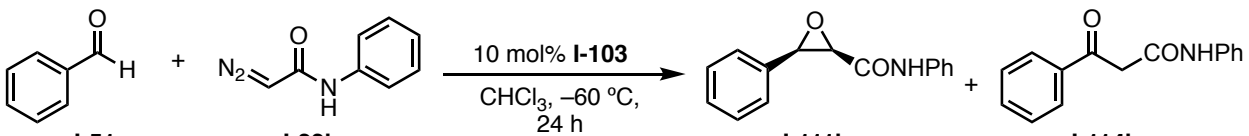
I-23b **I-112** **I-113**
74%

*2-oxo-2-(phenylamino)ethyl 4-methylbenzenesulfonate **I-113***: To a 10 mL round bottomed flask was added diazo acetamide **I-23b** (16.1 mg, 0.1 mmol), TsOH•H_2O (19.0 mg, 0.100 mmol) and $CDCl_3$ (1 mL). The reaction was then followed by ^1H NMR and after 3 h, the reaction mixure was purified by column chromatography (1:1 DCM/hexanes) to afford **I-113** (22.6 mg, 0.0740 mmol) in 74% yield.

Spectral data for **I-113**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.53 (s, 2H), 7.14 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.22 – 7.41 (m, 4H), 7.41 – 7.56 (m, 2H), 7.76 – 7.89 (m, 2H), 7.97 (s, 1H). These spectral data match those previously reported for this compound[4].

4.2.4 Optimization of asymmetric epoxidation using *N*-phenyl diazoacetamide **I-107b** (*Table 1.3*) -- illustrated by entry 16





I-51a 1.1 equiv **I-23b** **I-111b** 70%, 67% ee **I-114b** 5.1%

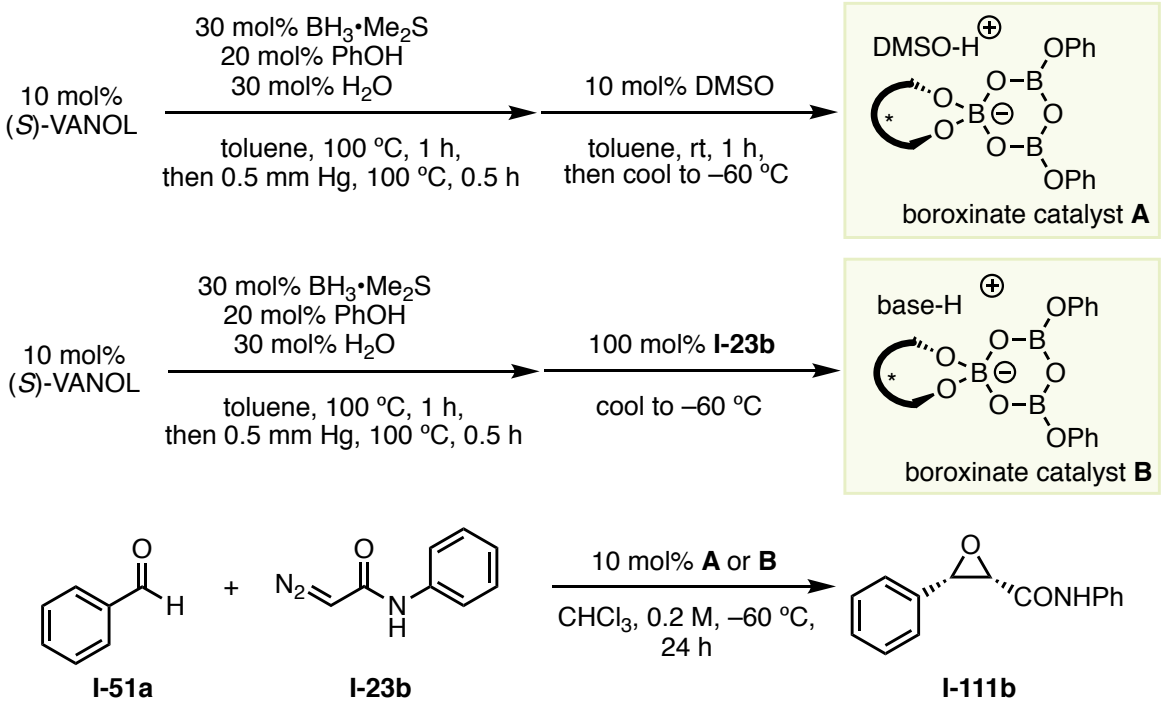
*Preparation of the catalyst stock solution **I-103***: To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its

14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-VANOL (22.0 mg, 0.0500 mmol) and commercial $B(OPh)_3$ (43.5 mg, 0.150 mmol) and water (2.7 μL, 0.050 mmol). Under an argon flow through the side-arm of the Schlenk flask, dry THF (1 mL) was added through the top of the Teflon valve to effect dissolution. The flask was sealed by closing the Teflon valve, and then placed in an 80 ºC oil bath for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 ºC (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. This was then completely dissolved in dry $CHCl_3$ (1 mL) under an argon flow through side-arm of the Schlenk flask. To the flask was added the dimethyl sulfoxide (3.6 μL, 0.050 mmol) or orther base indicated in the table (0.050 mmol) under a nitrogen flow through side-arm of the Schlenk flask. The resulting mixture was stirred for 1 h at room temperature to afford the solution of the precatalyst.

Asymmetric epoxidation protocol: The flask containing the precatalyst was cooled to –60 °C for 10 min. To the catalyst was then added diazoacetamide **I-23b** (80.6 mg, 0.500 mmol) followed by closing the Teflon valve and stirring the resulting mixture for 10 min at –60 °C. To the mixture containing diazoacetamide **I-23b** and catalyst was then added neat benzaldehyde **I-51a** (61 μL, 0.60 mmol) dropwise using a microsyringe and the resulting mixture was stirred for 24 h at –60 °C. The reaction was quenched by the addition of H_2O (0.5 mL) and was then warmed to room temperature. The reaction mixture

was then transferred to a 60 mL separatory funnel. The water layer was extracted with CH_2Cl_2 (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered to the 50 mL round bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. Purification of the crude epoxide epoxide by silica gel chromatography (17 mm × 300 mm column, 3:1 to 1:1 hexanes/ ethyl acetate as eluent) afforded pure *cis*-epoxide **I-111b** as a white solid (mp 101-103 ºC) in 70% isolated yield (83.9 mg, 0.351 mmol); *cis/trans*: 64:1. β-ketoamide side product **I-114b**: 5.1% yield. The optical purity of **I-111b** was determined to be 67% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 1 mL/min): retention times; R_t = 8.17 min (minor enantiomer, *ent*-**I-111b**) and R_t = 10.33 min (major enantiomer, **I-111b**).

4.2.5 KIE samples preparation (*Table 1.4*) -- illustrated by set 2

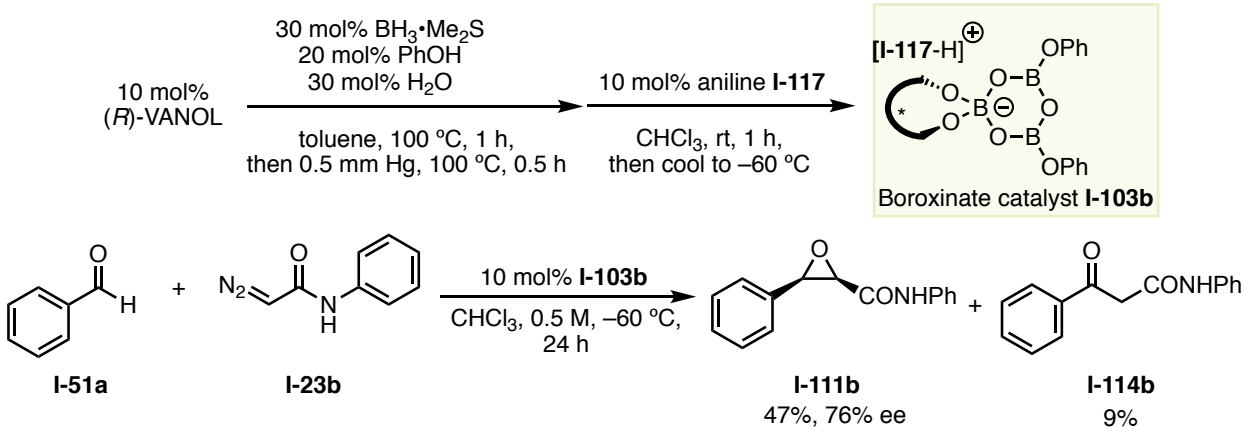


*Asymmetric epoxidation protocol for boroxinate catalyst **A**:* Catalyst **A** was prepared according to the general procedure in 4.2.2 described above on 0.24 mmol scale in two 50 mL Schlenk flasks. Both flasks containing the catalyst were cooled to –60 °C for 10 min and were diluted to 0.02 M by adding $CHCl_3$. *Sample 1 (20% conversion for **I-23b**):* To the catalyst was then added diazoacetamide **I-23b** (1.934 g, 12.00 mmol) followed by closing the Teflon valve and stirring the resulting mixture for 10 min at –60 °C. To the mixture containing diazoacetamide **I-23b** and catalyst was then added neat benzaldehyde **I-51a** (243 µL, 2.40 mmol) dropwise using a microsyringe and the resulting mixture was stirred for 24 h at –60 °C. *Sample 2 (20% conversion for **I-51a**):* To the catalyst was then added benzaldehyde **I-51a** (1.22 mL, 12.0 mmol) followed by closing the Teflon valve and stirring the resulting mixture for 10 min at –60 °C. To the mixture containing benzaldehyde **I-51a** and catalyst was then added diazoacetamide **I-23b** (387 g, 2.40 mmol) and the resulting mixture was stirred for 24 h at –60 °C. Both reactions were quenched by the addition of H_2O (2.0 mL) and was then warmed to room temperature. The reaction mixture was then *trans*ferred to a 60 mL separatory funnel. The water layer was extracted with CH_2Cl_2 (5 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered to the 100 mL round bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. Purification of the crude epoxide epoxide by silica gel chromatography (17 mm × 300 mm column, 3:1 to 1:1 hexanes/ ethyl acetate as eluent) afforded pure *cis*-epoxide **I-111b** as a white solid (mp 101-103 ºC) in 80% isolated yield (458 mg, 1.91 mmol) for *sample 1* and in 67% isolated

yield (386 mg, 1.61 mmol) for *sample 2*. The optical purity of **I-111b** was determined to be 90% *ee* for *sample 1* and 93% *ee* for *sample 2* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 1 mL/min): retention times; R_t = 8.17 min (major enantiomer, **22a**) and R_t = 10.33 min (minor enantiomer, *ent*-**22a**).

*General procedure for boroxinate catalyst **B**:* Catalyst **B** was prepared following general procedure in 4.2.2 except for no DMSO was added. The two samples were obtained and analyzed by the same procedure above.

4.2.6 Epoxidation catalyzed by boroxinate with aniline (*Table 1.5*) -- illustrated by entry 16

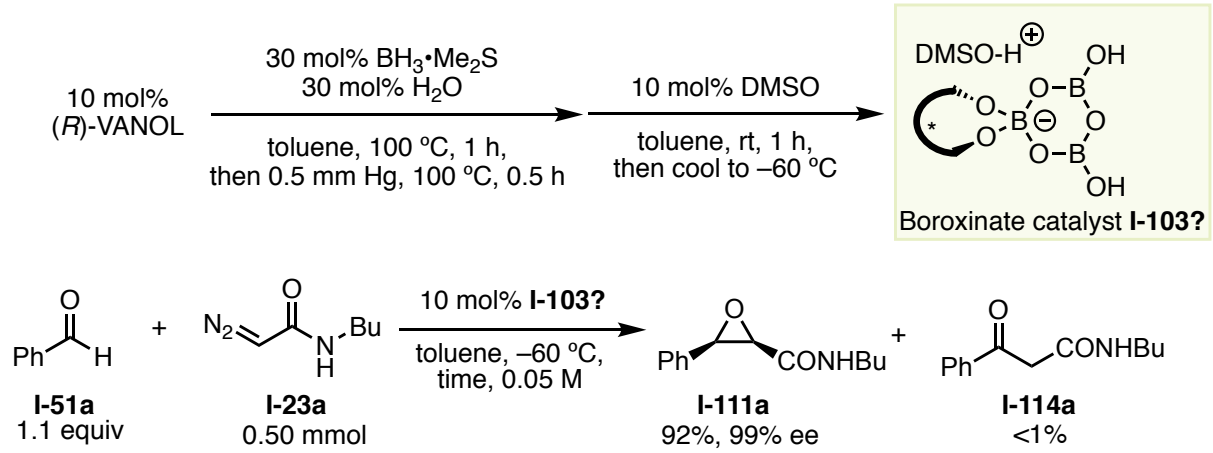


Preparation of the catalyst solution: Precatalyst for **I-103b** was prepared according to the general procedure in 4.2.2 described above. To the flask containing the pre-catalyst was added $CHCl_3$ (1 mL) and then aniline **I-117a** (0.05 mmol) under a nitrogen flow through side-arm of the Schlenk flask. The resulting mixture was stirred for 1 h at room temperature to give the precatalyst.

Asymmetric epoxidation protocol: The flask containing the catalyst was cooled to –60 °C for 10 min. To the catalyst was then added diazoacetamide **I-23b** (80.6 mg, 0.500

mmol) followed by closing the Teflon valve and stirring the resulting mixture for 10 min at –60 °C. To the mixture containing diazoacetamide **I-23b** and catalyst was then added neat benzaldehyde **I-51a** (56 μL, 0.55 mmol) dropwise using a microsyringe and the resulting mixture was stirred for 24 h at –60 °C. The reaction was quenched by the addition of H_2O (0.5 mL) and was then warmed to room temperature. The reaction mixture was then *trans*ferred to a 60 mL separatory funnel. The water layer was extracted with CH_2Cl_2 (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered to the 50 mL round bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. Purification of the crude epoxide epoxide by silica gel chromatography (17 mm × 300 mm column, 3:1 to 1:1 hexanes/ ethyl acetate as eluent) afforded pure *cis*-epoxide **I-111b** as a white solid (mp 101-103 ºC) in 47% isolated yield (56.2 mg, 0.235 mmol); *cis/trans*: 64:1. β-ketoamide side product **I-114b**: 9% yield. The optical purity of **I-111b** was determined to be 76% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 222 nm, flow-rate: 1 mL/min): retention times; R_t = 8.17 min (minor enantiomer, *ent*-**I-111b**) and R_t = 10.33 min (major enantiomer, **I-111b**).

4.2.7 Evolution of catalyst (*Table 1.6)* -- illustrated by entry 3



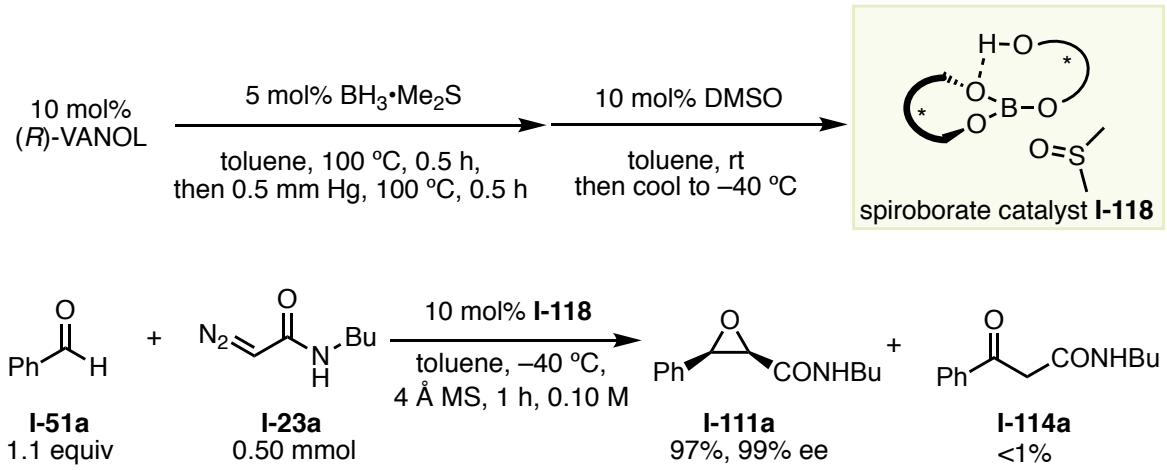
Preparation of the catalyst solution: To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-VANOL (22.0 mg, 0.0500 mmol). Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (1.5 mL) was added through the top of the Teflon valve to effect dissolution. After the addition of the toluene, BH_3•Me_2S (75 µL, 0.15 mmol, 2 M in toluene) and water (2.7 µL, 0.050 mmol) were added. The flask was sealed by closing the Teflon valve, and then placed in a 100 °C oil bath for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 100 °C (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. This was then completely dissolved in dry toluene (2 mL) under an argon flow through side-arm of the Schlenk flask to afford the solution of the pre-catalyst. To the flask containing the pre-catalyst was added the dimethyl sulfoxide

(3.6 μL, 0.050 mmol) under a nitrogen flow through side-arm of the Schlenk flask. The resulting mixture was stirred for 1 h at room temperature to give the precatalyst.

Asymmetric epoxidation protocol: The flask containing the catalyst was cooled to –60 °C for 10 min. Meanwhile, to a separate 15 mL flame-dried round bottom flask was added diazoacetamide **I-23a** (70.6mg, 0.500 mmol) and dry toluene (6.0 mL) to give the pre-made solution. To the catalyst solution was added pre-made solution of diazoacetamide **I-23a** via syringe. The flask containing the diazoacetamide **I-23a** was then rinsed with toluene (2 mL) and the rinse was then *trans*ferred to the flask containing the catalyst at –60 °C. This was then followed by closing the Teflon valve and stirring the resulting mixture for 10 min at –60 °C. To the mixture containing diazoacetamide **I-23a** and catalyst was then added neat benzaldehyde **I-51a** (56 μL, 0.55 mmol) dropwise using a microsyringe and the resulting mixture was stirred for 24 h at –60 °C. The reaction was quenched by the addition of H_2O (0.5 mL) and was then warmed to room temperature. The reaction mixture was then *trans*ferred to a 60 mL separatory funnel. The water layer was extracted with CH_2Cl_2 (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered to the 50 mL round bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. Purification of the crude epoxide by silica gel chromatography (17 mm × 300 mm column, 3:1 to 1:1 hexanes/ ethyl acetate as eluent) afforded pure *cis*-epoxide **I-111a** as a colorless semi-solid (105-106 ºC) in 92% isolated yield (100 mg, 0.457 mmol); *cis/trans*: >100:1. β-ketoamide side product **I-114a**: <1 % yield. The optical purity of **I-111a** was determined to be 99% *ee* by HPLC analysis

(PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times; R_t = 16.26 min (minor enantiomer, *ent*-**I-111a**) and R_t = 19.95 min (major enantiomer, **I-111a**).

4.2.8 Optimization of condition for epoxidation catalyzed by *meso*borate **I-118** (*Table 1.7)* -- illustrated by entry 9



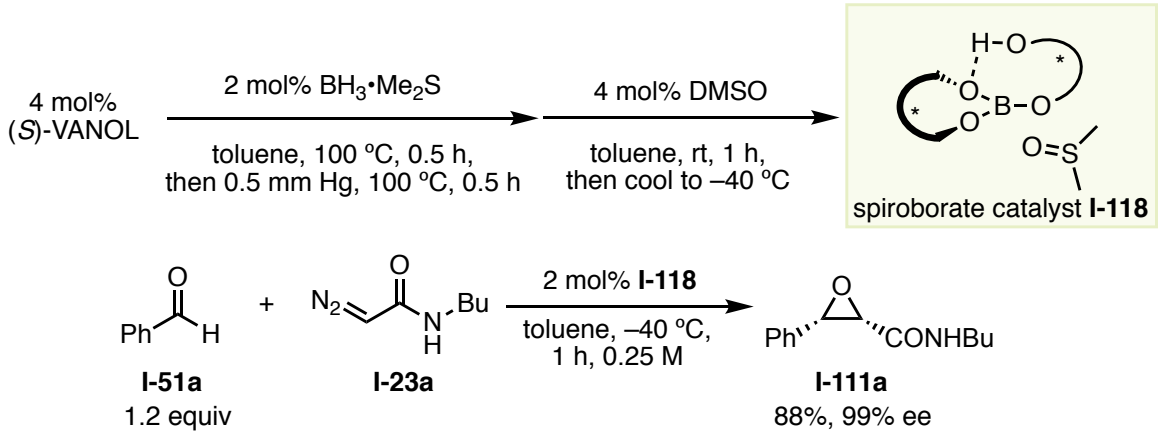
Preparation of the catalyst stock solution ***I-118****:* To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a T-shaped high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-VANOL (33.0 mg, 0.0750 mmol). Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (3 mL) was added through the top of the Teflon valve to effect dissolution. After the addition of the toluene, BH_3•Me_2S (19.0 µL, 0.0375 mmol, 2 M in toluene) was added. The flask was sealed by closing the Teflon valve, and then placed in a 100 ºC oil bath for 0.5 h. After 0.5 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 100 ºC (oil bath). The

flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. The residue was then completely dissolved in dry toluene (3 mL) under a nitrogen flow through side-arm of the Schlenk flask to afford the solution of the pre-catalyst. To the flask containing the pre-catalyst was added the dimethyl sulfoxide (5.4 μL, 0.075 mmol) under a nitrogen flow through side-arm of the Schlenk flask to give the solution of catalyst which was immediately cooled to –40 °C in preparation for initiation of the reaction.

Asymmetric epoxidation protocol: A 25 mL round bottom flask was added 100 mg 4 Å MS and then flame dried under vacuum. After the flask cooled to rt under N_2, the vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23a** (70.6 mg, 0.500 mmol). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous toluene (3 mL). Neat benzaldehyde **I-51a** (60 μL, 0.60 mmol, freshly distilled) was then added via syringe and a N_2 balloon was attached via a needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (2.0 mL, 0.025 mmol catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared. The reaction was quenched after 1 h by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered into a 50 mL

round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. No *trans* epoxide and *β*-ketoamide side product was observed by ^{1}H NMR in the crude reaction mixture. Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 3:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-111a** as a white solid in 99% isolated yield (106 mg, 0.483 mmol); *cis/trans*: >100:1. *β*-ketoamide side product: <1% yield. The optical purity of **I-111a** was determined to be >99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 24.63 min (minor enantiomer, *ent*- **I-111a**) and R_t = 31.46 min (major enantiomer, **I-111a**).

4.2.9 Catalyst loading and stability study (*Table 1.8 & 1.9)* -- illustrated by entry 3 for both

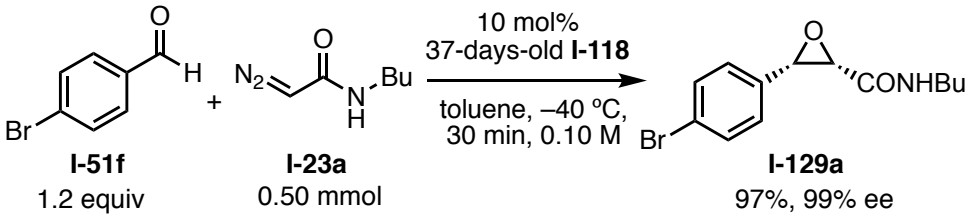


Catalyst **I-118** was prepared according to the general procedure in 4.2.8 described above.

*Asymmetric epoxidation with 4 mol% **I-118**:* A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a

rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23a** (70.6 mg, 0.500 mmol). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous toluene (1.2 mL). Neat benzaldehyde **I-51a** (60 µL, 0.60 mmol, freshly distilled) was then added via syringe and a N_2 balloon was attached via a needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (0.8 mL, 0.01 mmol catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared. The reaction was quenched after 1 h by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered into a 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. No *trans* epoxide and *β*-ketoamide side product was observed by ^{1}H NMR in the crude reaction mixture. Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 3:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-111a** as a white solid in 88% isolated yield (96.6 mg, 0.441 mmol); *cis/trans*: >100:1. *β*-ketoamide side product: <1% yield. The optical purity of **I-111a** was determined to be 99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1

mL/min): retention times: R_t = 24.63 min (major enantiomer, **I-111a**) and R_t = 31.46 min (minor enantiomer, *ent*-**I-111a**).

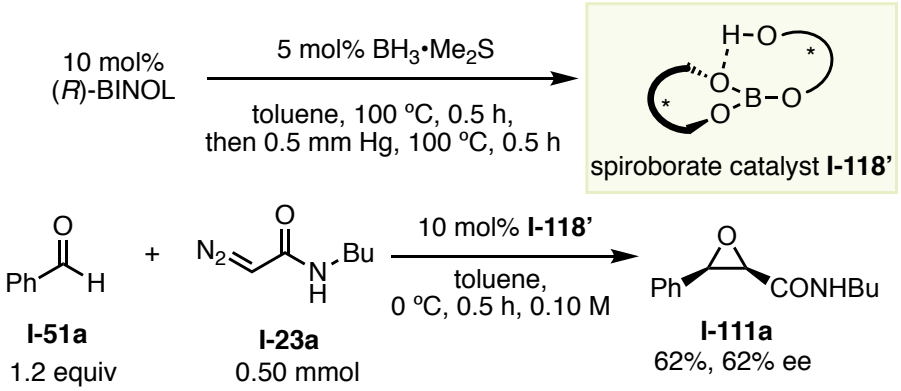


Catalyst **I-118** was prepared according to the general procedure in 4.2.8 described above. The Schlenk flask containing **I-118** was sealed by closing the Teflon valve, and then clamped on benchtop for 37 days.

*Asymmetric epoxidation with 37-day-old **I-118**:* A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23a** (70.6 mg, 0.500 mmol). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous toluene (3 mL). 4-bromobenzaldehyde **I-51f** (111 mg, 0.600 mmol) was then added and a N_2 balloon was attached via a needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (2.0 mL, 0.025 mmol catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared. The reaction was quenched after 30 min by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The

combined organic layer was filtered into a 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as a white solid. No *trans* epoxide and *β*-ketoamide side product was observed by ^{1}H NMR in the crude reaction mixture. Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 3:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-129a** as a white solid in 97% isolated yield (145 mg, 0.485 mmol); *cis/trans*: >100:1. *β*-ketoamide side product: <1% yield. The optical purity of **I-129a** was determined to be 99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 28.91 min (major enantiomer, **I-129a**) and R_t = 45.53 min (minor enantiomer, *ent*-**I-129a**).

4.2.10 Ligand effect in epoxidation catalyzed by *meso*borate **I-118** (*Table 1.10)* -- illustrated by entry 6



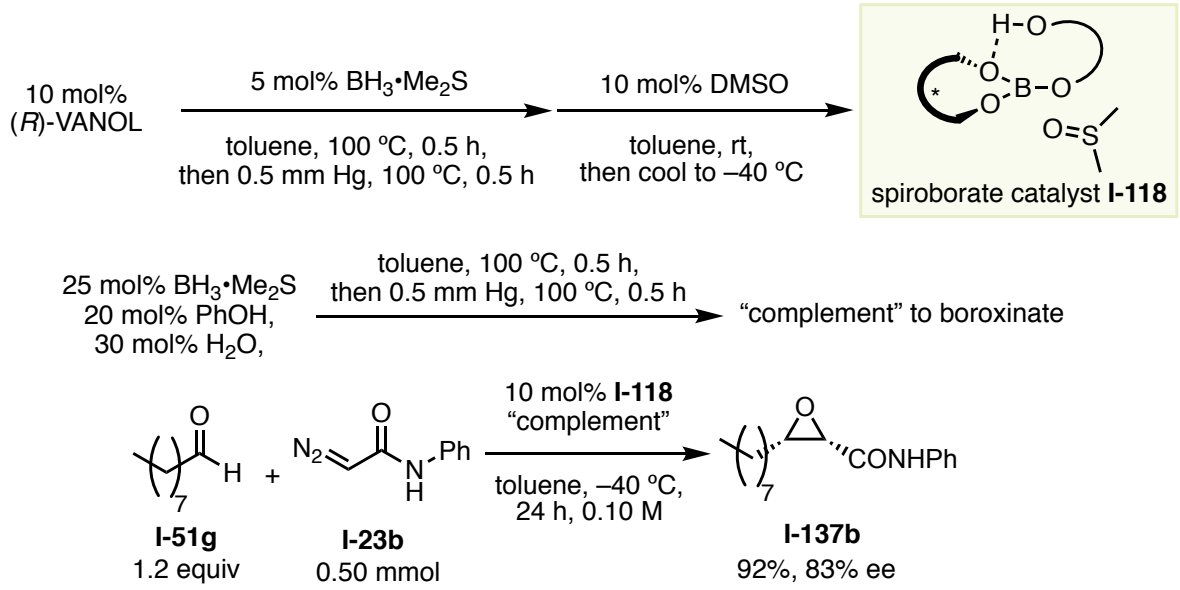
*Preparation of the catalyst stock solution **I-118**:* To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a T-shaped high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-BINOL (21.5 mg, 0.0750 mmol).

Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (3 mL) was added through the top of the Teflon valve to effect dissolution. After the addition of the toluene, BH_3•Me_2S (19.0 µL, 0.0375 mmol, 2 M in toluene) was added. The flask was sealed by closing the Teflon valve, and then placed in a 100 ºC oil bath for 0.5 h. After 0.5 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 100 ºC (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. The residue was then completely dissolved in dry toluene (3 mL) under a nitrogen flow through side-arm of the Schlenk flask to afford the solution of the pre-catalyst. The precatalyst was immediately cooled to –40 °C.

Asymmetric epoxidation protocol: A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23a** (70.6 mg, 0.500 mmol). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous toluene (3 mL). Neat benzaldehyde **I-51a** (60 µL, 0.60 mmol, freshly distilled) was then added via syringe and a N_2 balloon was attached via a needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (2 mL, 0.025 mmol catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared. The reaction was

quenched after 0.5 h by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered into a 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. No *trans* epoxide and *β*-ketoamide side product was observed by ^1H NMR in the crude reaction mixture. Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 3:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-111a** as a white solid in 62% isolated yield (68.2 mg, 0.311 mmol). The optical purity of **I-111a** was determined to be 62% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 24.63 min (minor enantiomer, *ent*- **I-111a**) and R_t = 31.46 min (major enantiomer, **I-111a**).

4.2.11 PhOH additive studies (*Table 1.11)* -- illustrated by entry 3

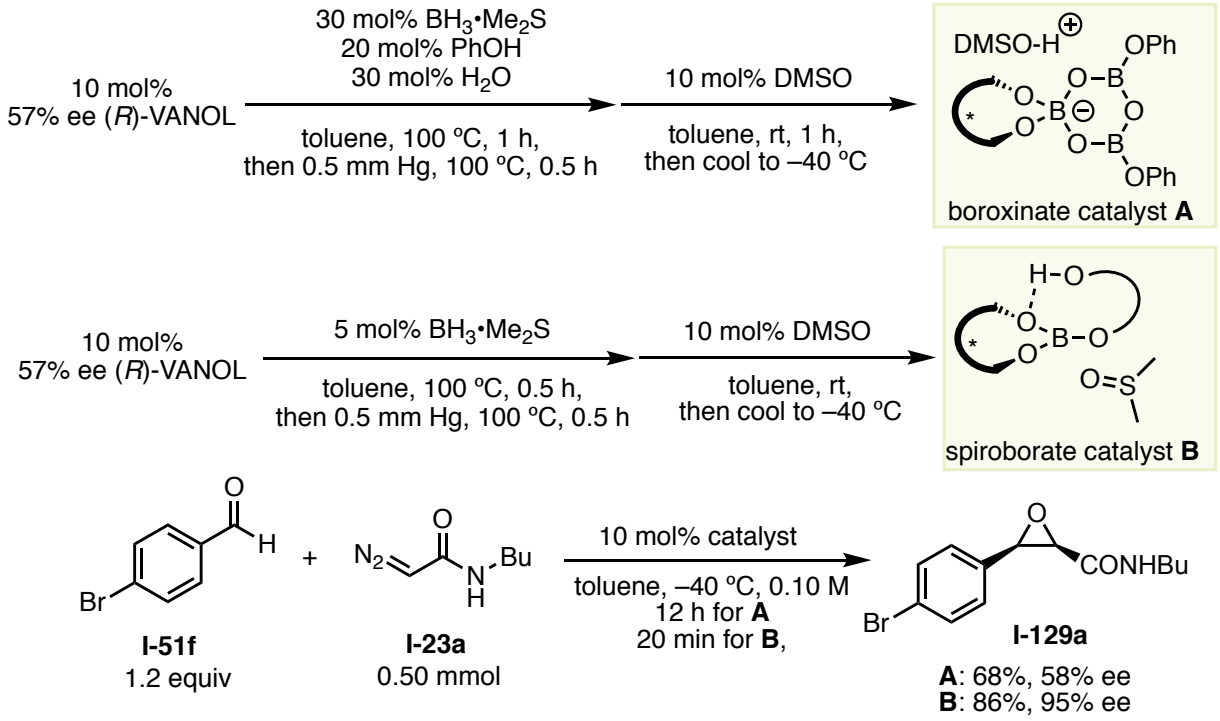


Catalyst **I-118** was prepared according to the general procedure in 4.2.8 described above. In another Schlenk flask, a solution of 25 mol% BH_3•SMe_2, 20 mol% PhOH and 30 mol% of H_2O was heated in toluene for 1 h and then all volatiles were removed at 100 °C at 0.5 mm Hg for 0.5 h to afford the mixture (complement substances of boroxinate catalyst). To the "complement" flask was added 3 mL toluene to dissolve all the solid. The solution was transfer to the catalyst **I-118**. And to the catalyst was added the dimethyl sulfoxide (5.4 µL, 0.075 mmol) under a nitrogen flow through side-arm of the Schlenk flask to give the solution of catalyst which was immediately cooled to –40 °C in preparation for initiation of the reaction.

Asymmetric epoxidation protocol: A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23b** (80.6 mg, 0.500 mmol). Subsequently, the septum was removed again to allow for the

addition of a dry stir bar and anhydrous toluene (3 mL). Neat benzaldehyde **I-51g** (103 μL, 0.60 mmol, freshly distilled) was then added via syringe and a N_2 balloon was attached via a needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (2.0 mL, 0.025 mmol catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared. The reaction was quenched after 24 h by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered into a 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as a colorless oil. No *trans* epoxide and *β*-ketoamide side product was observed by ^{1}H NMR in the crude reaction mixture. Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 10:1 to 4:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-137b** as a colorless oil in 92% isolated yield (127 mg, 0.461 mmol). The optical purity of **I-137b** was determined to be 83% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 4.89 min (minor enantiomer, *ent*-**I-137b**) and R_t = 9.23 min (major enantiomer, **I-137b**).

4.2.12 Nonlinear effect study on two catalytic systems (*Table 1.12)* -- illustrated by entry 7



Catalyst **A** was prepared according to the general procedure in 4.2.2 described above on a 0.075 mmol scale. Catalyst **B** was prepared according to the general procedure in 4.2.8 described above.

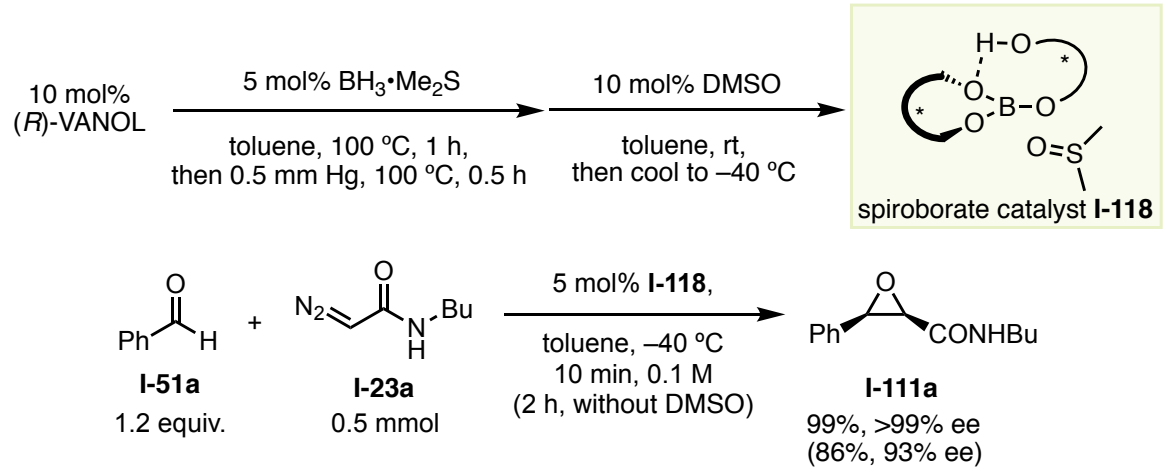
*Asymmetric epoxidation protocol for **A***: A 25 mL Schlenk flask was flame dried under vacuum and cooled to rt under N_2. Under a nitrogen flow through the side-arm of the Schlenk flask, diazoacetamide **I-23a** (70.6 mg, 0.500 mmol), a dry stir bar and anhydrous toluene (3 mL) was added. 4-bromobenzaldehyde **I-51f** (111 mg, 0.600 mmol) was then added. The mixture was stirred at rt for 10 min to effect dissolution. This Schlenk flask and the Schlenk flask containing the catalyst were both cooled to –60 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (2.0 mL, 0.025 mmol

catalyst) was quickly transferred to the Schlenk flask using a syringe. The resulting mixture was stirred until the yellow color disappeared. The reaction was quenched after 12 h by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered into a 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as as a white solid. Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 3:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-129a** as as a white solid in 68% isolated yield (112 mg, 0.342 mmol). The optical purity of **I-129a** was determined to be 58% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 28.91 min (major enantiomer, **I-129a**) and R_t = 45.53 min (minor enantiomer, *ent*-**I-129a**).

*Asymmetric epoxidation protocol for **B***: A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23a** (70.6 mg, 0.500 mmol). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous toluene (3 mL). 4-bromobenzaldehyde **I-51f** (111 mg, 0.600 mmol) was then added and a N_2 balloon was attached via a needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold

bath with a recirculating chiller for 10 min. The catalyst solution (2.0 mL, 0.025 mmol catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared. The reaction was quenched after 30 min by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered into a 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as a white solid. Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 3:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-129a** as a white solid in 86% isolated yield (129 mg, 0.432 mmol); The optical purity of **I-129a** was determined to be 95% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 28.91 min (major enantiomer, **I-129a**) and R_t = 45.53 min (minor enantiomer, *ent*-**I-129a**). The absolute configuration of **I-111b**, **I-137b** and **I-138b** are known[5] and that of **I-111a** was determined by conversion to the taxol side chain **I-146** (*Scheme 1.17*) and the rest were assumed to be homo-chiral.

4.2.13 General procedure **C** for substrate scope study with respect to aldehydes (*Scheme 1.14)* -- illustrated for **I-111a**



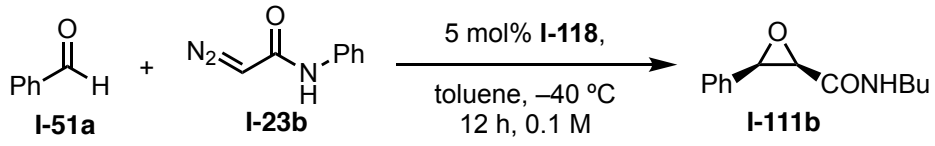
*Preparation of the catalyst **I-118** stock solution:* To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a T-shaped high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-VANOL (33.0 mg, 0.0750 mmol). Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (3 mL) was added through the top of the Teflon valve to effect dissolution. After the addition of the toluene, BH_3•Me_2S (19.0 µL, 0.0375 mmol, 2 M in toluene) was added. The flask was sealed by closing the Teflon valve, and then placed in a 100 °C oil bath for 0.5 h. After 0.5 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 100 °C (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. The residue was then completely dissolved in dry toluene (3 mL) under a nitrogen flow through side-arm of the Schlenk flask to afford the solution

of the pre-catalyst. To the flask containing the pre-catalyst was added the dimethyl sulfoxide (5.4 μL, 0.075 mmol) under a nitrogen flow through side-arm of the Schlenk flask to give the solution of catalyst which was immediately cooled to –40 °C in preparation for initiation of the reaction.

Asymmetric epoxidation protocol: A 25 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23a** (70.6 mg, 0.500 mmol). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous toluene (3 mL). Neat benzaldehyde **I-51a** (60 μL, 0.60 mmol, freshly distilled) was then added via syringe and a N_2 balloon was attached via a needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (2 mL, 0.025 mmol catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared (10 min). The reaction was quenched by the addition of H_2O (1 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with EtOAc (2 mL × 3) and dried over Na_2SO_4. The combined organic layer was filtered into a 50 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. The *cis/trans* ratio was determined by comparing the ^{1}H NMR integration of the ring methine (δ 3.77 for *cis*, δ 3.60 for *trans*) for

each epoxide in the crude reaction mixture. The yield of the acyclic *β*-ketoamide side product was determined by ^{1}H NMR analysis of the crude reaction mixture by integration of the methylene protons (*δ* 3.94) relative to the internal standard (Ph_3CH). Purification of the crude epoxide by silica gel chromatography (20 mm × 300 mm column, 3:1 to 1:1 hexanes/EtOAc as eluent) afforded pure *cis*-epoxide **I-111a** as a white solid (mp 50-53 ºC on >99% *ee* material) in 99% isolated yield (109 mg, 0.498 mmol); *cis/trans*: >100:1. *β*-ketoamide side product: <1% yield. The optical purity of **I-111a** was determined to be >99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 24.63 min (minor enantiomer, *ent*-**I-111a**) and R_t = 31.46 min (major enantiomer, **I-111a**). The reaction without DMSO with a reaction time of 2 hours afforded epoxide **I-111a** in 86% yield and 93% *ee*.

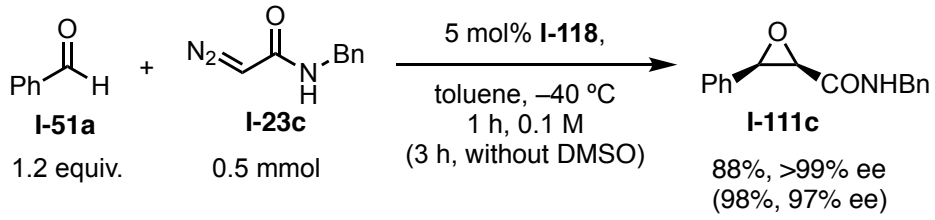
Spectral data for **I-111a**: R_f = 0.26 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 0.65 (t, *J* = 7.5 Hz, 3H), 0.80-1.00 (m, 4H), 2.75-2.83 (m, 1H), 2.98-3.07 (m, 1H), 3.70 (d, *J* = 5.0 Hz, 1H), 4.24 (d, *J* = 5.5 Hz, 1H), 5.85 (brs, 1H), 7.20-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) *δ* 13.46, 19.51, 31.06, 38.10, 56.17, 57.96, 126.38, 128.20, 128.27, 133.07, 165.86; IR (thin film) 3316 br, 3067 w, 2959 s, 2932 s, 2872 m, 1653 vs, 1545 s, 1456 m cm^{-1}; HRMS (ESI-TOF) *m/z* 219.1268 [(M^+); calcd. for $C_{13}H_{17}NO_2$: 219.1259]; $[\alpha]_D^{20}$ –4.3 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



I-51a 1.2 equiv. **I-23b** 0.5 mmol **I-111b** 93%, 98% ee

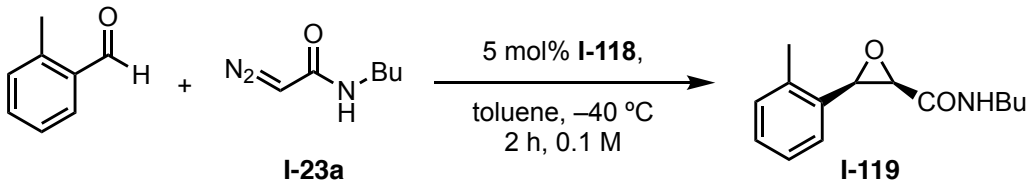
(2R,3R)-N,3-diphenyloxirane-2-carboxamide ***I-111b****:* The epoxide **I-111b** was prepared from aldehyde **I-51a** (61 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23b** (80.6 mg, 0.50 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 12 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/EtOAc as eluent) to give **I-111b** as a white solid (mp 105-108 ºC on 98% *ee* material) in 93% isolated yield (111d mg, 0.465 mmol); *cis/trans*: >100:1. The optical purity of **I-111b** was determined to be 98% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 12.09 min (minor enantiomer, *ent*-**I-111b**) and R_t = 15.49 min (major enantiomer, **I-111b**).

Spectral data for **I-111b**: R_f = 0.42 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81 (d, J = 5.0 Hz, 1H), 4.29 (d, J = 4.0 Hz, 1H), 6.90-6.97 (m, 1H), 7.06-7.12 (m, 4H), 7.14-7.22 (m, 3H), 7.29-7.32 (m, 2H), 7.58 (brs, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 56.46, 58.50, 120.14, 124.73, 126.25, 128.38, 128.52, 128.71, 132.64, 135.88, 164.35; IR (thin film) 3222 br, 3059 w, 1671 vs, 1597 m, 1526 vs, 1445 s cm^{-1}; HRMS (ESI-TOF) *m/z* 239.0954 [(M^+); calcd. for $C_{15}H_{13}NO_2$: 239.0946]; $[\alpha]_D^{20}$ –30.8 (*c* 1.0, CH_2Cl_2) on 98% *ee* material (HPLC). These data match that previously reported for this compound for the (2*S*,3*S*)-enantiomer: $[\alpha]_D^{20}$ 19.1 (*c* 0.90, CH_2Cl_2) on 99% *ee* material.[12]



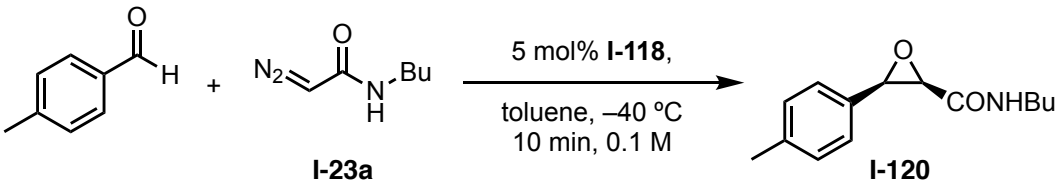
(2R,3R)-N-benzyl-3-phenyloxirane-2-carboxamide ***I-111c****:* The epoxide **I-111c** was prepared from aldehyde **I-51a** (61 μL, 0.60 mmol, 1.2 equiv), diazo compound **I-23c** (87.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 1 hour. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 2:1 hexanes/EtOAc as eluent) to give **I-111c** as a white solid (mp 63-65 ºC on >99% *ee* material) in 93% isolated yield (118 mg, 0.467 mmol); *cis/trans*: >100:1. The optical purity of **I-111c** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 95:5 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 14.70 min (major enantiomer, **I-111c**) and R_t = 16.90 min (minor enantiomer, *ent*-**I-111c**). The reaction without DMSO with a reaction time of 3 hours afforded epoxide **I-111c** in 47% yield and 91% *ee*.

Spectral data for **I-111c**: R_f = 0.23 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.73 (d, J = 4.5 Hz, 1H), 3.96 (dd, J = 15.0, 5.0 Hz, 1H), 4.21 (dd, J = 15.5, 5.5 Hz, 2H), 6.17 (brs, 1H), 6.61 (d, J = 7.0 Hz, 2H), 7.04-7.10 (m, 3H), 7.18-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 42.51, 56.24, 58.11, 126.41, 127.12, 127.26, 128.35, 128.38, 132.91, 136.93, 165.99 (one sp^2 carbon not located); IR (thin film) 3317 br, 3059 w, 3040 w, 2931 w, 1654 vs, 1535 s, 1454 m cm^{-1}; HRMS (ESI-TOF) *m/z* 254.1195 [(M+H$^+$); calcd. for $C_{16}H_{16}NO_2$: 254.1181]; $[\alpha]_D^{20}$ –37.0 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



(2R,3R)-N-butyl-3-(o-tolyl)oxirane-2-carboxamide ***I-119****:* The epoxide **I-119** was prepared from *o*-tolualdehyde (70 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 2 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/EtOAc as eluent) to give **I-119** as an off-white semi-solid (mp 38-40 °C on 97% *ee* material) in 89% isolated yield (104 mg, 0.447 mmol); *cis/trans*: >100:1. The optical purity of **I-119** was determined to be 97% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 17.95 min (minor enantiomer, *ent*-**I-119**) and R_t = 20.89 min (major enantiomer, **I-119**).

Spectral data for **I-119**: R_f = 0.29 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.63 (t, J = 7.0 Hz, 3H), 0.74-0.92 (m, 4H), 2.29 (s, 3H), 2.68-2.77 (m, 1H), 2.95-3.07 (m, 1H), 3.77 (d, J = 3.5 Hz, 1H), 4.18 (d, J = 3.0 Hz, 1H), 5.70 (brs, 1H), 7.04–7.11 (m, 2H), 7.12 (d, J = 7.0 Hz, 1H), 7.23 (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.49, 18.60, 19.49, 31.10, 38.10, 56.02, 57.58, 125.37, 126.05, 128.22, 129.92, 131.67, 136.61, 166.05; IR (thin film) 3331 br, 2959 vs, 2932 s, 2872 m, 1667 vs, 1537 vs, 1493 w, 1462 m cm^{-1}; HRMS (ESI-TOF) *m/z* 233.1419 [(M^+); calcd. for $C_{14}H_{19}NO_2$: 233.1416]; $[\alpha]_D^{20}$ –24.8 (*c* 1.0, CH_2Cl_2) on 97% *ee* material (HPLC).

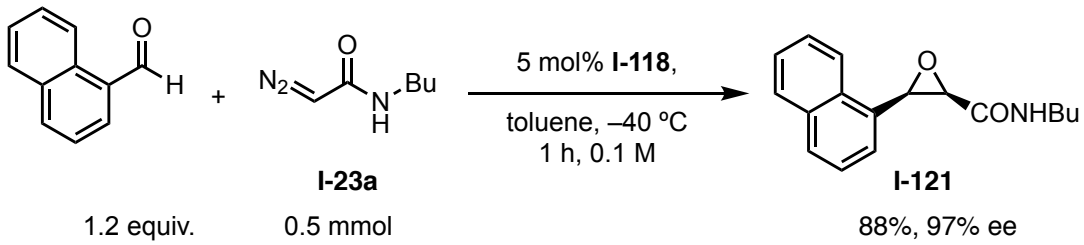


I-23a **I-120**

1.2 equiv. 0.5 mmol 94%, 99% ee

*(2R,3R)-N-butyl-3-(p-tolyl)oxirane-2-carboxamide **I-120**:* The epoxide **I-120** was prepared from *p*-tolualdehyde (71 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 10 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/EtOAc as eluent) to give **I-120** as an off-white solid (mp 54-57 ºC on 99% *ee* material) in 94% isolated yield (110 mg, 0.471 mmol); *cis/trans*: >100:1. The optical purity of **I-120** was determined to be 99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 25.13 min (minor enantiomer, *ent*-**I-120**) and R_t = 37.54 min (major enantiomer, **I-120**).

Spectral data for **I-120**: R_f = 0.23 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.65 (t, J = 7.0 Hz, 3H), 0.80-0.88 (m, 2H), 0.91-0.99 (m, 2H), 2.25 (s, 3H), 2.74-2.82 (m, 1H), 3.01-3.10 (m, 1H), 3.67 (d, J = 4.5 Hz, 1H), 4.20 (d, J = 4.5 Hz, 1H), 5.84 (brs, 1H), 7.06 (d, J = 7.5 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.50, 19.54, 21.03, 31.16, 38.13, 56.21, 57.95, 126.31, 128.86, 130.08, 138.05, 166.01; IR (thin film) 3310 br, 2957 vs, 2932 s, 2869 m, 1653 vs, 1545 vs, 1453 s cm^{-1}; HRMS (ESI-TOF) *m/z* 233.1436 [(M^+); calcd. for $C_{14}H_{19}NO_2$: 233.1416]; $[\alpha]_D^{20}$ –4.7 (*c* 1.0, CH_2Cl_2) on 99% *ee* material (HPLC).

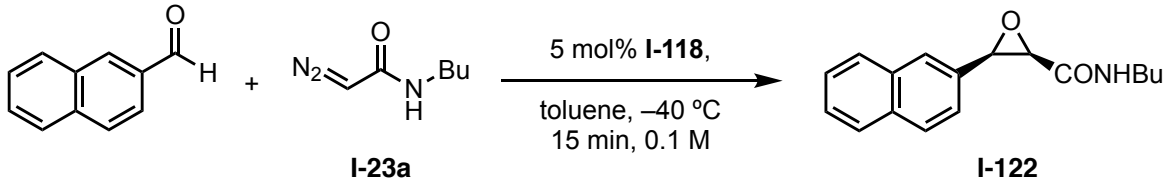


I-23a **I-121**

1.2 equiv. 0.5 mmol 88%, 97% ee

(2R,3R)-N-butyl-3-(naphthalen-1-yl)oxirane-2-carboxamide ***I-121****:* The epoxide **I-121** was prepared from 1-naphthaldehyde (82 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 1 hour. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/EtOAc as eluent) to give **I-121** as a colorless viscous oil in 88% isolated yield (119mg, 0.440 mmol); *cis/trans*: >100:1. The optical purity of **I-121** was determined to be 97% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 26.82 min (minor enantiomer, *ent*-**I-121**) and R_t = 59.42 min (major enantiomer, **I-121**).

Spectral data for **I-121**: R_f = 0.24 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.47 (t, J = 7.0 Hz, 3H), 0.54-0.62 (m, 2H), 0.63-0.70 (m, 2H), 2.58-2.65 (m, 1H), 2.85-2.93 (m, 1H), 3.92 (d, J = 5.5 Hz, 1H), 4.57 (d, J = 5.0 Hz, 1H), 5.71 (brs, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.39-7.49 (m, 3H), 7.72 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.29, 19.26, 30.93, 37.97, 56.03, 57.23, 123.49, 124.33, 124.62, 126.17, 126.66, 128.33, 128.78, 129.33, 130.97, 133.10, 166.03; IR (thin film) 3320 br, 3056 w, 2959 vs, 2932 s, 2872 m, 1663 vs, 1539 vs, 1464 w cm^{-1}; HRMS (ESI-TOF) *m/z* 269.1428 [(M^+); calcd. for $C_{17}H_{19}NO_2$: 269.1416]; $[\alpha]_D^{20}$ –112.0 (*c* 1.0, CH_2Cl_2) on 97% *ee* material (HPLC).



I-23a

1.2 equiv.

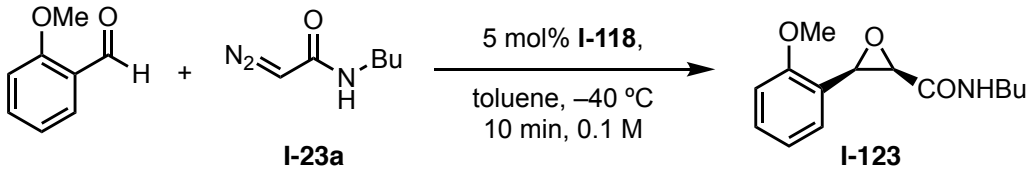
0.5 mmol

I-122

91%, >99% ee

*(2R,3R)-N-butyl-3-(naphthalen-2-yl)oxirane-2-carboxamide **I-122**:* The epoxide **I-122** was prepared from 2-naphthaldehyde (93.7 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 15 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/EtOAc as eluent) to give **I-122** as a white solid (mp 103-104 ºC on >99% *ee* material) in 91% isolated yield (122 mg, 0.454 mmol); *cis/trans*: >100:1. The optical purity of **I-122** was determined to be >99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 26.15 min (minor enantiomer, *ent*-**I-122**) and R_t = 67.17 min (major enantiomer, **I-122**).

Spectral data for **I-122**: R_f = 0.16 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.29 (t, J = 7.0 Hz, 3H), 0.52-0.61 (m, 2H), 0.68-0.76 (m, 2H), 2.63-2.71 (b m, 1H), 2.93-3.02 (m, 1H), 3.76 (d, J = 5.0 Hz, 1H), 4.35 (d, J = 4.5 Hz, 1H), 5.92 (brs, 1H), 7.34-7.40 (m, 3H), 7.67-7.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.04, 19.31, 31.05, 38.07, 56.36, 58.08, 123.84, 125.50, 126.20, 126.31, 127.57, 127.63, 128.09, 130.47, 132.62, 132.95, 165.80; IR (thin film) 3308 br, 3056 w, 2959 vs, 2932 s, 2872 m, 1651 vs, 1545 vs, 1437 w cm^{-1}; HRMS (ESI-TOF) *m/z* 269.1434 [(M^+); calcd. for $C_{17}H_{19}NO_2$: 269.1416]; $[\alpha]_D^{20}$ +55.7 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).

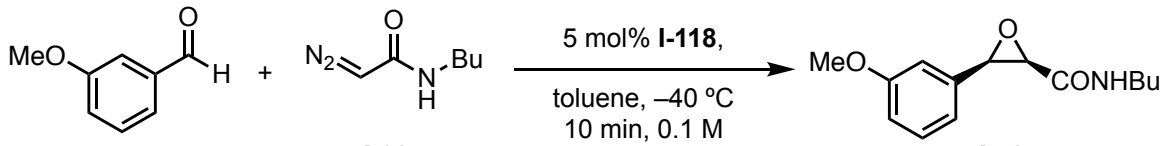


I-23a **I-123**

1.2 equiv. 0.5 mmol 92%, 94% ee

*(2R,3R)-N-butyl-3-(2-methoxyphenyl)oxirane-2-carboxamide **I-123**:* The epoxide **I-123** was prepared from o-Anisaldehyde (81.7 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 10 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/EtOAc as eluent) to give **I-123** as an off-white solid (mp 55-58 ºC on 94% *ee* material) in 92% isolated yield (114 mg, 0.458 mmol); *cis/trans*: >100:1. The optical purity of **I-123** was determined to be 94% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 28.21 min (minor enantiomer, *ent*-**I-123**) and R_t = 33.36 min (major enantiomer, **I-123**).

Spectral data for **I-123**: R_f = 0.23 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.66 (t, J = 7.5 Hz, 3H), 0.84-0.92 (m, 2H), 0.93-1.01 (m, 2H), 2.76-2.84 (m, 1H), 2.99-3.08 (m, 1H), 3.73 (d, J = 4.5 Hz, 1H), 3.76 (s, 3H), 4.24 (d, J = 5.0 Hz, 1H), 5.80 (brs, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 7.17-7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.47, 19.53, 31.15, 38.08, 55.41, 55.96, 56.17, 110.26, 119.79, 121.68, 127.07, 129.49, 158.03, 166.10; IR (thin film) 3310 br, 3075 w, 2959 vs, 2932 s, 2872 m, 1663 vs, 1539 vs, 1497 s, 1464 m cm^{-1}; HRMS (ESI-TOF) *m/z* 249.1373 [(M^+); calcd. for $C_{14}H_{19}NO_3$: 249.1365]; $[\alpha]_D^{20}$ –64.8 (*c* 1.0, CH_2Cl_2) on 94% *ee* material (HPLC).



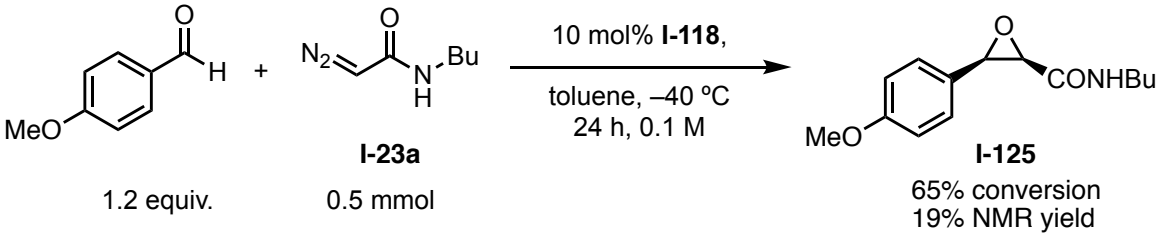
I-23a **I-124**

1.2 equiv. 0.5 mmol 92%, 97% ee

*(2R,3R)-N-butyl-3-(3-methoxyphenyl)oxirane-2-carboxamide **I-124***: The epoxide **I-124** was prepared from m-Anisaldehyde (73 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 10 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/EtOAc as eluent) to give **I-124** as a white solid (mp 58-60 ºC on 97% *ee* material) in 92% isolated yield (115 mg, 0.462 mmol); *cis/trans*: >100:1. The optical purity of **I-124** was determined to be 97% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 32.24 min (minor enantiomer, *ent*-**I-124**) and R_t = 53.87 min (major enantiomer, **I-124**).

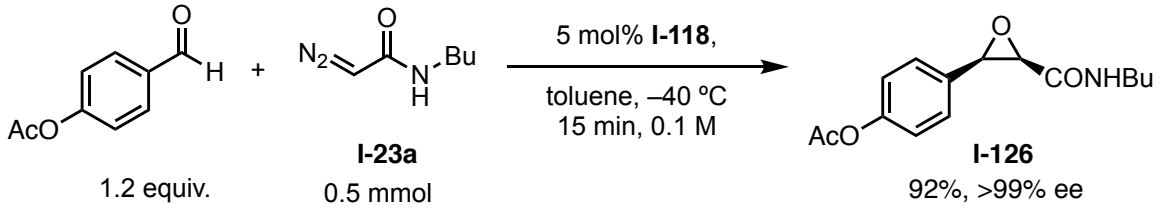
Spectral data for **I-124**: R_f = 0.19 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.66 (t, J = 7.5 Hz, 3H), 0.82-0.91 (m, 2H), 0.94-1.01 (m, 2H), 2.75-2.83 (m, 1H), 3.02-3.11 (m, 1H), 3.69 (d, J = 5.0 Hz, 1H), 3.70 (s, 3H), 4.22 (d, J = 5.0 Hz, 1H), 5.89 (brs, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.82 (s, 1H), 6.86 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.45, 19.49, 31.13, 38.12, 55.04, 56.17, 57.87, 111.85, 113.83, 118.57, 129.36, 134.54, 159.039, 165.82; IR (thin film) 3287 br, 3077 w, 2959 vs, 2934 s, 2872 m, 1655 vs, 1604 s, 1543 vs, 1493 w, 1466 m, 1435 m cm^{-1}; HRMS

(ESI-TOF) *m/z* 249.1365 [(M^+); calcd. for $C_{14}H_{19}NO_3$: 249.1365]; $[\alpha]_D^{20}$ +1.6 (*c* 1.0, CH_2Cl_2) on 97% *ee* material (HPLC).



1.2 equiv. | **I-23a** 0.5 mmol | **I-125** 65% conversion 19% NMR yield

(2R,3R)-N-butyl-3-(4-methoxyphenyl)oxirane-2-carboxamide ***I-125****:* The epoxide **I-125** was prepared from p-Anisaldehyde (73 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the 10 mol% (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 24 hours. The reaction went to 65% conversion. The NMR yield was determined to be 19% from the crude ^{1}H NMR spectrum by integration of the methylene protons relative to the internal standard (Ph_3CH).

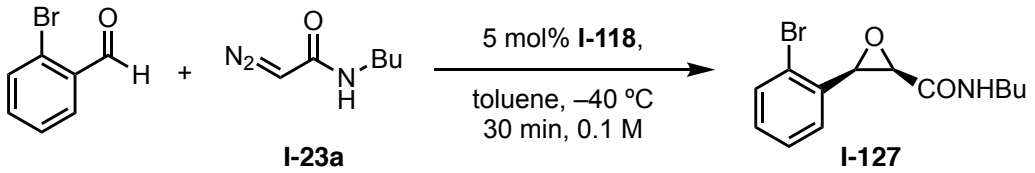


1.2 equiv. | **I-23a** 0.5 mmol | **I-126** 92%, >99% ee

4-((2R,3R)-3-(butylcarbamoyl)oxiran-2-yl)phenyl acetate ***I-126****:* The epoxide **I-126** was prepared from 4-formylphenyl acetate (84 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 15 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-126** as a white solid (mp 112-113 ºC on >99% *ee* material) in 92% isolated yield (127 mg, 0.459 mmol); *cis/trans*: >100:1. The optical purity of **I-126** was determined to be >99% *ee* by HPLC (PIRKLE COVALENT

(*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 53.00 min (minor enantiomer, *ent*-**I-126**) and R_t = 90.09 min (major enantiomer, **I-126**).

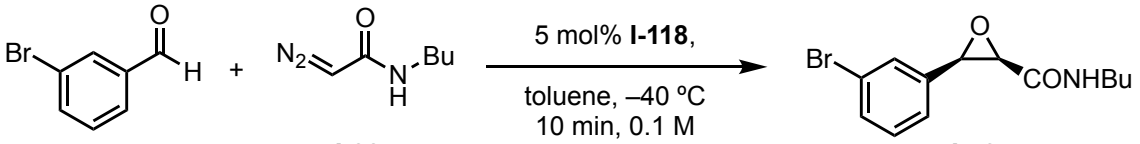
Spectral data for **I-126**: R_f = 0.15 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.68 (t, J = 7.0 Hz, 3H), 0.87-0.96 (m, 2H), 0.96-1.04 (m, 2H), 2.20 (s, 3H), 2.77-2.85 (m, 1H), 2.95-3.07 (m, 1H), 3.69 (d, J = 4.5 Hz, 1H), 4.20 (d, J = 4.0 Hz, 1H), 5.93 (brs, 1H), 7.99 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.27, 19.46, 20.83, 30.96, 38.04, 56.11, 57.37, 121.38, 127.51, 130.54, 150.49, 165.61, 168.86; IR (thin film) 3308 br, 3056 w, 2957 s, 2932 s, 2874 m, 1761 vs, 1657 vs, 1541 m, 1514 vs, 1431 w, 1219 vs, 1200 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 277.1322 [(M^+); calcd. for $C_{15}H_{19}NO_4$: 277.1314]; $[\alpha]_D^{20}$ –2.9(*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



*(2R,3R)-3-(2-bromophenyl)-N-butyloxirane-2-carboxamide **I-127**:* The epoxide **I-127** was prepared from 2-bromobenzaldehyde (71 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 30 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-127** as a yellow oil in 94% isolated yield (141 mg, 0.472 mmol); *cis/trans*: >100:1. The optical purity of **I-127** was determined to be 90% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1

column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 19.69 min (minor enantiomer, *ent*-**I-127**) and R_t = 30.57 min (major enantiomer, **I-127**).

Spectral data for **I-127**: R_f = 0.34 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.65 (t, J = 7.0 Hz, 3H), 0.82-0.91 (m, 2H), 0.91-1.00 (m, 2H), 2.75-2.85 (m, 1H), 3.00-3.10 (m, 1H), 3.82 (d, J = 5.4 Hz, 1H), 4.21 (d, J = 5.4 Hz, 1H), 5.84 (brs, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.40, 19.45, 31.12, 38.08, 56.28, 58.56, 122.51, 126.72, 128.02, 129.68, 132.34, 133.03, 165.14; IR (thin film) 3308 br, 3069, 2959 vs, 2932 vs, 2872 s, 1662 vs, 1539 s, 1474, 1439 s cm^{-1}; HRMS (ESI-TOF) *m/z* 297.0348 [(M^+); calcd. for $C_{13}H_{16}{}^{79}BrNO_2$: 297.0364]; $[\alpha]_D^{20}$ –63.5 (*c* 1.0, CH_2Cl_2) on 90% *ee* material (HPLC).



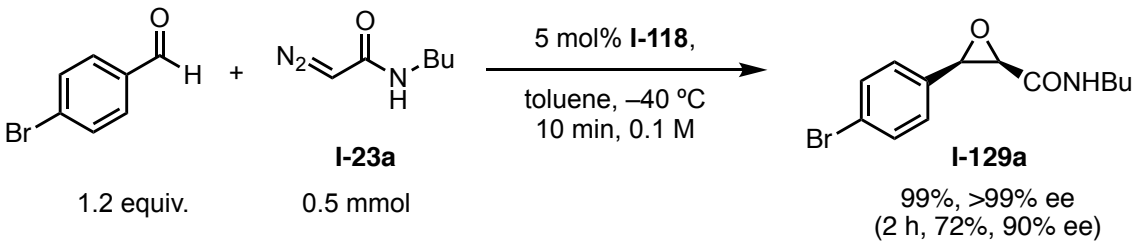
I-23a 1.2 equiv. 0.5 mmol

I-124 96%, 98% ee

(2R,3R)-3-(3-bromophenyl)-N-butyloxirane-2-carboxamide ***I-124****:* The epoxide **I-124** was prepared from 3-bromobenaldehyde (70 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 10 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-124** as an off-white solid (mp 74-76 ºC on 98% *ee* material) in 96% isolated yield (143 mg, 0.478 mmol); *cis/trans*: >100:1. The optical purity of **I-124** was determined to be 98% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min):

retention times: R_t = 18.05 min (minor enantiomer, *ent*-**I-124**) and R_t = 26.19 min (major enantiomer, **I-124**).

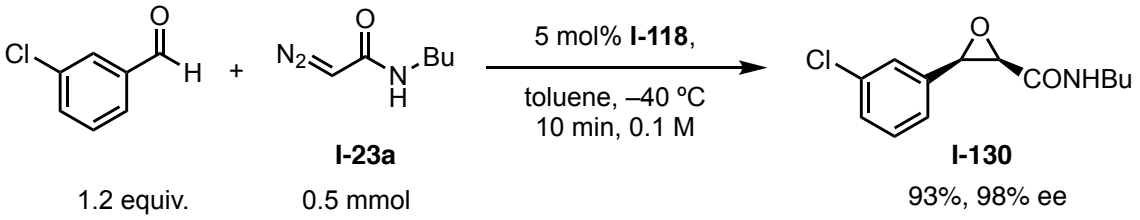
Spectral data for **I-124**: R_f = 0.19 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (t, J = 7.5 Hz, 3H), 0.86-0.95 (m, 2H), 0.99-1.06 (m, 2H), 2.77-2.85 (m, 1H), 3.08-3.16 (m, 1H), 3.72 (d, J = 4.5 Hz, 1H), 4.21 (d, J = 5.0 Hz, 1H), 5.93 (brs, 1H), 7.14 (t, J = 7.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.53, 19.61, 31.26, 38.22, 56.30, 57.16, 122.34, 125.18, 129.36, 129.85, 131.45, 135.34, 165.33; IR (thin film) 3299 br, 2959 vs, 2932 s, 2872 m, 1659 vs, 1599 w, 1541 vs, 1437 w cm^{-1}; HRMS (ESI-TOF) *m/z* 297.0393 [(M^+); calcd. for $C_{13}H_{16}{}^{79}BrNO_2$: 297.0364]; $[\alpha]_D^{20}$ +26.1 (*c* 1.0, CH_2Cl_2) on 98% *ee* material (HPLC).



(2R,3R)-3-(4-bromophenyl)-N-butyloxirane-2-carboxamide ***I-129a***: The epoxide **I-129a** was prepared from 4-bromobenzaldehyde (111 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 10 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129a** as a white solid (mp 109-111 °C on >99% *ee* material) in 99% isolated yield (148 mg, 0.495 mmol); *cis/trans*: >100:1. The optical purity of **I-129a** was determined to be >99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1

mL/min): retention times: R_t = 28.91 min (minor enantiomer, *ent*-**I-129a**) and R_t = 45.53 min (major enantiomer, **I-129a**). The reaction without DMSO with a reaction time of 2 hours afforded epoxide **I-129a** in 72% yield and 90% *ee*.

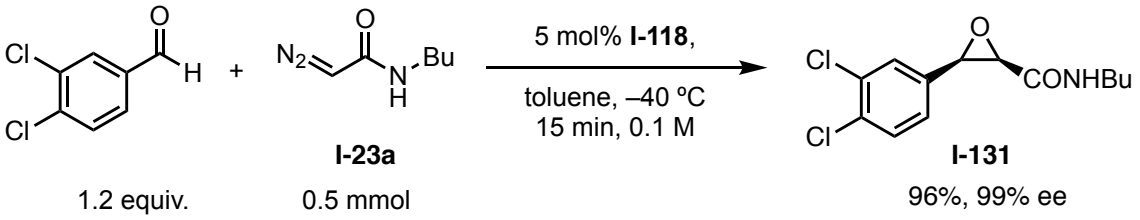
Spectral data for **I-129a**: R_f = 0.16 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (t, J = 7.5 Hz, 3H), 0.86-0.95 (m, 2H), 0.99-1.06 (m, 2H), 2.77-2.85 (m, 1H), 3.02-3.12 (m, 1H), 3.71 (d, J = 4.5 Hz, 1H), 4.19 (d, J = 4.0 Hz, 1H), 5.87 (brs, 1H), 7.17 (d, J = 7.5 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.51, 19.57, 31.20, 38.19, 56.14, 57.34, 122.41, 128.14, 131.37, 132.14, 165.48; IR (thin film) 3299 br, 2957 s, 2930 s, 2863 m, 1653 vs, 1545 vs, 1491 w, 1435 w cm^{-1}; HRMS (ESI-TOF) *m/z* 297.0387 [(M^+); calcd. for $C_{13}H_{16}{}^{79}BrNO_2$: 297.0364]; $[\alpha]_D^{20}$ –7.2 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



(2R,3R)-N-butyl-3-(3-chlorophenyl)oxirane-2-carboxamide ***I-130****:* The epoxide **I-130** was prepared from 3-chlorobenzaldehyde (68 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 10 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-130** as a white solid (mp 61-63 °C on 98% *ee* material) in 93% isolated yield (119 mg, 0.467 mmol); *cis/trans*: >100:1. The optical purity of **I-130** was determined to be 98% *ee* by HPLC (PIRKLE COVALENT

(*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 26.05 min (minor enantiomer, *ent*-**I-130**) and R_t = 38.42 min (major enantiomer, **I-130**).

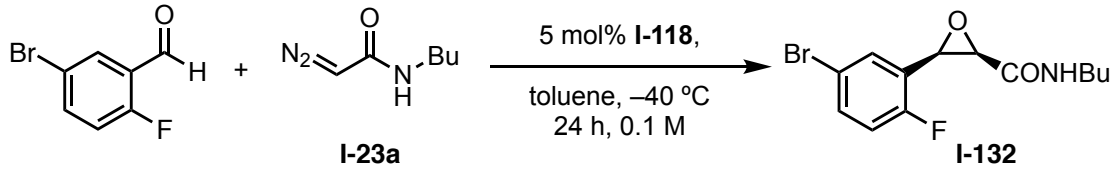
Spectral data for **I-130**: R_f = 0.21 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.69 (t, J = 7.0 Hz, 3H), 0.84-0.95 (m, 2H), 0.97-1.06 (m, 2H), 2.76-2.85 (m, 1H), 3.06-3.12 (m, 1H), 3.72 (d, J = 5.0 Hz, 1H), 4.21 (d, J = 4.5 Hz, 1H), 5.97 (brs, 1H), 7.26–7.24 (m, 3H), 7.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.45, 19.55, 31.21, 38.18, 56.27, 57.21, 124.67, 126.46, 128.47, 129.56, 134.21, 135.08, 165.32; IR (thin film) 3270 br, 3073 w, 2961 s, 2932 s, 2874 m, 1653 vs, 1601 w, 1549 vs, 1435 m cm^{-1}; HRMS (ESI-TOF) *m/z* 253.0868 [(M^+); calcd. for $C_{13}H_{16}{}^{35}ClNO_2$: 253.0870]; $[\alpha]_D^{20}$ +18.0 (*c* 1.0, CH_2Cl_2) on 98% *ee* material (HPLC).



(2R,3R)-N-butyl-3-(3,4-dichlorophenyl)oxirane-2-carboxamide ***I-131****:* The epoxide **I-131** was prepared from 3,4-dichlorobenzaldehyde (105 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 15 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-131** as an off-white semi-solid (mp 48-50 ºC on 99% *ee* material) in 96% isolated yield (138 mg, 0.480 mmol); *cis/trans*: >100:1. The optical purity of **I-131** was determined to be 99% *ee* by HPLC

(PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 17.75 min (minor enantiomer, *ent*-**I-131**) and R_t = 26.29 min (major enantiomer, **I-131**).

Spectral data for **I-131**: R_f = 0.18 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (t, J = 7.0 Hz, 3H), 0.86-0.95 (m, 2H), 1.00-1.09 (m, 2H), 2.79-2.87 (m, 1H), 3.10-3.19 (m, 1H), 3.73 (d, J = 5.0 Hz, 1H), 4.18 (d, J = 4.5 Hz, 1H), 6.00 (brs, 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.47, 19.61, 31.33, 38.28, 56.34, 56.69, 125.88, 128.38, 130.29, 132.54, 132.59, 133.32, 165.13; IR (thin film) 3299 br, 2959 vs, 2932 s, 2872 m, 1660 vs, 1543 vs, 1474 m cm^{-1}; HRMS (ESI-TOF) *m/z* 287.0502 [(M^+); calcd. for $C_{13}H_{15}{}^{35}Cl_2NO_2$: 287.0480]; $[\alpha]_D^{20}$ 10.9 (*c* 1.0, CH_2Cl_2) on 99% *ee* material (HPLC).

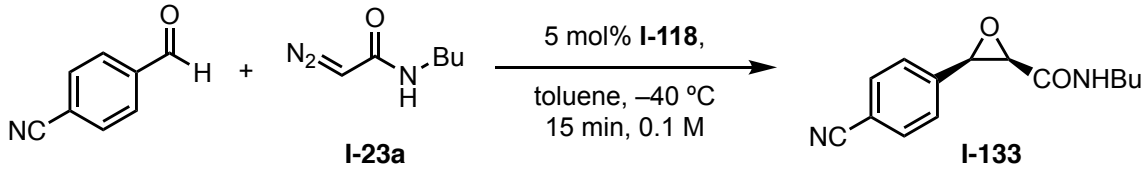


1.2 equiv. **I-23a** 0.5 mmol **I-132** 82%, 63% ee

(2R,3R)-3-(5-bromo-2-fluorophenyl)-N-butyloxirane-2-carboxamide ***I-132****:* The epoxide **I-132** was prepared from 5-bromo-2-fluorobenzaldehyde (72 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 24 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-132** as a white solid (mp 70-73 ºC on 63% *ee* material) in 82% isolated yield (129 mg, 0.409 mmol); *cis/trans*: >100:1. The optical purity of **I-132** was determined to be 63% *ee* by HPLC

(PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 18.55 min (minor enantiomer, *ent*-**I-132**) and R_t = 25.68 min (major enantiomer, **I-132**).

Spectral data for **I-132**: R_f = 0.39 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (t, J = 7.0 Hz, 3H), 0.90-1.01 (m, 2H), 1.03-1.15 (m, 2H), 2.80-2.89 (m, 1H), 3.15-3.24 (m, 1H), 3.79 (d, J = 4.5 Hz, 1H), 4.26 (d, J = 5.0 Hz, 1H), 6.03 (brs, 1H), 6.90 (t, J = 9.0 Hz, 1H), 7.32-7.37 (m, 1H), 7.39 (d, J = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.55, 19.68, 31.38, 38.33, 53.46 (d, J_{CF} = 3.9 Hz), 56.02, 116.23 (d, J_{CF} = 3.5 Hz), 117.22 (d, J_{CF} = 21.8 Hz), 122.95 (d, J_{CF} = 15.8 Hz), 130.65 (d, J_{CF} = 3.7 Hz), 132.90 (d, J_{CF} = 7.9 Hz), 160.12 (d, J_{CF} = 249.6 Hz), 164.93; IR (thin film) 3285 br, 3071 w, 2959 vs, 2932 s, 2872 m, 1655 vs, 1547 vs, 1485 vs, 1439 w, 1408 m cm^{-1}; HRMS (ESI-TOF) *m/z* 315.0287 [(M^+); calcd. for $C_{13}H_{15}{}^{79}BrFNO_2$: 315.0270]; $[\alpha]_D^{20}$ +49.5 (*c* 1.0, CH_2Cl_2) on 63% *ee* material (HPLC).



I-23a

1.2 equiv. 0.5 mmol

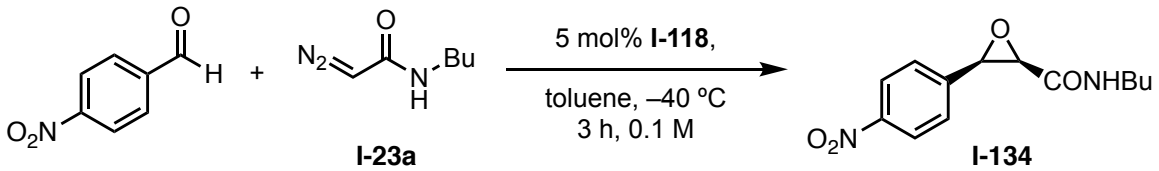
I-133

98%, 96% ee

(2R,3R)-N-butyl-3-(4-cyanophenyl)oxirane-2-carboxamide ***I-133****:* The epoxide **I-133** was prepared from aldehyde **31** (78.7 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 15 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 2:1 to 1:2 hexanes/ EtOAc as eluent) to give **I-133** as an off-white semi-solid

(mp 76-78 ºC on 96% *ee* material) in 98% isolated yield (120 mg, 0.489 mmol); *cis/trans*: >100:1. The optical purity of **I-133** was determined to be 96% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 74.00 min (minor enantiomer, *ent*-**I-133**) and R_t = 79.59 min (major enantiomer, **I-133**).

Spectral data for **I-133**: R_f = 0.07 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (t, J = 7.5 Hz, 3H), 0.85-0.95 (m, 2H), 0.98-1.07 (m, 2H), 2.80-2.89 (m, 1H), 3.00-3.08 (m, 1H), 3.78 (d, J = 5.5 Hz, 1H), 4.28 (d, J = 5.0 Hz, 1H), 6.01 (brs, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.37, 19.46, 31.09, 38.13, 56.31, 57.08, 112.11, 118.07, 127.22, 131.88, 138.31, 164.92; IR (thin film) 3310 br, 3065 w, 2961 vs, 2934 s, 2874 s, 2230 vs, 1663 vs, 1612 m, 1541 vs, 1466 m, 1437 m cm^{-1}; HRMS (ESI-TOF) *m/z* 244.1218 [(M^+); calcd. for $C_{14}H_{16}N_2O_2$: 244.1212]; $[\alpha]_D^{20}$ −18.3 (*c* 1.0, CH_2Cl_2) on 96% *ee* material (HPLC).



I-23a

1.2 equiv. 0.5 mmol

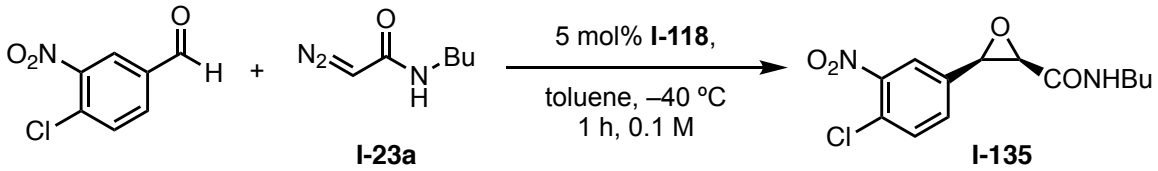
I-134

87%, 94% ee

*(2R,3R)-N-butyl-3-(4-nitrophenyl)oxirane-2-carboxamide **I-134**:* The epoxide **I-134** was prepared from 4-nitrobenzaldehyde (90.7 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 3 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 2:1 to 1:2 hexanes/ EtOAc as eluent) to give **I-134** as a white solid (mp 92-95

ºC on 94% *ee* material) in 87% isolated yield (115 mg, 0.434 mmol); *cis/trans*: >100:1. The optical purity of **I-134** was determined to be 94% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 50.34 min (minor enantiomer, *ent*-**I-134**) and R_t = 57.11 min (major enantiomer, **I-134**).

Spectral data for **I-134**: R_f = 0.07 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.65 (t, J = 7.5 Hz, 3H), 0.84-0.94 (m, 2H), 0.98-1.06 (m, 2H), 2.82-2.90 (m, 1H), 2.98-3.07 (m, 1H), 3.80 (d, J = 5.0 Hz, 1H), 4.32 (d, J = 4.5 Hz, 1H), 5.97 (brs, 1H), 7.51 (d, J = 9.0 Hz, 2H), 8.15 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.36, 19.57, 31.22, 38.28, 56.45, 57.09, 123.42, 127.52, 140.27, 147.78, 164.91; IR (thin film) 3314 br, 3081 w, 2959 vs, 2934 s, 2872 m, 1661 vs, 1605 s 1522 vs, 1466 w, 1437 w, 1346 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 264.1132 [(M^+); calcd. for $C_{13}H_{16}N_2O_4$: 264.1110]; $[\alpha]_D^{20}$ –30.5 (*c* 1.0, CH_2Cl_2) on 94% *ee* material (HPLC).



1.2 equiv.

I-23a

0.5 mmol

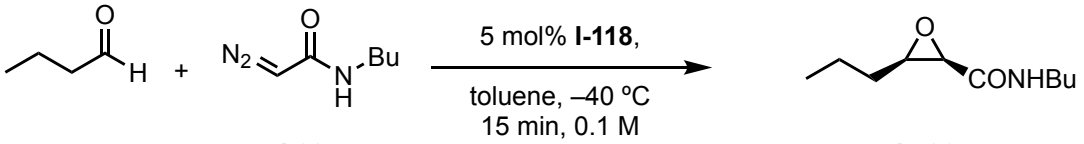
I-135

98%, 89% ee

(2R,3R)-N-butyl-3-(4-chloro-3-nitrophenyl)oxirane-2-carboxamide ***I-135:*** The epoxide **I-135** was prepared from 4-chloro-3-nitrobenzaldehyde (111.3 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 1 hour. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 2:1 to 1:2 hexanes/ EtOAc as eluent) to give **I-**

135 as a white solid (mp 59-62 ºC on 89% *ee* material) in 98% isolated yield (146 mg, 0.488 mmol); *cis/trans*: >100:1. The optical purity of **I-135** was determined to be 89% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 43.78 min (minor enantiomer, *ent*-**I-135**) and R_t = 53.87 min (major enantiomer, **I-135**).

Spectral data for **I-135**: R_f = 0.08 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.71 (t, J = 7.0 Hz, 3H), 0.88-0.98 (m, 2H), 1.02-1.14 (m, 2H), 2.85-2.93 (m, 1H), 3.06-3.15 (m, 1H), 3.80 (d, J = 4.0 Hz, 1H), 4.27 (d, J = 4.5 Hz, 1H), 6.21 (brs, 1H), 7.46-7.52 (m, 2H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.39, 19.58, 31.25, 38.38, 56.27, 56.58, 123.55, 126.88, 131.20, 131.77, 133.77, 147.54, 164.76; IR (thin film) 3303 br, 3081 w, 2961 s, 2934 s, 2874 m, 1661 vs, 1537 vs, 1493 w, 1466 w, 1350 s cm^{-1}; HRMS (ESI-TOF) *m/z* 298.0731 [(M^+); calcd. for $C_{13}H_{15}{}^{35}ClN_2O_4$: 298.0720]; $[\alpha]_D^{20}$ –18.2 (*c* 1.0, CH_2Cl_2) on 89% *ee* material (HPLC).



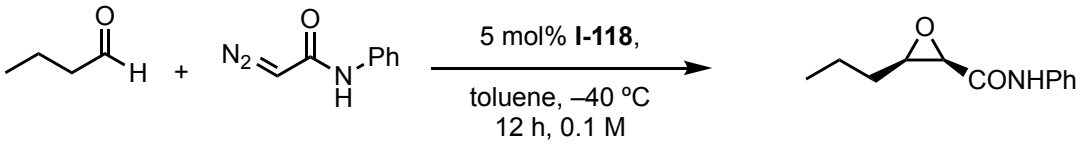
I-23a — 1.2 equiv. — 0.5 mmol

I-136a — 87%, 96% ee

*(2R,3R)-N-butyl-3-propyloxirane-2-carboxamide **I-136a**:* The epoxide **I-136a** was prepared from butyraldehyde (55 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 15 minutes. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-136a** as a colorless oil in 87% isolated yield

(80.6 mg, 0.435 mmol); *cis/trans*: >100:1. The optical purity of **I-136a** was determined to be 96% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 11.83 min (minor enantiomer, *ent*- **I-136a**) and R_t = 15.07 min (major enantiomer, **I-136a**).

Spectral data for **I-136a**: R_f = 0.24 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, J = 7.0 Hz, 3H), 0.85-0.90 (m, 3H), 1.26 (td, J = 10.0 Hz, 8Hz, 2H), 1.38-1.46 (m, 6H), 3.06-3.10 (m, 1H), 3.16 (septet, J = 6.5 Hz, 1H), 3.23 (septet, J = 6.5 Hz, 1H), 3.41 (d, J = 5.0 Hz, 1H), 6.12 (brs, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.56, 13.76, 19.32, 19.95, 29.53, 31.51, 38.48, 55.16, 58.30, 167.29; IR (thin film) 3303 br, 2961 vs, 2931 vs, 2874 s, 1661 vs, 1539 vs, 1466 m, cm^{-1}; HRMS (ESI-TOF) *m/z* 185.1419 [(M^+); calcd. for $C_{10}H_{19}NO_2$: 185.1416]; $[\alpha]_D^{20}$ +24.4 (*c* 1.0, CH_2Cl_2) on 96% *ee* material (HPLC).



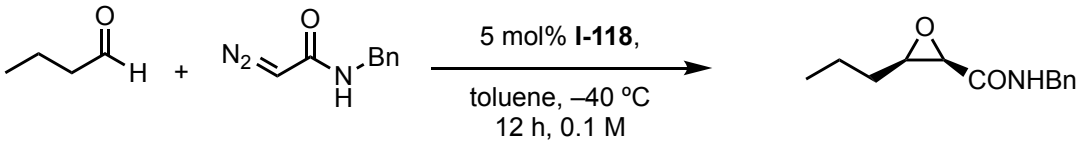
I-23b 1.2 equiv. 0.5 mmol

I-136b 94%, 90% ee

*(2R,3R)-N-phenyl-3-propyloxirane-2-carboxamide **I-136b**:* The epoxide **I-136b** was prepared from butyraldehyde (55 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23b** (80.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 12 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-136b** as a colorless oil in 94% isolated yield (96.3 mg, 0.469 mmol); *cis/trans*: >100:1. The optical purity of **I-136b** was determined to be 90% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm,

flow-rate: 1 mL/min): retention times: R_t = 5.63 min (minor enantiomer, *ent*-**I-136b**) and R_t = 10.66 min (major enantiomer, **I-136b**).

Spectral data for **I-136b**: R_f = 0.48 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, J = 7.0 Hz, 3H), 1.41-1.55 (m, 4H), 3.18 (q, J = 5.5Hz, 1H), 3.41 (d, J = 5.0 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.85 (brs, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.73, 19.38, 29.60, 55.35, 58.94, 119.68, 124.69, 128.99, 136.44, 165.45; IR (thin film) 3297 br, 3141 w, 3061 w, 2963 vs, 2934 s, 2874 m, 1680 vs, 1601 vs, 1536 vs, 1499 s, 1444 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 205.1113 [(M^+); calcd. for $C_{12}H_{15}NO_2$: 205.1103]; $[\alpha]_D^{20}$ +31.3 (*c* 1.0, CH_2Cl_2) on 90% *ee* material (HPLC). These data match that previously reported for this compound for the (2*S*,3*S*)-enantiomer: $[\alpha]_D^{20}$ –31.6 (*c* 0.78, CH_2Cl_2) on >99% *ee* material[5].



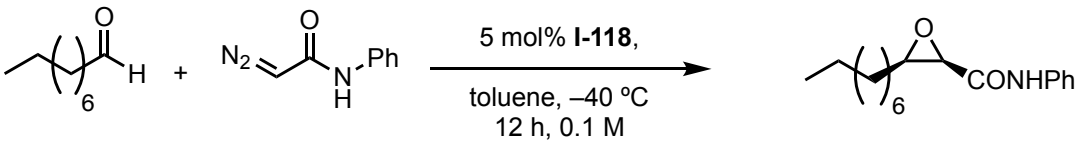
I-23c 0.5 mmol (1.2 equiv.)

I-136c 93%, >99% ee

*(2R,3R)-N-benzyl-3-propyloxirane-2-carboxamide **I-136c**:* The epoxide **I-136c** was prepared from butyraldehyde (55 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23c** (87.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 12 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-136c** as an off-white solid (mp 46-48 ºC on >99% *ee* material) 96% isolated yield (105 mg, 0.478 mmol); *cis/trans*: >100:1. The optical purity of **I-136c** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6

hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 8.23 min (minor enantiomer, *ent*-**I-136c**) and R_t = 9.03 min (major enantiomer, **I-136c**).

Spectral data for **I-136c**: R_f = 0.28 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (t, J = 7.0 Hz, 3H), 1.38 (m, 4H), 3.06 (d, J = 4.5 Hz, 1H), 3.43 (d, J = 4.5 Hz, 1H), 4.31 (dd, J = 14.5, 5.5 Hz, 1H), 4.43 (dd, J = 14.5, 6.0 Hz, 1H), 6.52 (brs, 1H), 7.17-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.66, 19.20, 29.45, 42.74, 55.02, 58.31, 127.49, 127.74, 128.44, 137.62, 167.19; IR (thin film) 3308 br, 3141 w, 3061 w, 2961 vs, 2932 s, 2873 m, 1665 vs, 1535 vs, 1497 w, 1455 s, 1428 w cm^{-1}; HRMS (ESI-TOF) *m/z* 220.1348 [(M+H$^+$); calcd. for $C_{13}H_{18}NO_2$: 220.1338]; $[\alpha]_D^{20}$ –2.8 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



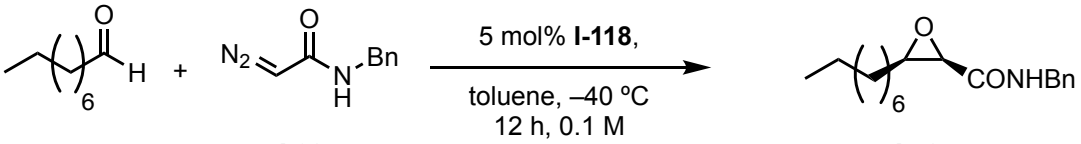
I-23b 1.2 equiv. 0.5 mmol

I-137b 88%, 89% ee

*(2R,3R)-3-octyl-N-phenyloxirane-2-carboxamide **I-137b**:* The epoxide **I-137b** was prepared from nonanal (103 µL, 0.600 mmol, 1.20 equiv), diazo compound **I-23b** (80.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 12 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-137b** as a colorless oil in 88% isolated yield (121 mg, 0.441 mmol); *cis/trans*: >100:1. The optical purity of **I-137b** was determined to be 89% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm,

flow-rate: 1 mL/min): retention times: R_t = 4.89 min (minor enantiomer, *ent*-**I-137b**) and R_t = 9.23 min (major enantiomer, **I-137b**).

Spectral data for **I-137b**: R_f = 0.60 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.78 (t, J = 7.0 Hz, 3H), 1.09-1.28 (m, 10H), 1.36-1.47 (m, 2H), 1.48-1.55 (m, 2H), 3.16 (q, J = 6.0 Hz, 1H), 3.53 (d, J = 4.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 8.0 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.87 (brs, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.95, 22.47, 25.92, 27.58, 28.96, 29.07, 29.19, 31.65, 55.40, 59.07, 119.68, 124.65, 128.94, 136.44, 165.47; IR (thin film) 3299 br, 3141 w, 3061 w, 2928 vs, 2857 s, 1682 vs, 1603 vs, 1536 vs, 1501 s, 1445 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 275.1901 [(M^+); calcd. for $C_{17}H_{25}NO_2$: 275.1885]; $[\alpha]_D^{20}$ +25.9 (*c* 1.0, CH_2Cl_2) on 89% *ee* material (HPLC).



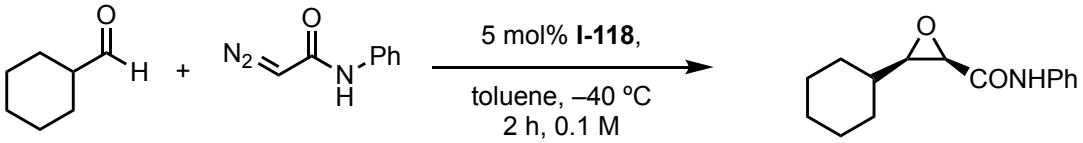
I-23c — 1.2 equiv. — 0.5 mmol

I-137c — 93%, >99% ee (12 h, 82%, >99% ee)

*(2R,3R)-N-benzyl-3-octyloxirane-2-carboxamide **I-137c**:* The epoxide **I-137c** was prepared from nonanal (103 µL, 0.600 mmol, 1.20 equiv), diazo compound **I-23c** (87.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 12 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-137c** as a white solid (mp 53-55 ºC on >99% *ee* material) in 93% isolated yield (134 mg, 0.464 mmol); *cis/trans*: >100:1. The optical purity of **I-137c** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 6.52 min (minor

enantiomer, *ent*-**I-137c**) and R_t = 7.25 min (major enantiomer, **I-137c**). The reaction without DMSO with a reaction time of 12 hours afforded epoxide **I-137c** in 82% yield and 99% *ee*.

Spectral data for **I-137c**: R_f = 0.39 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (t, J = 7.0 Hz, 3H), 1.17-1.23 (m, 10H), 1.33-1.41 (m, 4H), 3.06 (dd, J = 11.0, 6.0 Hz, 1H), 3.44 (d, J = 5.0 Hz, 1H), 4.30 (dd, J = 14.5, 6.0 Hz, 1H), 4.34 (dd, J = 14.5, 6.5 Hz, 1H), 6.49 (brs, 1H); 7.17-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.97, 22.51, 25.85, 27.53, 20.01, 29.14, 29.18, 31.67, 42.77, 55.13, 58.53, 127.51, 127.77, 128.57, 137.62, 167.19; IR (thin film) 3330 br, 3141 w, 3061 w, 2953 s, 2926 vs, 2855 s, 1656 vs, 1533 vs, 1455 m, 1425 m cm^{-1}; HRMS (ESI-TOF) *m/z* 290.2132 [(M+H$^+$); calcd. for $C_{18}H_{28}NO_2$: 290.2120]; $[\alpha]_D^{20}$ –12.7 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



I-23b 0.5 mmol

1.2 equiv.

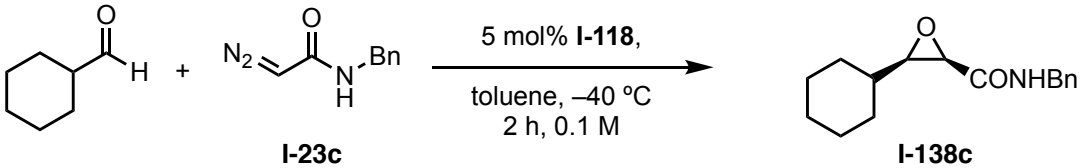
I-138b

99%, 98% ee

(2R,3R)-3-cyclohexyl-N-phenyloxirane-2-carboxamide ***I-138b***: The epoxide **I-138b** was prepared from cyclohexanecarbaldehyde (73 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23b** (80.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 12 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-138b** as a white solid (mp 70-72 ºC on 96% *ee* material) in 99% isolated yield (122 mg, 0.497 mmol); *cis/trans*: >100:1. The optical purity of **I-138b** was determined to be 98% *ee* by HPLC (Daicel Chirapak OD-

H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 5.73 min (minor enantiomer, *ent*-**I-138b**) and R_t = 8.45 min (major enantiomer, **I-138b**).

Spectral data for **I-138b**: R_f = 0.55 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00-1.22 (m, 6H), 1.52-1.71 (m, 4H), 1.90 (d, J = 4.5 Hz, 1H), 2.91 (q, J = 4.5 Hz, 1H), 3.56 (d, J = 5.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 8.0 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.85 (brs, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 25.00, 25.84, 28.29, 30.42, 36.81, 55.46, 63.17, 119.83, 124.71, 129.02, 136.47, 165.53 (one sp^3 carbon not located); IR (thin film) 3293 br, 3141 w, 3061 w, 2928 vs, 2853 m, 1676 vs, 1601 vs, 1536 vs, 1499 s, 1446 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 245.1428 [(M^+); calcd. for $C_{15}H_{19}NO_2$: 245.1416]; $[\alpha]_D^{20}$ +25.7 (*c* 1.0, CH_2Cl_2) on 98% *ee* material (HPLC). These data match that previously reported for this compound for the (2*S*,3*S*)-enantiomer: $[\alpha]_D^{20}$ –20.9 (*c* 0.76, CH_2Cl_2) on >99% *ee* material[5].



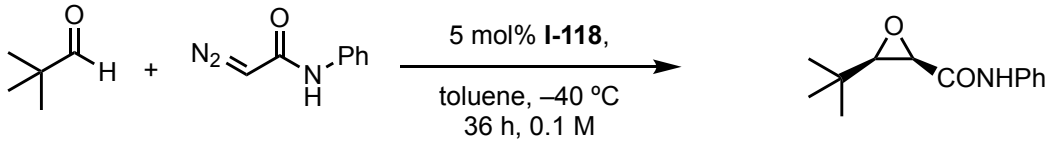
I-23c 1.2 equiv. 0.5 mmol

I-138c 92%, >99% ee (1 h, 93%, >99% ee)

*(2R,3R)-N-benzyl-3-cyclohexyloxirane-2-carboxamide **I-138c***: The epoxide **I-138c** was prepared from cyclohexanecarbaldehyde (73 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23c** (87.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 2 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-138c** as a white solid (mp 70-73 ºC on >99% *ee* material) in 99% isolated yield (129 mg, 0.498 mmol); *cis/trans*: >100:1.

The optical purity of **I-138c** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 7.56 min (minor enantiomer, *ent*-**I-138c**) and R_t = 7.83 min (major enantiomer, **I-138c**).

Spectral data for **I-138c**: R_f = 0.34 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85-1.10 (m, 6H), 1.52-1.61 (m, 4H), 1.75 (d, J = 11.0 Hz, 1H), 2.79 (s, 1H), 3.45 (d, J = 3.5 Hz, 1H), 4.22 (dd, J = 14.5, 5.0 Hz, 1H), 4.55 (dd, J = 14.5, 7.0 Hz, 1H), 6.51 (brs, 1H), 7.18-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 25.06, 25.85, 28.22, 30.30, 36.50, 42.70, 55.08, 62.60, 127.51, 127.79, 128.60, 137.80, 167.26 (one sp^3 carbon not located); IR (thin film) 3307 br, 3141 w, 3061 w, 2928 vs, 2852 m, 1666 vs, 1532 vs, 1499 w, 1450 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 260.1660 [(M+H$^+$); calcd. for $C_{16}H_{22}NO_2$: 260.1651]; $[\alpha]_D^{20}$ –31.9 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



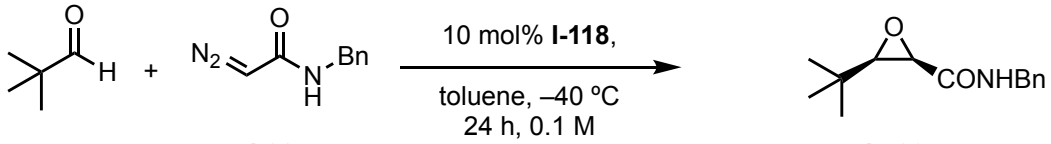
I-23b 0.5 mmol 1.2 equiv.

I-139b 70%, 92% ee

*(2R,3R)-3-(tert-butyl)-N-phenyloxirane-2-carboxamide **I-139b**:* The epoxide **I-139b** was prepared from pivalaldehyde (65 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23b** (80.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 36 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-139b** as a white solid (mp 86-89 ºC on 92% *ee* material) in 70% isolated yield (76.7 mg, 0.350 mmol); *cis/trans*: >100:1. The optical purity

of **I-139b** was determined to be 92% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 6.38 min (minor enantiomer, *ent*-**I-139b**) and R_t = 8.97 min (major enantiomer, **I-139b**).

Spectral data for **I-139b**: R_f = 0.55 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (s, 9H), 2.99 (d, J = 5.0 Hz, 1H), 3.51 (d, J = 5.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.95 (brs, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 26.46, 31.80, 56.07, 67.83, 119.59, 124.69, 129.04, 136.72, 165.45; IR (thin film) 3324 br, 3141 w, 3061 m, 2961 vs, 2870 m, 1682 vs, 1601 vs, 1537 vs, 1501 s, 1483 s, 1466 m, 1445 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 219.1245 [(M^+); calcd. for $C_{13}H_{17}NO_2$: 219.1259]; $[\alpha]_D^{20}$ +41.6 (*c* 1.0, CH_2Cl_2) on 92% *ee* material (HPLC).



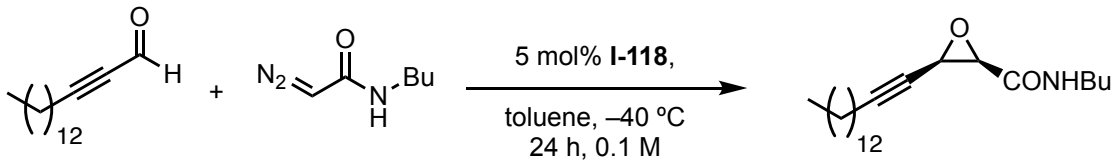
I-23c 1.2 equiv. 0.5 mmol

I-139c 47%, >99% ee

(2R,3R)-N-benzyl-3-(tert-butyl)oxirane-2-carboxamide ***I-139c****:* The epoxide **I-139c** was prepared from pivalaldehyde (65 µL, 0.60 mmol, 1.2 equiv), diazo compound **I-23c** (87.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** (10 mol% catalyst loading) with a reaction time of 24 hours. The reaction went to 78% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 10:1 to 4:1 hexanes/ EtOAc as eluent) to give **I-139c** as a white solid (mp 120-122 ºC on >99% *ee* material) in 47% isolated yield (55.1 mg, 0.236 mmol); *cis/trans*: >100:1. The optical purity of **I-139c** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min):

retention times: R_t = 7.14 min (major enantiomer, **I-139c**) and R_t = 13.32 min (minor enantiomer, *ent*-**I-139c**).

Spectral data for **I-139c**: R_f = 0.35 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (s, 9H), 1.47 (d, J = 5.0 Hz, 1H), 1.37 (d, J = 5.0 Hz, 1H), 4.20 (dd, J = 14.0, 5.0 Hz, 1H), 4.48 (dd, J = 14.0, 6.0 Hz, 1H), 6.45 (brs, 1H), 7.20-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 26.46, 31.78, 43.35, 55.93, 67.25, 127.73, 128.24, 128.71, 136.90, 167.27; IR (thin film) 3328 brs, 2953 s, 2870 m, 1653 vs, 1546 s, 1496 w, 1481 w, 1452 m, 1422 m, 1363 m cm^{-1}; HRMS (ESI-TOF) *m/z* 234.1508 [(M+H$^+$); calcd. for $C_{14}H_{20}NO_2$: 234.1494]; $[\alpha]_D^{20}$ +5.0 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



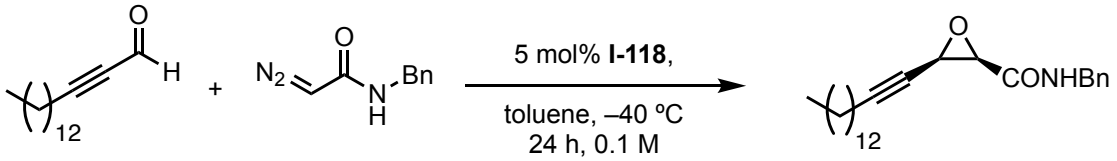
I-23a — 1.2 equiv. — 0.5 mmol

I-141a — 63%, 91% ee

(2R,3R)-N-butyl-3-(pentadec-1-yn-1-yl)oxirane-2-carboxamide ***I-141a****:* The epoxide **I-141a** was prepared from hexadec-2-ynal (167.5 µL, 0.600 mmol, 1.20 equiv, prepared[6] by 1-pentadecyne and DMF), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.0 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 24 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-141a** as a white solid (mp 43-45 ºC on 91% *ee* material) in 63% isolated yield (111 mg, 0.317 mmol); *cis/trans*: >100:1. The optical purity of **I-141a** was determined to be 91% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm,

flow-rate: 1 mL/min): retention times: R_t = 5.35 min (minor enantiomer, *ent*-**I-141a**) and R_t = 5.66 min (major enantiomer, **I-141a**).

Spectral data for **I-141a**: R_f = 0.45 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (t, J = 7.0 Hz, 3H), 0.86 (t, J = 7.0 Hz, 3H), 1.19 (s, 18H), 1.25-1.34 (m, 4H), 1.37-1.47 (m, 4H), 2.10 (t, J = 7.5 Hz, 2H), 3.13-3.20 (m, 1H), 3.25-3.32 (m, 1H), 3.49 (d, J = 4.0 Hz, 1H), 3.56 (d, J = 4.0 Hz, 1H), 6.27 (t, J = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.41, 13.75, 18.38, 19.69, 22.36, 27.92, 28.53, 28.80, 29.03, 29.17, 29.32, 29.33, 29.35, 31.42, 31.60, 38.29, 45.69, 55.47, 72.55, 87.63, 165.82 (one sp^3 carbon not located); IR (thin film) 3295 br, 2924 vs, 2853 s, 2245 w,1657 vs, 1545 vs, 1468 s cm^{-1}; HRMS (ESI-TOF) *m/z* 349.3003 [(M^+); calcd. for $C_{22}H_{39}NO_2$: 349.2981]; $[\alpha]_D^{20}$ –13.0 (*c* 1.0, CH_2Cl_2) on 91% *ee* material (HPLC).



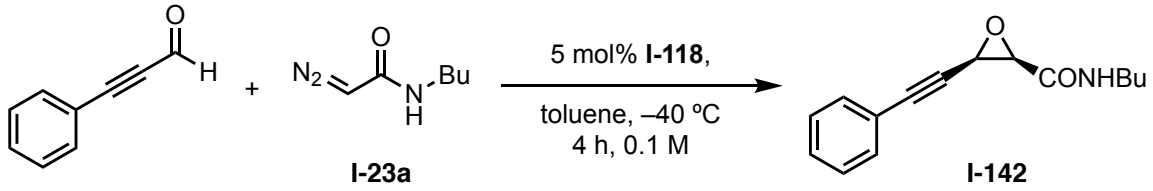
I-23c 1.2 equiv. 0.5 mmol

I-141c 63%, >99% ee (1 h, 79%, 93% ee)

(2R,3R)-N-benzyl-3-(pentadec-1-yn-1-yl)oxirane-2-carboxamide ***I-141c:*** The epoxide **I-141c** was prepared from hexadec-2-ynal (168 µL, 0.600 mmol, 1.20 equiv, prepared[13] by 1-pentadecyne and DMF), diazo compound **I-23c** (87.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 24 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-141c** as a white solid (mp 55-57 ºC on >99% *ee* material) in 63%

isolated yield (123 mg, 0.322 mmol); *cis/trans*: >100:1. The optical purity of **I-141c** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 6.01 min (minor enantiomer, *ent*-**I-141c**) and R_t = 7.15 min (major enantiomer, **I-141c**). The reaction without DMSO with a reaction time of 24 hours afforded epoxide **I-141c** in 75% yield and 93% *ee*.

Spectral data for **I-141c**: R_f = 0.43 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (t, J = 7.0 Hz, 3H), 1.18-1.22 (m, 20H), 1.32 (m, 2H), 1.96 (t, J = 7.0 Hz, 2H), 3.53 (d, J = 4.5 Hz, 1H), 3.57 (d, J = 4.5 Hz, 1H), 4.32 (dd, J = 15.0, 5.5 Hz, 1H), 4.50 (dd, J = 14.5, 6.5 Hz, 1H), 6.47 (t, J = 5.5 Hz, 1H), 7.18-7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.05, 18.54, 22.61, 28.08, 28.77, 29.02, 29.28, 29.40, 29.55, 29.57, 29.59, 31.83, 42.86, 46.13, 55.73, 72.56, 88.49, 127.46, 127.77, 128.54, 137.53, 166.15 (one sp^3 carbon not located); IR (thin film) 3293 br, 2917 vs, 2849 s, 2245 w,1658 vs, 1543 s, 1467 w, 1452 w cm^{-1}; HRMS (ESI-TOF) *m/z* 384.2912 [(M+H$^+$); calcd. for $C_{25}H_{38}NO_2$: 384.2903]; $[\alpha]_D^{20}$ –34.2 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



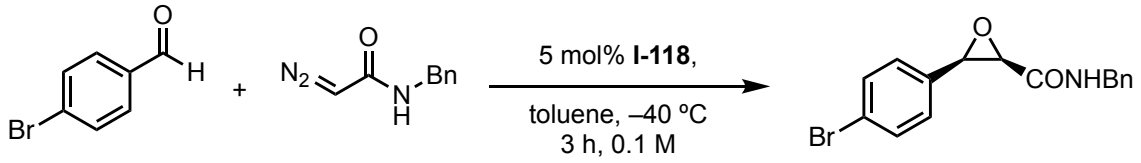
1.2 equiv. **I-23a** 0.5 mmol **I-142** 53%, 93% ee

*(2R,3R)-N-butyl-3-(phenylethynyl)oxirane-2-carboxamide **I-142**:* The epoxide **I-142** was prepared from 3-phenylpropiolaldehyde (74 µL, 0.60 mmol, 1.2 equiv, prepared[13] by phenylacetylene and DMF), diazo compound **I-23a** (70.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a

reaction time of 4 hours. The reaction went to 89% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 3:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-142** as a white solid (mp 59-62 ºC on 93% *ee* material) in 53% isolated yield (64.9 mg, 0.267 mmol); *cis/trans*: >100:1. The optical purity of **I-142** was determined to be 93% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 8.15 min (minor enantiomer, *ent*-**I-142**) and R_t = 8.74 min (major enantiomer, **I-142**).

Spectral data for **I-142**: R_f = 0.31 (1:1 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.70 (t, J = 7.0 Hz, 3H), 1.16-1.27 (m, 2H), 1.33-1.43 (m, 2H), 3.10-3.19 (m, 1H), 3.29-3.37 (m, 1H), 3.63 (d, J = 4.0 Hz, 1H), 3.80 (d, J = 4.5 Hz, 1H), 6.22 (brs, 1H), 7.20–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.52, 19.96, 31.72, 38.68, 46.17, 56.07, 81.54, 86.45, 121.16, 128.33, 129.21, 131.88, 165.77; IR (thin film) 3297 br, 3085 w, 2957 vs, 2930 vs, 2870 m, 2200 w, 1657 vs, 1599 w, 1549 vs, 1493 s, 1445 s cm^{-1}; HRMS (ESI-TOF) *m/z* 243.1269 [(M^+); calcd. for $C_{15}H_{17}NO_2$: 243.1259]; $[\alpha]_D^{20}$ –6.2 (*c* 1.0, CH_2Cl_2) on 93% *ee* material (HPLC).

4.2.14 Substrate scope with respect to diazoacetamides (*Scheme 1.15)*



I-23c

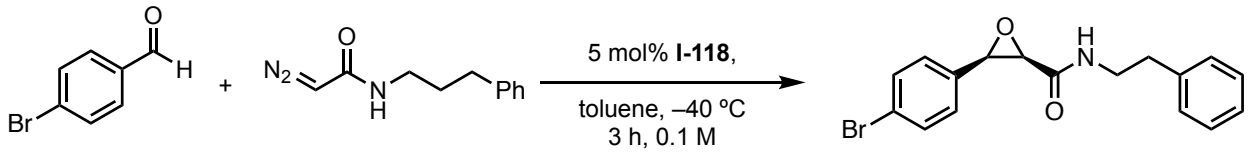
1.2 equiv. 0.5 mmol

I-129c

90%, >99% ee

*(2R,3R)-N-benzyl-3-(4-bromophenyl)oxirane-2-carboxamide **I-129c**:* The epoxide **I-129c** was prepared from 4-bromobenzaldehyde (111 mg, 0.60 mmol, 1.2 equiv), diazo compound **I-23c** (87.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 3 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129c** as a white solid (mp 104-107 ºC on >99% *ee* material) in 90% isolated yield (150 mg, 0.450 mmol); *cis/trans*: >100:1. The optical purity of **I-129c** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 14.53 min (major enantiomer, **I-129c**) and minor enantiomer was not located.

Spectral data for **I-129c**: R_f = 0.30 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (d, *J* = 4.8 Hz, 1H), 3.98 (dd, *J* = 14.8, 4.6 Hz, 1H), 4.25 (d, *J* = 4.8 Hz, 1H), 4.43 (dd, *J* = 14.8, 7.5 Hz, 1H), 6.28 (t, *J* = 6.1 Hz, 1H), 6.63 – 6.81 (m, 2H), 7.11 – 7.25 (m, 5H), 7.32 – 7.43 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 42.73, 56.27, 57.68, 122.69, 127.46, 127.51, 128.24, 128.58, 131.68, 131.99, 136.95, 165.88. HRMS (ESI-TOF) *m/z* 330.0126 [(M–H$^+$); calcd. for $C_{16}H_{13}{}^{79}BrNO_2$: 330.0130]; $[\alpha]_D^{20}$ +57.6 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



I-23d

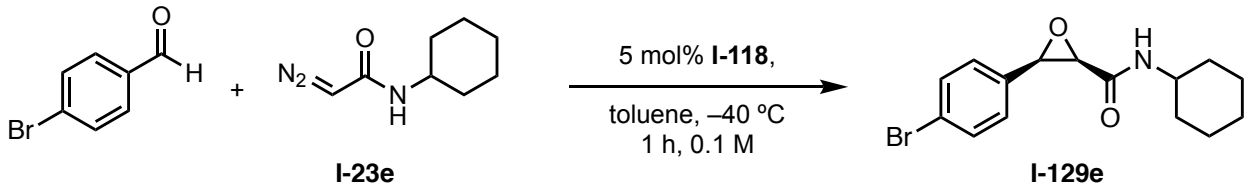
1.2 equiv. 0.5 mmol

I-129d

88%, >99% ee

(2R,3R)-3-(4-bromophenyl)-N-phenethyloxirane-2-carboxamide ***I-129d****:* The epoxide **I-129d** was prepared from 4-bromobenzaldehyde (111 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23d** (94.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 3 hours. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129d** as a white solid (mp 122-124 ºC on >99% *ee* material) in 88% isolated yield (153 mg, 0.442 mmol); *cis/trans*: >100:1. The optical purity of **I-129d** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 14.22 min (major enantiomer, **I-129d**) and minor enantiomer was not located.

Spectral data for **I-129d**: R_f = 0.34 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (ddt, *J* = 43.3, 13.9, 7.1 Hz, 2H), 3.21 – 3.36 (m, 2H), 3.75 (d, *J* = 4.8 Hz, 1H), 4.19 (d, *J* = 4.8 Hz, 1H), 5.99 (t, *J* = 6.0 Hz, 1H), 6.97 – 7.03 (m, 2H), 7.07 – 7.13 (m, 2H), 7.18 – 7.30 (m, 3H), 7.35 – 7.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.01, 39.68, 56.30, 57.62, 122.58, 126.68, 128.21, 128.46, 128.72, 131.56, 132.01, 138.09, 166.21. HRMS (ESI-TOF) *m/z* 344.0283 [(M–H$^+$); calcd. for $C_{17}H_{15}{}^{79}BrNO_2$: 344.0286]; $[\alpha]_D^{20}$ +24.4 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



I-23e

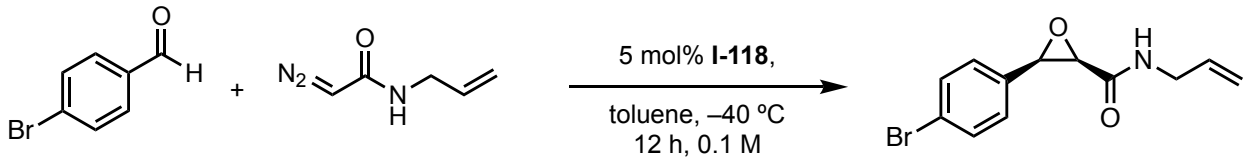
1.2 equiv. 0.5 mmol

I-129e

91%, >99% ee

(2R,3R)-3-(4-bromophenyl)-N-cyclohexyloxirane-2-carboxamide ***I-129e****:* The epoxide **I-129e** was prepared from 4-bromobenzaldehyde (111 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23e** (83.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 1 hour. The reaction went to 100% conversion. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129e** as a white solid (mp 176-177 ºC on >99% *ee* material) in 91% isolated yield (148 mg, 0.456 mmol); *cis/trans*: >100:1. The optical purity of **I-129e** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 5.74 min (major enantiomer, **I-129e**) and minor enantiomer was not located.

Spectral data for **I-129e**: R_f = 0.35 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.48 – 0.66 (m, 1H), 0.93 – 1.34 (m, 5H), 1.34 – 1.67 (m, 3H), 1.75 (d, *J* = 12.5 Hz, 1H), 3.51 (tt, *J* = 10.9, 9.1, 6.7 Hz, 1H), 3.67 – 3.75 (m, 1H), 4.23 (dd, *J* = 4.9, 2.2 Hz, 1H), 5.69 (d, *J* = 8.9 Hz, 1H), 7.16 – 7.27 (m, 3H), 7.40 – 7.51 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.45, 24.59, 25.26, 32.38, 32.76, 47.32, 56.19, 57.57, 122.53, 128.34, 131.49, 132.27, 164.61. HRMS (ESI-TOF) *m/z* 322.0445 [(M–H$^+$); calcd. for $C_{15}H_{17}{}^{79}BrNO_2$: 322.0443]; $[\alpha]_D^{20}$ +15.1 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



I-23g

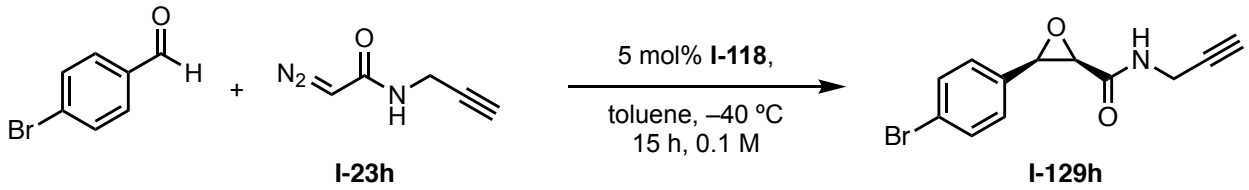
1.2 equiv. 0.5 mmol

I-129g

47%, >99% ee

*(2R,3R)-N-allyl-3-(4-bromophenyl)oxirane-2-carboxamide **I-129g**:* The epoxide **I-129g** was prepared from 4-bromobenzaldehyde (111 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23g** (62.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 12 hours. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129g** as a white solid (mp 96-98 ºC on >99% *ee* material) in 47% isolated yield (66.2 mg, 0.235 mmol); *cis/trans*: >100:1. The optical purity of **I-129e** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 9.58 min (major enantiomer, **I-129g**) and minor enantiomer was not located.

Spectral data for **I-129g**: R_f = 0.42 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 – 3.57 (m, 1H), 3.65 (dddt, *J* = 15.5, 6.9, 5.4, 1.6 Hz, 1H), 3.76 (d, *J* = 4.8 Hz, 1H), 4.24 (d, *J* = 4.8 Hz, 1H), 4.71 – 4.81 (m, 1H), 4.93 (dq, *J* = 10.2, 1.3 Hz, 1H), 5.33 (dddd, *J* = 17.1, 10.3, 6.1, 5.4 Hz, 1H), 5.92 (s, 1H), 7.14 – 7.23 (m, 2H), 7.42 – 7.48 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 41.04, 56.27, 57.62, 116.79, 122.66, 128.28, 131.63, 132.08, 132.85, 165.84. HRMS (ESI-TOF) *m/z* 279.9986 [(M–H$^+$); calcd. for $C_{12}H_{11}{}^{79}BrNO_2$: 279.9979]; $[\alpha]_D^{20}$ ND.



I-23h

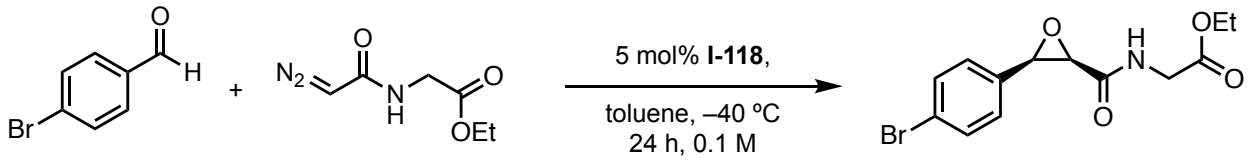
1.2 equiv. 0.5 mmol

I-129h

97%, 94% ee

(2R,3R)-3-(4-bromophenyl)-N-(prop-2-yn-1-yl)oxirane-2-carboxamide ***I-129h****:* The epoxide **I-129h** was prepared from 4-bromobenzaldehyde (111 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23h** (61.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 15 hours. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129h** as a white solid (mp 118-119 ºC on >99% *ee* material) in 97% isolated yield (136 mg, 0.487 mmol); *cis/trans*: >100:1. The optical purity of **I-129h** was determined to be 94% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 14.21 min (major enantiomer, **I-129h**) and R_t = 12.89 min (minor enantiomer, *ent*-**I-129h**).

Spectral data for **I-129h**: R_f = 0.44 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (t, *J* = 2.6 Hz, 1H), 3.71 (ddd, *J* = 17.6, 5.1, 2.6 Hz, 1H), 3.77 (d, *J* = 4.8 Hz, 1H), 3.79 (dd, *J* = 6.3, 2.6 Hz, 1H), 4.23 (d, *J* = 4.7 Hz, 1H), 6.14 (t, *J* = 5.7 Hz, 1H), 7.09 – 7.27 (m, 2H), 7.33 – 7.53 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.11, 56.27, 57.64, 71.48, 78.32, 122.70, 128.21, 131.67, 131.85, 165.63. HRMS (ESI-TOF) *m/z* 277.9817 [($M–H^+$); calcd. for $C_{12}H_9{}^{79}BrNO_2$: 277.9817]; $[\alpha]_D^{20}$ +51.0 (*c* 1.0, CH_2Cl_2) on 94% *ee* material (HPLC).



I-23i

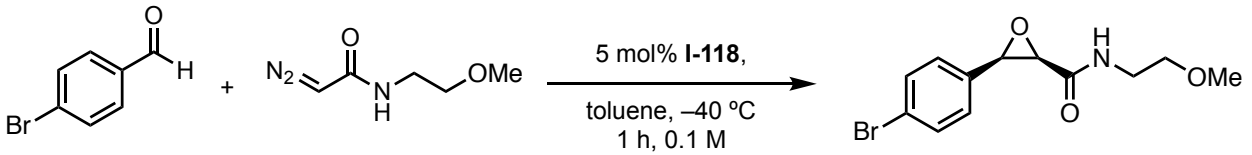
1.2 equiv. 0.5 mmol

I-129i

90%, >99% ee

ethyl ((2R,3R)-3-(4-bromophenyl)oxirane-2-carbonyl)glycinate ***I-129i****:* The epoxide **I-129i** was prepared from 4-bromobenzaldehyde (111 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23i** (85.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 24 hours. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129i** as a white solid (mp 75-77 °C on >99% *ee* material) in 90% isolated yield (147 mg, 0.448 mmol); *cis/trans*: >100:1. The optical purity of **I-129i** was determined to be >99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 11.95 min (major enantiomer, **I-129i**) and minor enantiomer was not located.

Spectral data for **I-129i**: R_f = 0.31 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3H), 3.62 (dd, *J* = 18.4, 5.2 Hz, 1H), 3.77 (d, *J* = 4.7 Hz, 1H), 3.82 (dd, *J* = 18.3, 5.3 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.22 (d, *J* = 4.7 Hz, 1H), 6.51 (t, *J* = 5.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.09, 40.51, 56.56, 57.71, 61.68, 122.59, 128.19, 131.54, 131.54, 166.03, 168.89. HRMS (ESI-TOF) *m/z* 326.0035 [(M–H$^+$); calcd. for $C_{13}H_{13}{}^{79}BrNO_4$: 326.0033]; $[\alpha]_D^{20}$ –1.0 (*c* 1.0, CH_2Cl_2) on >99% *ee* material (HPLC).



I-23j

1.2 equiv. 0.5 mmol

I-129j

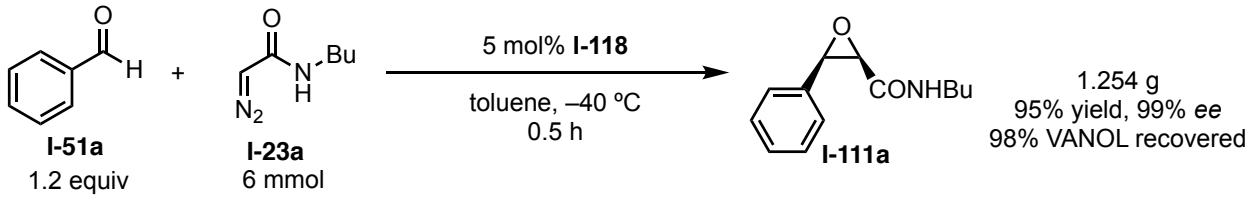
93%, 90% ee

(2R,3R)-3-(4-bromophenyl)-N-(2-methoxyethyl)oxirane-2-carboxamide ***I-129j***:

The epoxide **I-129j** was prepared from 4-bromobenzaldehyde (111 mg, 0.600 mmol, 1.20 equiv), diazo compound **I-23j** (71.6 mg, 0.500 mmol, 1.00 equiv) and the (*R*)-VANOL catalyst solution by the general procedure **C** with a reaction time of 1 hour. The crude epoxide was purified by column chromatography (silica gel, 20 × 250 mm, 4:1 to 1:1 hexanes/ EtOAc as eluent) to give **I-129j** as a white solid (mp 76-79 ºC on >99% *ee* material) in 93% isolated yield (140 mg, 0.467 mmol); *cis/trans*: >100:1. The optical purity of **I-129j** was determined to be 90% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 14.21 min (major enantiomer, **I-129j**) and R_t = 12.89 min (minor enantiomer, *ent*-**I-129j**)

Spectral data for **I-129j**: R_f = 0.36 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.76 – 2.82 (m, 1H), 3.05 (dddd, *J* = 13.8, 8.1, 4.9, 3.4 Hz, 1H), 3.16 (s, m, 4H), 3.25 (dddd, *J* = 13.9, 6.9, 5.6, 3.4 Hz, 1H), 3.74 (d, *J* = 4.7 Hz, 1H), 4.20 (d, *J* = 4.8 Hz, 1H), 6.26 (t, *J* = 6.1 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.25, 56.37, 57.49, 58.68, 70.73, 122.44, 128.27, 131.45, 132.16, 165.72. HRMS (ESI-TOF) *m/z* 298.0084 [(M–H$^+$); calcd. for $C_{12}H_{13}{}^{79}BrNO_3$: 298.0084]; $[\alpha]_D^{20}$ +44.8 (*c* 1.0, CH_2Cl_2) on 90% *ee* material (HPLC).

4.2.15 Gram-scale synthesis of *cis*-epoxide **I-108a** (*Scheme 1.16)*



I-51a
1.2 equiv

I-23a
6 mmol

I-111a

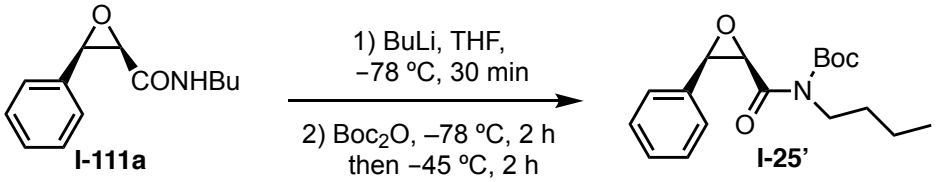
*Preparation of the catalyst **I-118** solution:* To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a T-shaped high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-VANOL (289 mg, 0.660 mmol). Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (12 mL) was added through the top of the Teflon valve to effect dissolution. After the addition of the toluene, BH_3•Me_2S (165 µL, 0.330 mmol, 2 M in toluene) was added. The flask was sealed by closing the Teflon valve, and then placed in a 100 ºC oil bath for 0.5 h. After 0.5 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 100 ºC (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. The residue was then completely dissolved in dry toluene (12 mL) under a nitrogen flow through side-arm of the Schlenk flask to afford the solution of the pre-catalyst. To the flask containing the pre-catalyst was added the dimethyl sulfoxide (48 µL, 0.66 mmol) under a nitrogen flow through side-arm of the Schlenk flask to give the solution of catalyst which was then directly cooled to –40 °C to initiate the reaction.

Asymmetric epoxidation: A 250 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of diazoacetamide **I-23a** (846.5 mg, 6.000 mmol). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous toluene (50 mL). Neat benzaldehyde **I-51a** (0.730 mL, 7.20 mmol, freshly distilled) was then added via syringe and a N_2 balloon was attached via needle in the septum. The mixture was stirred at rt for 10 min to effect dissolution. The round bottom flask and the Schlenk flask containing the catalyst were both cooled to –40 °C in a cold bath with a recirculating chiller for 10 min. The catalyst solution (10 mL, 5% catalyst) was quickly transferred to the round bottom flask using a syringe. The resulting mixture was stirred until the yellow color disappeared (0.5 h). The reaction was quenched by the addition of H_2O (5 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 125 mL separatory funnel. The water layer was extracted with EtOAc (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and then filtered into a 250 mL round bottom flask. The resulting solution was then concentrated under vacuum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude epoxide as an off-white semi-solid. Purification of the crude epoxide by silica gel chromatography [20 mm × 300 mm column, 5:1 to recover VANOL ligand (281.4 mg, 98.6%) then 1:1 hexanes/EtOAc as eluent] afforded pure *cis*-epoxide **I-111a** as a white solid in 95% isolated yield (1.254 g, 5.720 mmol). The optical purity of **I-111a** was determined to be >99% *ee* by HPLC (PIRKLE COVALENT (*R,R*) WHELK-O 1 column, 93:7 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention

times: R_t = 23.31 min (minor enantiomer, *ent*-**I-111a**) and R_t = 32.32 min (major enantiomer, **I-111a**).

If this large-scale reaction was carried out in the presence of 4 Å molecular sieves, the reaction was much slower. After 17 h the epoxide **I-111a** was obtained in 54% yield and 92% ee. After 80 h, epoxide **I-111a** was obtained in 86% yield and 97% ee.

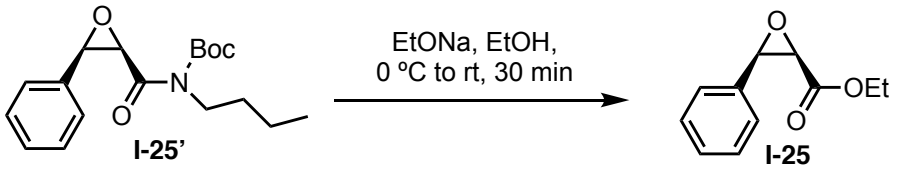
4.2.16 Synthesis of Taxol-side chain **I-146** (*Scheme 1.18)*



t-butyl butyl((2R,3R)-3-phenyloxirane-2-carbonyl)carbamate ***I-25':*** A 100 mL round bottom flask was flame dried under vacuum and cooled to rt under N_2. The vacuum adapter was replaced with a rubber septum. The septum was removed briefly to allow introduction of **I-111a** (657.8 mg, 3.000 mmol, 99% *ee*). Subsequently, the septum was removed again to allow for the addition of a dry stir bar and anhydrous THF (20 mL). A N_2 balloon was attached via a needle in the septum. The mixture was stirred at –78 °C for 10 min. A solution of *n*-butyllithium (1.25 mL, 3.00 mmol, 2.42 M in hexanes) was added dropwise to the round bottom flask using a syringe over a period of 5 minutes. The resulting mixture was stirred was stirred at –78 °C for 30 min. Meanwhile, to another flame-dried 25 mL single-necked round-bottom flask was added Boc anhydride (1.31 g, 6.00 mmol) and dry THF (10 mL). This solution was added to the 100 mL round bottom flask at –78 °C using a syringe over a period of 5 min. The resulting mixture was stirred at –78 °C for 2 h then warmed up to –45 °C. After a total reaction time of 4 h, the reaction

was quenched by the addition of saturated aq NH_4Cl solution (5 mL) and was then warmed to room temperature. The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with diethyl ether (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and then filtered into a 100 mL round bottom flask. The resulting solution was then concentrated under vacuum to afford the crude product as an off-white oil. Purification of the crude product by silica gel chromatography [20 mm × 300 mm column, 6:1 hexanes/EtOAc as eluent] afforded the pure title compound as a colorless oil in 90% isolated yield (865 mg, 2.71 mmol). The optical purity of the title compound was determined to be 99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 3.30 min (minor enantiomer, *ent*-**I-25'**) and R_t = 5.09 min (major enantiomer, **I-25'**).

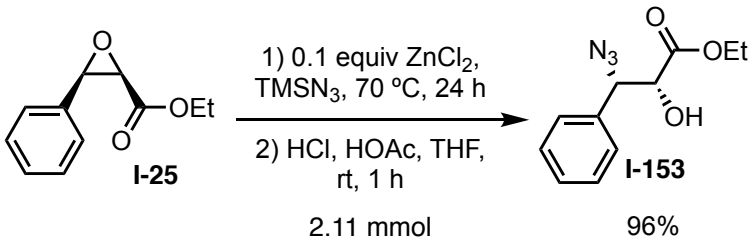
Spectral data for **I-25'**: R_f = 0.26 (1:6 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (t, J = 7.5 Hz, 3H), 0.84-0.98 (m, 4H), 1.43 (s, 9H), 3.26 (dt, J = 14.0, 7.0 Hz, 1H), 3.42 (dt, J = 14.0, 6.5 Hz, 1H), 4.28 (d, J = 4.5 Hz, 1H), 4.33 (d, J = 4.5 Hz, 1H), 7.17-7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.97, 19.61, 27.91, 29.92, 43.54, 75.83, 61.46, 83.30, 126.10, 127.96, 128.09, 133.76, 152.58, 167.95; IR (thin film) 3451 br w, 2965 vs, 2934 s. 2874 w, 1734 vs, 1707 vs, 1497 w, 1456 w, 1370 s, 1219 w, 1148 s cm^{-1}; HRMS (ESI-TOF) *m/z* 320.1860 [(M+H^+); calcd. for $C_{18}H_{26}NO_4$: 320.1862]; $[\alpha]_D^{20}$ +106.4 (*c* 1.0, CH_2Cl_2) on 99% *ee* material (HPLC). The product **I-25'** was obtained in 97% yield in a separate run on 2.6 mmol scale.



ethyl (2R,3R)-3-phenyloxirane-2-carboxylate ***I-25****:* A solution of the above carbamate **I-25'** (844 mg, 2.64 mmol) in 30 mL ethanol was cooled in an ice bath. A solution of EtONa (5.28mL, freshly prepared by sodium with ethanol, 1M in EtOH) was added dropwise using a syringe. After being stirred at 0°C for 10 min, the reaction mixture was warmed up to rt for 30 min. The reaction was quenched by the addition of saturated aq. NH_4Cl solution (5 mL). The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and then filtered into a 100 mL round bottom flask. The resulting solution was then concentrated under vacuum to afford the crude product as an off-white oil. Purification of the crude product by silica gel chromatography [20 mm × 300 mm column, 2:1 to 1:1 hexanes/ CH_2Cl_2 as eluent] afforded **I-25** as a colorless oil in 80% isolated yield (405 mg, 2.11 mmol). The optical purity of title compound was determined to be 99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 4.03 min (minor enantiomer, *ent*-**I-25**) and R_t = 5.24 min (major enantiomer, **I-25**).

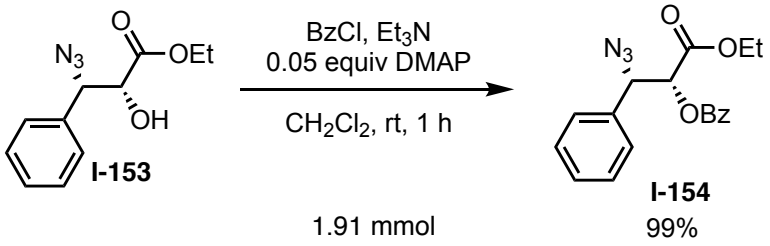
Spectral data for **I-25**: R_f = 0.11 (1:1 CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 7.5 Hz, 3H), 3.71 (d, J = 7.0 Hz, 1H), 3.84-3.93 (m, 2H), 4.15 (d, J = 7.0 Hz, 1H), 7.16-7.24 (m, 3H), 7.32 (d, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.60, 55.49, 57.07, 60.87, 126.39, 127.72, 128.14, 132.70, 166.33; IR (thin film) 3440 br, 2984

w, 1754 vs, 1653s, 1204 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 193.0869 [$(M+H^+)$; calcd. for $C_{11}H_{13}O_3$: 193.0865]; $[\alpha]_D^{20}$ +8.5 (*c* 1.0, CH_2Cl_2) on 99% *ee* material (HPLC). (lit.[12] $[\alpha]_D^{20}$ 22.2 (*c* 1.12, $CHCl_3$)). These NMR data match that previously reported for this compound[5, 7].



ethyl (2R,3S)-3-azido-2-hydroxy-3-phenylpropanoate ***I-153****:* A neat mixture of epoxy ester **I-25** (405 mg, 2.11 mmol), azidotrimethylsilane (0.340 mL, 2.53 mmol) and zinc chloride (28.6 mg, 0.210 mmol) was stirred at 70°C for 24 h. The reaction mixture was cooled to rt followed by addition of THF (2 mL), acetic acid (0.2 mL) and conc HCl (0.1 mL). The resulting solution was stirred for 1 h and then quench with saturated aq $NaHCO_3$ solution (5 mL). The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and then filtered into a 100 mL round bottom flask. The resulting solution was then concentrated under vacuum to afford the crude product as colorless oil. Purification of the crude product by silica gel chromatography [20 mm × 300 mm column, 5:1 hexanes/ether as eluent] afforded **I-153** as a colorless oil in 96% isolated yield (475 mg, 2.02 mmol). The optical purity of title compound was determined to be 99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 4.80 min (major enantiomer, **I-153**) and R_t = 6.78 min (minor enantiomer, *ent*-**I-153**).

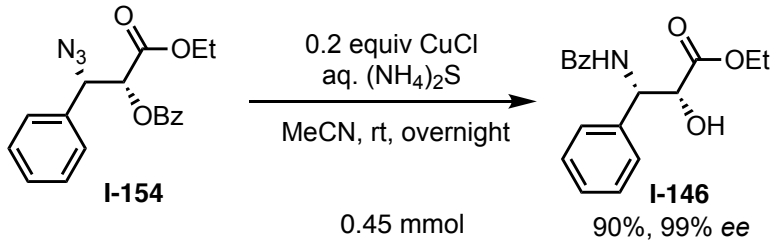
Spectral data for **I-153**: R_f = 0.13 (1:4 ether/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, J = 7.0 Hz, 3H), 3.04 (br, 1H), 4.22 (t, J = 7.0 Hz, 2H), 4.31 (br, 1H), 4.78 (d, J = 3.5 Hz, 1H), 7.28-7.37 (m, 3H), 7.39 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.08, 62.46, 67.11, 73.83, 127.83, 128.77, 128.83, 135.52, 171.89; IR (thin film) 3470 br, 2984 w, 2107 vs, 1736 vs, 1455 w cm^{-1}; HRMS (ESI-TOF) *m/z* 258.0861 [(M+Na$^+$); calcd. for $C_{11}H_{13}N_3O_3Na$: 258.0855]; $[\alpha]_D^{20}$ +144.6 (*c* 1.0, CH_2Cl_2) on 99% *ee* material (HPLC). (lit.[15] $[\alpha]_D^{20}$ 133.5 (*c* 2.0, $CHCl_3$)). These NMR data matches that previously reported for this compound[7].



ethyl (2R,3S)-3-azido-2-O-benzoyl-3-phenylpropionate ***I-154****:* To a solution of the above hydroxyl azide **I-153** (450 mg, 1.91 mmol) and triethylamine (0.32 mL, 2.30 mmol) in CH_2Cl_2 (5 mL) was added benzoyl chloride (0.250 mL, 2.11 mmol) and 4-dimethylaminopyridine (12.2 mg, 0.100 mmol). After being stirred at rt for 1 h, the reaction mixture was quenched by addition of H_2O (1 mL). The reaction mixture was then transferred to a 60 mL separatory funnel. The water layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and then filtered into a 100 mL round bottom flask. The resulting solution was then concentrated under vacuum to afford the crude product as a colorless oil. Purification of the crude product by silica gel chromatography [20 mm × 300 mm column, 10:1 hexanes/EtOAc as eluent] afforded **I-154** as a colorless oil in 99% isolated yield (646 mg, 1.90 mmol). The optical purity of title

compound was determined to be 99% *ee* by HPLC (Daicel Chirapak OD-H column, 94:6 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 3.77 min (minor enantiomer, *ent*-**I-154**) and R_t = 5.36min (major enantiomer, **I-154**).

Spectral data for **I-154**: R_f = 0.24 (1:8 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (t, J = 7.0 Hz, 3H), 4.04-4.14 (m, 2H), 5.09 (d, J = 5.5 Hz, 1H), 5.39 (d, J = 5.5 Hz, 1H), 7.26-7.38 (m, 5H), 7.41 (t, J = 8.0 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 8.03 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.86, 61.98, 65.59, 75.60, 127.54, 128.54, 128.75, 128.90, 129.12, 130.02, 133.64, 134.55, 165.55, 167.31; IR (thin film) 3438 br, 2107 vs, 1728 vs, 1653 w, 1603 w, 1495 w, 1453 w cm^{-1}; HRMS (ESI-TOF) *m/z* 340.1295 [(M+H$^+$); calcd. for $C_{18}H_{18}N_3O_4$: 340.1297]; $[\alpha]_D^{20}$ +125.7 (*c* 1.0, CH_2Cl_2) on 99% *ee* material (HPLC). These NMR data matches that previously reported for this compound.[14]



Ethyl (2R,3S)-3-benzamido-2-hydroxy-3-phenylpropanoate ***I-146****:* To a solution of the azido benzoate **I-154** (153 mg, 0.45 mmol) and CuCl (8.9 mg, 0.090 mmol) in CH_3CN (3 mL) was added aqueous $(NH_4)_2S$ (40–48 wt% solution in water, 1.13 mmol, 192 µL).[5] After being stirring for 12 h at room temperature, the reaction mixture was poured into a mixture of water (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. Purification of the crude product by silica gel chromatography [20 mm × 300 mm column, 3:1 hexanes/EtOAc as eluent] afforded **I-146** as a white solid (mp 165-

167 ºC on 99% *ee* material) in 90% isolated yield (128 mg, 0.410 mmol). The optical purity of title compound was determined to be 99% *ee* by HPLC (Daicel Chirapak AD-H column, 80:20 hexane/2-propanol at 220 nm, flow-rate: 1 mL/min): retention times: R_t = 9.47 min (major enantiomer, **I-146**) and R_t = 10.98 min (minor enantiomer, *ent*-**I-146**).

Spectral data for **I-146**: R_f = 0.12 (1:2 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.21 (t, J = 7.0 Hz, 3H), 3.65 (br, 1H), 4.18 (m, 2H), 4.52 (d, J = 2.0 Hz, 1H), 5.67 (dd, J = 9.0, 2.0 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 2H), 7.32-7.49 (m, 6H), 7.74 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.02, 55.14, 61.93, 73.56, 126.83, 127.13, 127.45, 128.34, 128.38, 131.43, 134.27, 138.98, 166.83, 172.62; IR (thin film) 3416 br, 3351 vs, 2977 w, 2926 w,1719 vs, 1638 vs, 1528 s cm^{-1}; HRMS (ESI-TOF) *m/z* 314.1399 [(M+H$^+$); calcd. for $C_{18}H_{20}NO_4$: 314.1392]; $[\alpha]_D^{20}$ –19.7 (*c* 1.0, $CHCl_3$) on 99% *ee* material (HPLC). (lit.[6] $[\alpha]_D^{20}$ –21.6 (*c* 1.0, $CHCl_3$); lit.[7] $[\alpha]_D^{20}$ –21.7 (*c* 1.0, $CHCl_3$)). These NMR data matches that previously reported for this compound[7].

4.2.17 NMR studies and DFT calculations[8]

3D Geometries of DFT optimized structrues

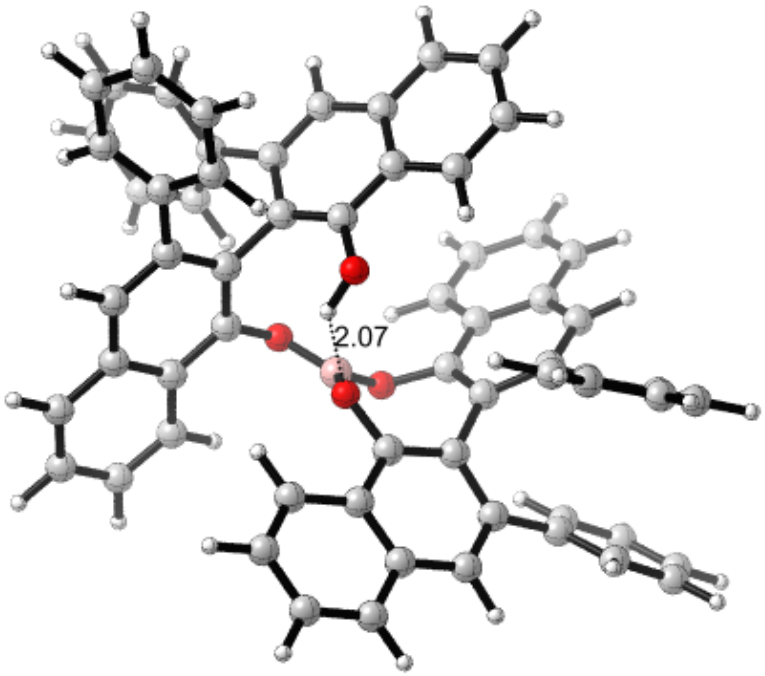


Figure 4.2 Geometries of 2:1 *meso*borate catalyst at the B3LYP/6-31G(d) level

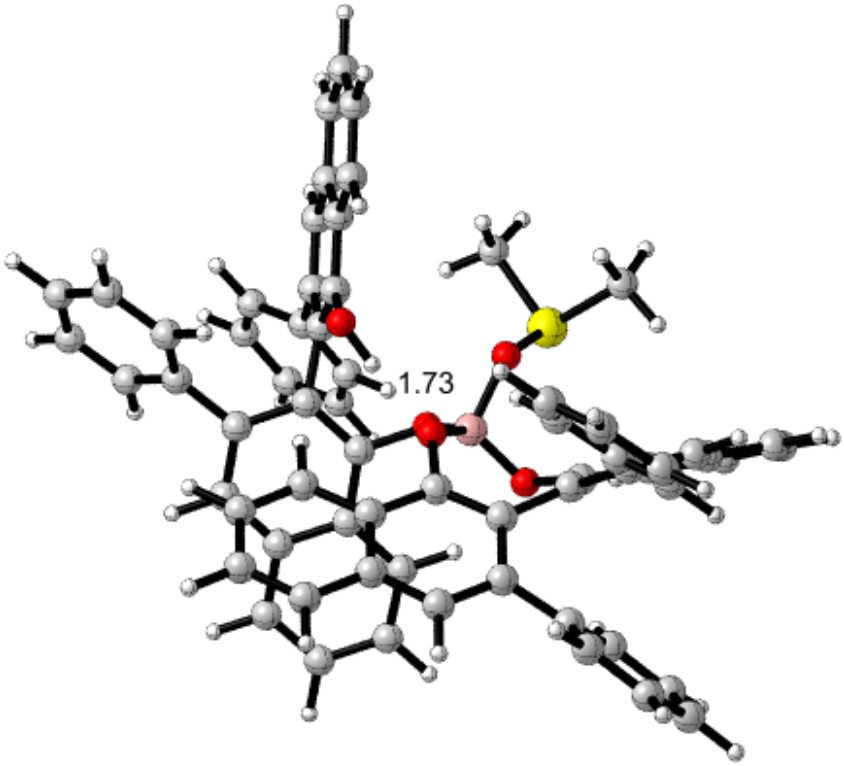


Figure 4.3 Geometries of DMSO-*meso*borate complex at the B3LYP/6-31G(d) level

Cartesian coordinates & SCF energies for computed structures

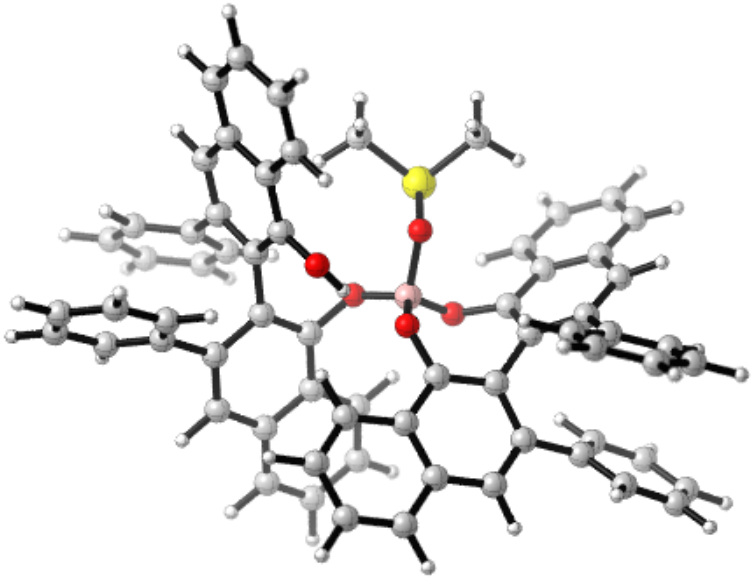
Conformational searches were carried out using Spartan'08[16,17] with *Molecular Mechanics*. Full geometry optimizations were carried out using the Gaussian 03 package[18] at the B3LYP/6-31G(d) level of theory in the gas phase.

2:1 *meso*borate catalyst

H	-2.149907	6.741085	2.028961
C	-2.059818	5.739062	1.618366
H	-4.178442	5.441892	1.458460
C	-3.189485	5.017288	1.304036
C	-0.641607	3.914162	0.880567
C	-3.088129	3.705433	0.770437
C	-0.776598	5.182024	1.402976
C	-1.791793	3.145626	0.560628
C	-4.225360	2.952167	0.390102
H	0.109603	5.761267	1.646750
H	0.342616	3.494664	0.708351
C	-4.134088	1.671159	-0.119037
H	-5.201176	3.425236	0.453793
C	-2.836181	1.046726	-0.232528
C	-1.722699	1.822578	0.040344
C	-2.687693	-0.384298	-0.633257
C	-1.853240	-0.727114	-1.684592
C	-3.413912	-2.707989	-0.530973
C	-1.829467	-2.024410	-2.269010
C	-3.420451	-1.441922	0.020056
C	-2.671367	-3.025381	-1.695735
C	-1.023256	-2.345580	-3.391706
H	-3.317505	-5.084758	-1.836297
H	-3.948567	-3.507014	-0.025023
C	-1.064960	-3.610828	-3.935281
H	-0.383902	-1.578387	-3.813304
H	-0.448716	-3.849700	-4.797661
C	-1.901143	-4.606241	-3.374798
H	-1.920255	-5.600920	-3.811984
C	-2.682122	-4.320508	-2.277085
O	-0.973492	0.202166	-2.231273
O	-0.436366	1.332146	-0.159914
C	-4.085325	-1.248659	1.339114
C	-5.261038	-1.046303	3.891103
C	-3.402351	-0.626751	2.398446
C	-5.365161	-1.770790	1.585183
C	-5.947379	-1.671095	2.848289
C	-3.985922	-0.525721	3.660778
H	-2.398005	-0.246432	2.237432
H	-5.914492	-2.234469	0.770973
H	-6.942465	-2.075625	3.015036
H	-3.437626	-0.047270	4.468089
H	-5.714796	-0.967708	4.875591
C	-5.386867	1.035420	-0.619031
C	-7.815342	0.016920	-1.625422
C	-6.565265	1.092680	0.143550
C	-5.450809	0.457972	-1.898104
C	-6.651889	-0.046633	-2.394826
C	-7.766813	0.590001	-0.353479
H	-6.528586	1.512001	1.144810
H	-4.557988	0.419874	-2.514017
H	-6.678946	-0.482742	-3.389974
H	-8.664040	0.639271	0.258126
H	-8.751062	-0.376023	-2.014278
H	3.599722	6.369644	-2.117407
C	3.320557	5.346613	-1.880443
H	4.771893	5.145111	-0.314305
C	3.972922	4.667599	-0.876264
C	1.918041	3.419082	-2.324582
C	3.622346	3.328670	-0.555428
C	2.287727	4.714183	-2.613491
C	2.568008	2.700088	-1.286530
C	4.279740	2.598753	0.465386
H	1.784970	5.254751	-3.410561
H	1.137348	2.933559	-2.900235
C	3.939870	1.296660	0.778144
H	5.069467	3.088289	1.028997
C	2.884332	0.642487	0.047435
C	2.228217	1.361630	-0.938283
C	2.567690	-0.806220	0.288306
C	1.568167	-1.169241	1.181894

C	3.143203	-3.157576	0.009590
C	1.317423	-2.532628	1.524082
C	3.363143	-1.835677	-0.322967
C	2.132417	-3.540461	0.926556
C	0.295418	-2.909018	2.433700
H	2.514336	-5.666460	0.810348
H	3.745209	-3.930894	-0.459726
C	0.092414	-4.236372	2.743181
H	-0.324837	-2.137051	2.874555
H	-0.695105	-4.516243	3.437633
C	0.899813	-5.239944	2.156262
H	0.729362	-6.283566	2.407808
C	1.894162	-4.898831	1.267128
O	0.805165	-0.248385	1.851276
H	0.778064	0.584236	1.346920
O	1.249935	0.739090	-1.703806
C	4.449950	-1.519088	-1.296599
C	6.514745	-1.029024	-3.148087
C	4.185093	-0.861897	-2.508763
C	5.765952	-1.930698	-1.032018
C	6.789891	-1.686484	-1.948288
C	5.208464	-0.620403	-3.425055
H	3.169101	-0.558538	-2.740829
H	5.984045	-2.429502	-0.092004
H	7.803282	-2.008448	-1.721815
H	4.982645	-0.115716	-4.361015
H	7.310970	-0.838135	-3.862969
C	4.697305	0.608701	1.864900
C	6.181587	-0.575774	3.941768
C	6.096440	0.521338	1.788385
C	4.053024	0.095504	3.001935
C	4.790617	-0.490126	4.030184
C	6.832676	-0.068059	2.816826
H	6.602995	0.900712	0.905415
H	2.973599	0.169610	3.087621
H	4.275191	-0.878101	4.904827
H	7.914773	-0.132602	2.735796
H	6.753148	-1.035243	4.743957
B	-0.068160	0.756704	-1.356994

SCF energy: -2789.467451



DMSO-*meso*borate complex 1

H	0.251693	-6.113521	2.168677
C	0.509882	-5.111922	1.834842
H	2.563361	-5.593005	1.442103
C	1.794340	-4.824018	1.433212
C	-0.166801	-2.828526	1.381206
C	2.147820	-3.520268	0.996556
C	-0.477884	-4.101384	1.807547
C	1.150039	-2.497839	0.968884
C	3.453337	-3.220291	0.542120
H	-1.494469	-4.328029	2.116850
H	-0.939375	-2.074556	1.364871
C	3.814067	-1.952730	0.136375
H	4.173529	-4.029656	0.461783
C	2.850959	-0.880364	0.210458
C	1.533096	-1.185724	0.538253

C	3.277284	0.520507	-0.082125	C	-2.057741	-2.943263	-2.006722
C	2.605595	1.233807	-1.065223	C	0.138012	-2.740183	-3.755306
C	4.893449	2.340968	0.076283	C	-1.273066	-1.749576	-2.045060
C	3.136963	2.432957	-1.626644	C	-3.167201	-3.010877	-1.129562
C	4.406856	1.140783	0.563710	H	0.980714	-2.669659	-4.437965
C	4.321334	2.985905	-1.047282	H	0.410739	-0.762475	-2.976956
C	2.542036	3.074444	-2.746309	C	-3.532184	-1.946879	-0.329504
H	5.743271	4.615230	-1.149950	H	-3.737643	-3.934641	-1.079329
H	5.723446	2.823525	0.584848	C	-2.771150	-0.726162	-0.379039
C	3.091901	4.228080	-3.265004	C	-1.648932	-0.662593	-1.194190
H	1.663574	2.623260	-3.195643	C	-3.268285	0.479210	0.366691
H	2.640119	4.702877	-4.132169	C	-2.750742	0.824240	1.610726
C	4.250532	4.793816	-2.679138	C	-4.981569	2.205597	0.629684
H	4.673399	5.705368	-3.093328	C	-3.348344	1.843869	2.417618
C	4.848407	4.186721	-1.595789	C	-4.393412	1.218457	-0.142637
O	1.407649	0.790788	-1.545319	C	-4.496588	2.530753	1.920301
O	0.550183	-0.225152	0.525644	C	-2.828195	2.188452	3.693060
C	5.015779	0.590583	1.806709	H	-5.967995	4.058902	2.347382
C	6.171181	-0.291373	4.221999	H	-5.827898	2.758901	0.231475
C	4.212955	0.126965	2.862589	C	-3.429840	3.170654	4.450602
C	6.408777	0.604804	1.988125	H	-1.954515	1.657077	4.053104
C	6.980961	0.169593	3.182490	H	-3.027348	3.425665	5.427409
C	4.785048	-0.309929	4.056412	C	-4.574026	3.849544	3.964696
H	3.133441	0.123761	2.751447	H	-5.042223	4.619021	4.573098
H	7.046593	0.933076	1.172594	C	-5.091436	3.538908	2.726935
H	8.062001	0.181057	3.296294	O	-1.703673	0.172544	2.191567
H	4.143648	-0.661345	4.860463	H	-1.013118	-0.073043	1.538494
H	6.616220	-0.634701	5.152289	O	-0.929839	0.503847	-1.263520
C	5.172570	-1.786708	-0.458119	C	-4.967114	0.957507	-1.495851
C	7.721344	-1.669057	-1.659563	C	-6.112838	0.577358	-4.040595
C	6.298637	-2.330615	0.180914	C	-4.172204	0.990535	-2.653471
C	5.350079	-1.184394	-1.715185	C	-6.346072	0.732702	-1.638354
C	6.610430	-1.125902	-2.308131	C	-6.913795	0.542742	-2.898428
C	7.559334	-2.274145	-0.412242	C	-4.740918	0.803572	-3.912699
H	6.181590	-2.783589	1.161095	H	-3.105411	1.172575	-2.567335
H	4.491069	-0.776592	-2.238415	H	-6.967411	0.684800	-0.748727
H	6.722409	-0.661611	-3.284764	H	-7.982244	0.362108	-2.986063
H	8.416482	-2.698254	0.104854	H	-4.108526	0.834904	-4.796144
H	8.703074	-1.623504	-2.124017	H	-6.553452	0.427461	-5.022813
H	-0.363253	-4.766821	-4.348958	C	-4.708235	-2.112052	0.575047
C	-0.625535	-3.930442	-3.706256	C	-6.923791	-2.536949	2.262134
H	-2.294505	-4.936763	-2.811027	C	-5.952540	-2.490977	0.047165
C	-1.699454	-4.027434	-2.851011	C	-4.592259	-1.953454	1.965908
C	-0.175616	-1.672298	-2.942858	C	-5.689620	-2.165153	2.799823

C	-7.051024	-2.700097	0.882236
H	-6.057375	-2.602107	-1.028297
H	-3.634258	-1.676985	2.396586
H	-5.577572	-2.041841	3.874015
H	-8.007105	-2.988209	0.452052
H	-7.778402	-2.699236	2.913922
B	0.330813	0.683885	-0.585829
O	0.201781	2.073786	0.194453
S	-0.177872	3.360566	-0.651196
C	-1.789868	3.859317	0.004966
H	-2.026244	4.848177	-0.399245
H	-1.756224	3.870306	1.096099
H	-2.520049	3.125787	-0.339489
C	0.863163	4.609562	0.151700
H	1.896877	4.393231	-0.121248
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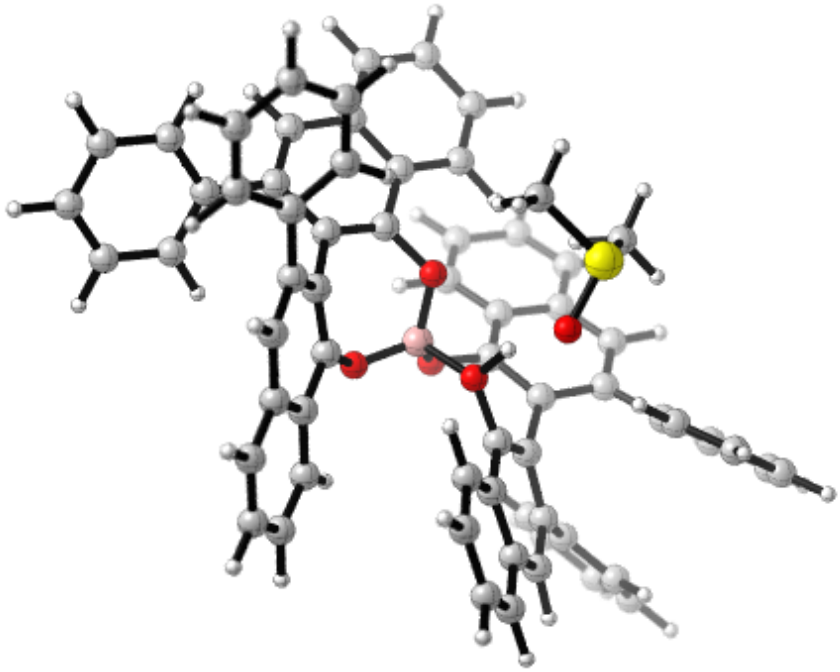
H	0.572175	5.595371	-0.221099

SCF energy: -3342.674345



DMSO-*spiro*borate complex 2

H	-2.500565	-6.486789	-2.177798
C	-2.394091	-5.429078	-1.950978
H	-4.153705	-5.356918	-0.724688
C	-3.315456	-4.802513	-1.140565
C	-1.156197	-3.361985	-2.212430
C	-3.199518	-3.417996	-0.844907
C	-1.310191	-4.701148	-2.497522
C	-2.090444	-2.694816	-1.379029
C	-4.125872	-2.737808	-0.015121
H	-0.593333	-5.204107	-3.140389
H	-0.329987	-2.794045	-2.624278
C	-4.045033	-1.376950	0.217004
H	-4.908150	-3.315098	0.470114
C	-2.980310	-0.621948	-0.393359
C	-1.977228	-1.302473	-1.077794
C	-2.958648	0.870245	-0.356102
C	-1.861812	1.543709	0.143650
C	-4.071865	3.022116	-0.583173
C	-1.837708	2.936033	0.417157
C	-4.079319	1.658501	-0.806317
C	-2.999477	3.687327	0.059972
C	-0.754357	3.590823	1.058722
H	-3.907198	5.650528	0.052715
H	-4.906866	3.617851	-0.942003
C	-0.822102	4.939460	1.328376
H	0.121502	3.017943	1.338239
H	0.011688	5.432669	1.819745
C	-1.963276	5.692062	0.960870
H	-1.997009	6.756970	1.174733
C	-3.026523	5.079386	0.336761
O	-0.704606	0.807093	0.452391
O	-0.896991	-0.635887	-1.557053
C	-5.214600	1.075875	-1.575601

C	-7.365579	0.114451	-3.120796
C	-4.989347	0.230575	-2.674879
C	-6.537901	1.432777	-1.269655
C	-7.602960	0.956381	-2.032978
C	-6.054216	-0.245589	-3.438245
H	-3.972684	-0.039721	-2.942131
H	-6.729551	2.066436	-0.408220
H	-8.619897	1.238675	-1.772348
H	-5.856035	-0.893933	-4.287736
H	-8.194897	-0.257625	-3.716679
C	-5.014295	-0.770111	1.174583
C	-6.842193	0.227513	3.078636
C	-6.375909	-1.113009	1.119728
C	-4.587652	0.087025	2.205011
C	-5.492887	0.578557	3.145909
C	-7.279810	-0.621110	2.060200
H	-6.727726	-1.748452	0.312495
H	-3.541337	0.367203	2.279512
H	-5.138847	1.237701	3.934512
H	-8.329653	-0.894116	1.990232
H	-7.546137	0.614138	3.811030
H	2.511616	-6.844548	0.356339
C	2.399317	-5.768229	0.255295
H	4.409482	-5.461600	-0.427614
C	3.456683	-5.000000	-0.178956
C	1.002616	-3.795358	0.428782
C	3.330905	-3.591940	-0.310462
C	1.159467	-5.158627	0.558710
C	2.081175	-2.976089	0.005664
C	4.389272	-2.782454	-0.787459
H	0.319676	-5.771108	0.875659
H	0.042322	-3.334769	0.623457
C	4.283960	-1.408135	-0.868772
H	5.293828	-3.268048	-1.142666
C	3.075672	-0.759367	-0.417917
C	1.979056	-1.552554	-0.094301
C	3.003558	0.726711	-0.291477
C	1.972977	1.411072	-0.925161
C	4.008650	2.871562	0.291246
C	2.005545	2.826408	-1.113124
C	4.010982	1.493167	0.402648
C	3.060072	3.565683	-0.499359
C	1.050798	3.503797	-1.914996
H	3.900515	5.538517	-0.207322
H	4.743567	3.450856	0.842994
C	1.136067	4.867020	-2.095225
H	0.266304	2.924602	-2.388126
H	0.404803	5.378486	-2.715080
C	2.165247	5.609339	-1.467800
H	2.215964	6.685763	-1.610585
C	3.103291	4.973165	-0.684578
O	0.922012	0.745827	-1.478013
O	0.772035	-0.994279	0.241818
C	5.019402	0.876138	1.310082
C	6.914269	-0.152712	3.134766
C	4.674151	-0.140066	2.216962
C	6.339414	1.358808	1.336201
C	7.274642	0.854467	2.237838
C	5.609458	-0.648673	3.117277
H	3.661948	-0.530249	2.217929
H	6.638835	2.114495	0.616282
H	8.290548	1.241238	2.230405
H	5.316257	-1.433396	3.810565
H	7.642815	-0.550315	3.836529
C	5.407372	-0.666453	-1.509952
C	7.546566	0.591563	-2.846537
C	6.739837	-0.965507	-1.181268
C	5.168438	0.276117	-2.523943
C	6.226815	0.898249	-3.184141
C	7.798766	-0.344539	-1.842425
H	6.941595	-1.670994	-0.380099
H	4.146966	0.510175	-2.806102
H	6.018138	1.619472	-3.970116
H	8.821807	-0.586451	-1.565324
H	8.370841	1.077739	-3.362169
B	0.102086	-0.097798	-0.685997
H	-0.661316	0.552594	1.451299
O	-0.903279	0.525765	2.962154
S	-0.667837	-0.643889	3.936786
C	-1.476169	-2.109442	3.214581
H	-2.549928	-1.910009	3.196225
H	-1.266721	-2.976650	3.847912
H	-1.105551	-2.268482	2.200005
C	1.062714	-1.165377	3.705572
H	1.235378	-1.366109	2.646062
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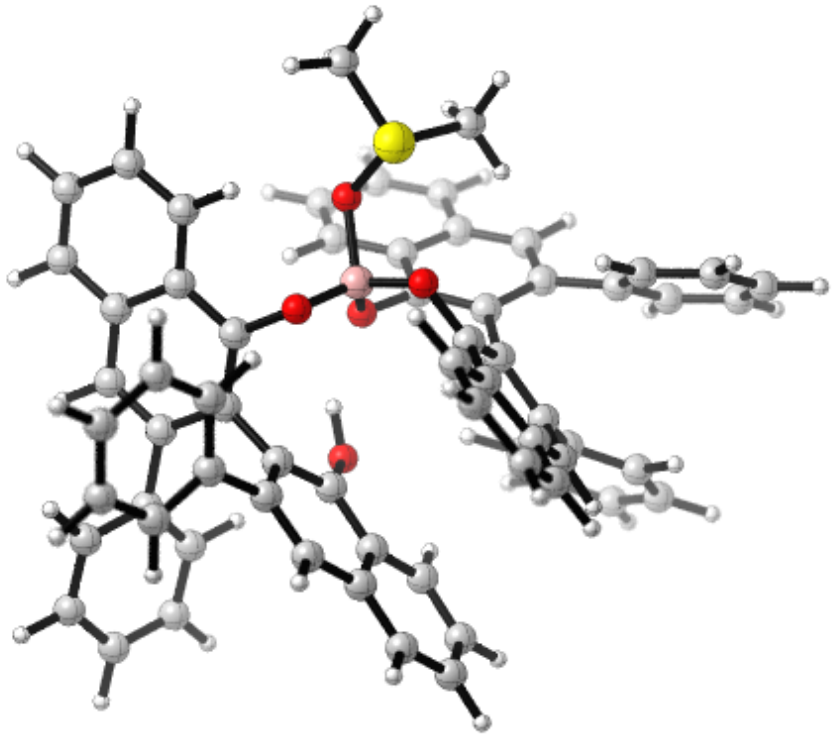
H	1.692893	-0.338924	4.042068

SCF energy: -3342.670736



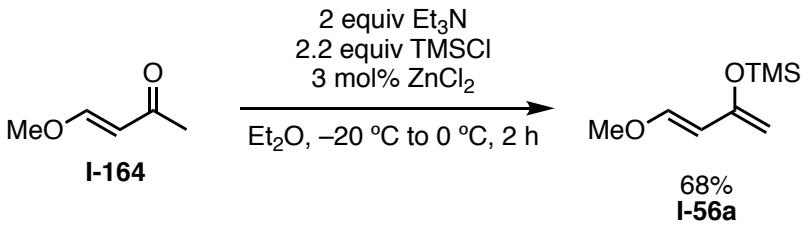
DMSO-*meso*borate complex 3

H	-0.390757	-6.820630	-0.346274
C	-0.577422	-5.754663	-0.450931
H	-2.151141	-5.727089	1.006275
C	-1.556596	-5.148249	0.303202
C	-0.035371	-3.641328	-1.507742
C	-1.821037	-3.758559	0.174170
C	0.187166	-4.994260	-1.368227
C	-1.037232	-2.993026	-0.741128
C	-2.836381	-3.111593	0.919052
H	0.958229	-5.478779	-1.961426
H	0.549952	-3.055507	-2.205803
C	-3.113477	-1.768129	0.758532
H	-3.409343	-3.690626	1.638315
C	-2.351507	-0.988254	-0.178250
C	-1.311156	-1.596835	-0.867307
C	-2.801150	0.400484	-0.536353
C	-2.340438	1.522192	0.143300
C	-4.355419	1.813035	-1.782788
C	-2.943870	2.807974	-0.045547
C	-3.825854	0.562448	-1.535171
C	-3.953845	2.951495	-1.045964
C	-2.625801	3.931067	0.761655
H	-5.302148	4.327702	-2.027335
H	-5.114102	1.927441	-2.552386
C	-3.237462	5.148270	0.557327
H	-1.904058	3.797978	1.554677
H	-2.992315	5.995347	1.194035
C	-4.195868	5.304872	-0.472019
H	-4.665146	6.272087	-0.632198
C	-4.547258	4.226479	-1.251086
O	-1.370220	1.387348	1.105894
O	-0.552908	-0.915238	-1.781934
C	-4.375177	-0.588827	-2.314035
C	-5.493487	-2.668482	-3.846204
C	-3.570218	-1.362697	-3.164849
C	-5.748774	-0.871221	-2.249077
C	-6.303585	-1.904138	-3.005716
C	-4.126789	-2.392309	-3.922991
H	-2.508683	-1.148683	-3.237333
H	-6.377722	-0.284377	-1.585382
H	-7.368596	-2.111506	-2.935509
H	-3.488247	-2.979845	-4.577803
H	-5.922953	-3.473760	-4.436768
C	-4.230729	-1.183298	1.556877
C	-6.341918	-0.188175	3.134571
C	-5.513818	-1.748814	1.482879
C	-4.022679	-0.110475	2.438659

C	-5.068951	0.379693	3.219581
C	-6.560965	-1.255132	2.262465
H	-5.687627	-2.571323	0.794647
H	-3.032643	0.326035	2.520322
H	-4.887695	1.207245	3.901410
H	-7.548432	-1.703676	2.185081
H	-7.155756	0.198286	3.743064
H	0.243205	-4.203341	5.017443
C	0.472070	-3.399838	4.322253
C	1.288355	-3.637163	3.238942
C	0.191041	-1.086429	3.654522
C	1.597642	-2.599335	2.320914
C	-0.082598	-2.113778	4.530458
C	1.040291	-1.303385	2.539091
C	2.403742	-2.815288	1.176206
H	-0.237946	-0.100814	3.795805
C	2.718857	-1.802709	0.290952
H	2.731252	-3.827673	0.958605
C	2.246849	-0.467204	0.555589
C	1.375474	-0.267120	1.620391
C	2.685255	0.707259	-0.256522
C	1.727040	1.557327	-0.799142
C	4.409421	2.028658	-1.368818
C	2.055242	2.612632	-1.699125
C	4.077000	1.000174	-0.504309
C	3.432021	2.829240	-2.009771
C	1.066173	3.441857	-2.290889
H	4.821671	4.036338	-3.148630
H	5.457252	2.263660	-1.533985
C	1.430769	4.437874	-3.170393
H	0.025374	3.271008	-2.040400
H	0.667785	5.062717	-3.626822
C	2.794852	4.655317	-3.484563
H	3.067487	5.445066	-4.179743
C	3.772695	3.871785	-2.913018
O	0.398457	1.387290	-0.495149
O	0.865462	0.981323	1.870257
C	5.191818	0.301977	0.199607
C	7.393766	-0.853809	1.533788
C	5.151494	0.055498	1.582297
C	6.358284	-0.050898	-0.499433
C	7.447115	-0.620017	0.158558
C	6.239103	-0.515789	2.241654
H	4.259594	0.306732	2.147701
H	6.390442	0.089039	-1.575780
H	8.333757	-0.893502	-0.407616
H	6.182469	-0.695488	3.312201
H	8.240476	-1.301171	2.047822
C	3.476193	-2.158324	-0.942042
C	4.847219	-2.950291	-3.275511
C	4.593304	-3.006613	-0.870765
C	3.054121	-1.720357	-2.209343
C	3.734176	-2.111397	-3.362409
C	5.271841	-3.398840	-2.023740
H	4.948921	-3.333033	0.102410
H	2.169424	-1.097201	-2.290856
H	3.384944	-1.766102	-4.332188
H	6.139881	-4.048298	-1.941963
H	5.376089	-3.254122	-4.175269
B	0.018234	1.616338	0.881911
H	1.704098	-4.626710	3.065663
H	-0.465311	0.016089	-1.491386
H	-0.735826	-1.941408	5.381730
O	0.347823	3.184760	1.137132
S	1.120437	3.573294	2.460456
C	0.739804	5.347883	2.507177
H	-0.320185	5.448219	2.747548
H	0.946236	5.780672	1.525621
H	1.346676	5.817791	3.285858
C	2.869483	3.681267	1.977710
H	3.199570	2.668049	1.747951
H	3.432534	4.084499	2.824775
H	2.965162	4.316167	1.094217

SCF energy: -3342.671877

4.2.18 Synthesis of Danishefsky's diene **I-56a** and related compound **I-56b-d** (*Scheme 1.21*)



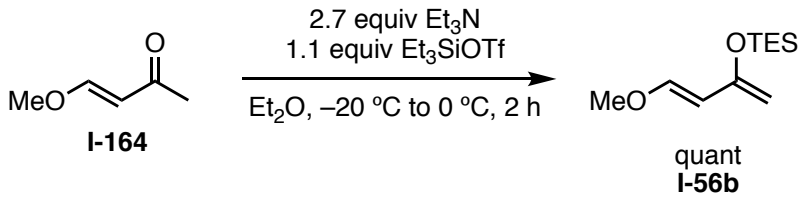
I-164

68%
I-56a

*4-Methoxy-2-trimethylsilyloxy-1,3-butadiene **I-56a***: To a 250 mL round bottomed flask anhydrous powdered zinc chloride (164 mg, 1.20 mmol) was added to dry triethylamine (11.2 mL, 80.0 mmol), and the mixture was stirred for 1 h at rt until the salt was suspended in the amine. The mixture was cooled to –20 ºC in a cold bath for 10 min. To this mixture was added 4-methoxy-3-buten-2-one **I-164** (4.5 mL, 40 mmol) in dry Et_2O (10 mL) at –20 ºC followed by trimethylchlorosilane (10.2 mL, 80.0 mol) in one portion. A slight exothermic reaction ensued. After 30 min the reaction temperature was raised to 0 ºC and stirring continued for 2 h. The reaction mixture was added to dry ether (100 mL) and filtered through a pad of celite. The filtrate and combined ethereal washings were concentrated. Purification by vacuum distillation (15 mm Hg, 77 ºC) gave 4-methoxy-2-trimethylsilyloxy-1,3-butadiene **I-56a** (4.687 g, 27.20 mmol) as a light-yellow liquid in 68% yield.

Spectral data for **I-56a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21 (d, J = 0.8 Hz, 9H), 3.57 (d, J = 0.8 Hz, 3H), 4.07 (dq, J = 20.7, 0.8 Hz, 2H), 5.34 (dd, J = 12.4, 0.8 Hz, 1H), 6.81 (d, J = 12.3 Hz, 1H). These spectral data match those previously reported for this compound[9].

General procedure **D**[9] for synthesis of silyl enol dienes (*Scheme 1.21*) -- illustrated for the synthesis of (*E*)-triethyl((4-methoxybuta-1,3-dien-2-yl)oxy)silane **I-56b**.

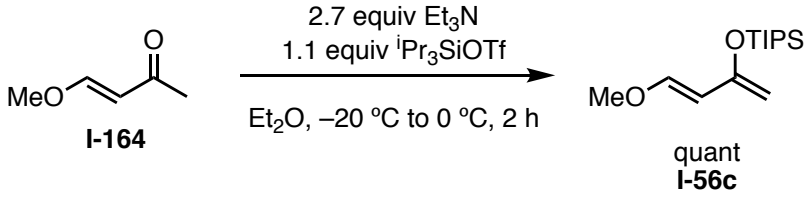


I-164

quant
I-56b

*(E)-triethyl((4-methoxybuta-1,3-dien-2-yl)oxy)silane **I-56b***: An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, a solution of (*E*)-4-methoxybut-3-en-2-one **I-164** (1.53 mL, 15.0 mmol) and Et_3N (5.70 mL, 40.8 mmol, 2.73 equiv) in anhydrous Et_2O (30 mL) was added and cooled to –20 °C in a cold bath. TESOTf (3.80 mL, 16.8 mmol, 1.12 equiv) was then added dropwise at –20°C. The mixture was then warmed to 0 °C and stirred for 2 h at the same temperature. The mixture was then diluted with hexanes (20 mL) and washed with ice cold saturated aqueous $NaHCO_3$, and brine. After volatile material was removed under reduced pressure, purification of the crude product by flash column chromatography (neutral alumina, EtOAc/hexanes 1:3) gave **I-56b** (3.218 g, 15.00 mmol) as a yellow liquid in 100% yield.

Spectral data for **I-56b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 – 0.78 (m, 6H), 0.99 (t, *J* = 7.9 Hz, 9H), 3.58 (s, 3H), 4.02 – 4.16 (m, 2H), 5.35 (d, *J* = 12.4 Hz, 1H), 6.89 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 4.94, 6.74, 56.42, 90.46, 103.13, 150.19, 154.11. These spectral data match those previously reported for this compound[9].

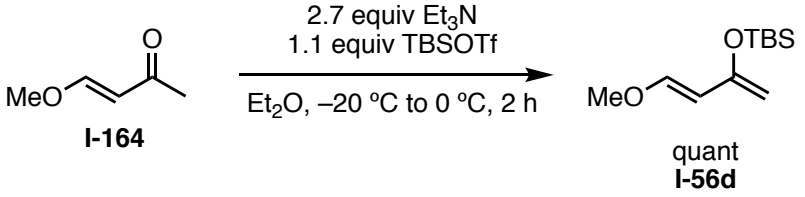


I-164

quant
I-56c

(E)-triisopropyl((4-methoxybuta-1,3-dien-2-yl)oxy)silane ***I-56c***: Silane **I-56c** was prepared by General Procedure **D** with TIPSOTf (4.60 mL, 16.8 mmol) and was obtained (3.850 g, 15.00 mmol) as a yellow liquid in 100% yield.

Spectral data for **I-56c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, *J* = 7.3 Hz, 18H), 1.15 – 1.33 (m, 3H), 3.59 (s, 3H), 4.05 (q, *J* = 1.2 Hz, 2H), 5.34 (d, *J* = 12.4 Hz, 1H), 6.96 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.81, 18.08, 56.34, 90.04, 103.25, 150.15, 154.33. These spectral data match those previously reported for this compound[9].



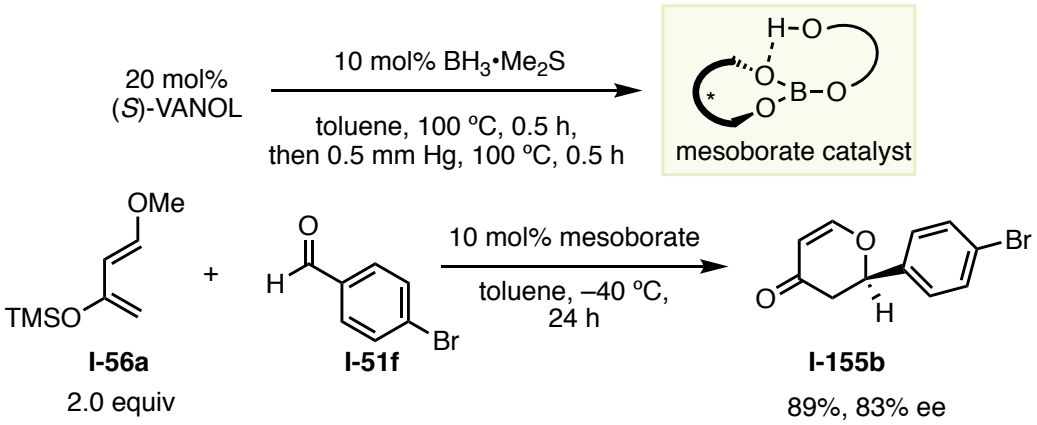
I-164

quant
I-56d

(E)-tert-butyl((4-methoxybuta-1,3-dien-2-yl)oxy)dimethylsilane ***I-56d***: Silane **I-56d** was prepared by General Procedure **D** with TBSOTf (3.86 mL, 16.8 mmol) and was obtained (3.216 g, 15.00 mmol) as a yellow liquid in 100% yield.

Spectral data for **I-56d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.96 (s, 9H), 3.58 (s, 3H), 4.01 – 4.18 (m, 2H), 5.35 (d, *J* = 12.4 Hz, 1H), 6.88 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ -4.64, 25.69, 25.82, 56.38, 90.87, 103.25, 150.20, 154.14. These spectral data match those previously reported for this compound[9].

4.2.19 General procedure **E** for HDA reactions catalyzed by *meso*borate **I-118** (*Table 1.13*) -- illustrated for the reaction of 4-bromobenzaldehyde **I-51f** and Danishefsky's diene **I-56a** with VANOL ligand

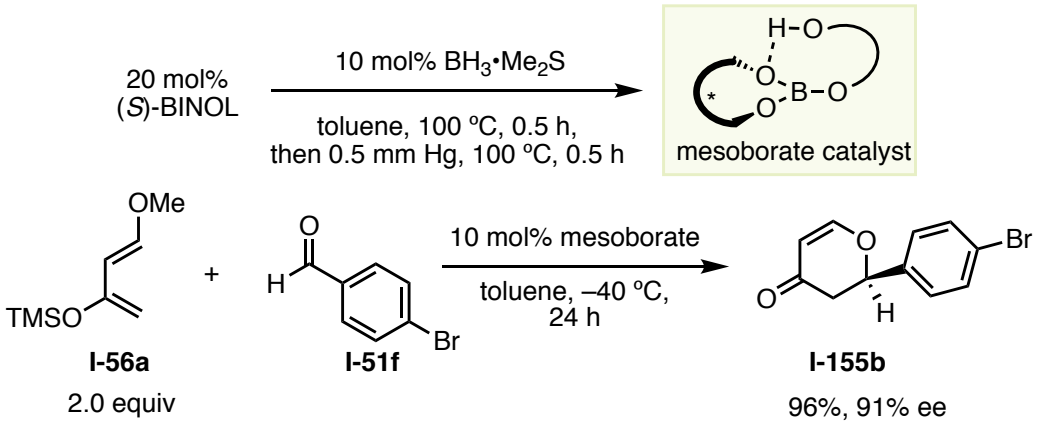


Preparation of the pre-catalyst solution: *meso*Borate precatalyst was prepared (0.125 mmol in 2.50 mL toluene) according to the General Procedure **C** (4.2.13) without adding DMSO.

(R)-2-(4-bromophenyl)-2,3-dihydro-4H-pyran-4-one ***I-155b***: To another 50 mL flame-dried home-made Schlenk flask was added 4-bromobenzaldehdye (92.5 mg, 0.500 mmol) and dry toluene (3 mL) and cooled to –40 °C for 10 min. To the aldehyde solution was then added diene **I-56a** (195 μL, 1.00 mmol, 2.00 equiv). Precatalyst stock solution (2.0 mL, 0.10 mmol) at –40 °C was transferred to the reaction mixture using syringe. After the reaction mixture was stirred at –40 °C for 1 h, 0.5 mL of 1 M HCl was added to quench the reaction and was warmed to rt. After the mixture was stirred for 0.5 h, saturated $NaHCO_3$ (5 mL) was added and the mixture was stirred for 10 min, and the layers were separated. The aqueous layer was extracted with EtOAc (3x5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product

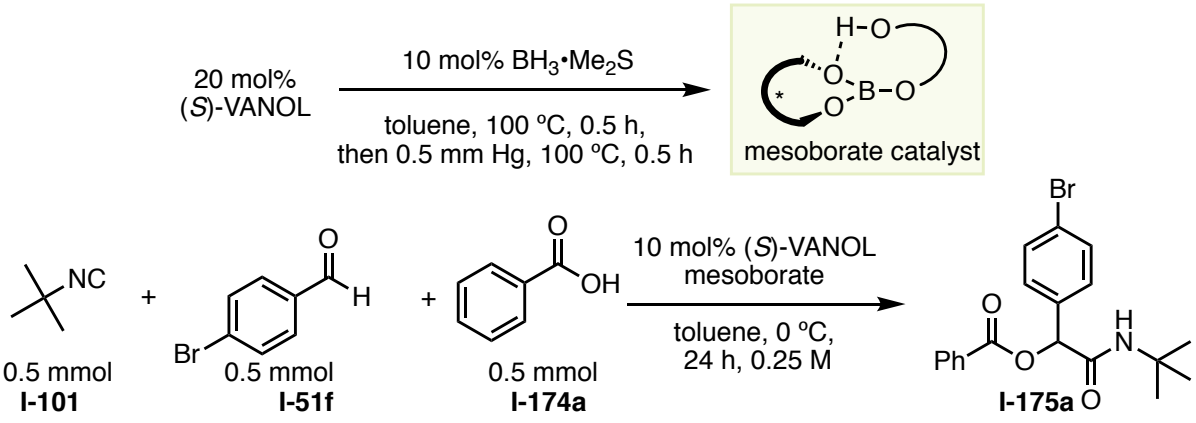
was purified by flash chromatography (hexanes/EtOAc, 4:1, silica gel) to afford **I-155b** as a yellow solid (113 mg, 0.446 mmol) in 89% yield. The optical purity of **I-155b** was determined to be 83% *ee* by HPLC (Chiralcel OD column, 90:10 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 13.30 min (minor enantiomer, ***ent*-I-155b**) and R_t = 17.83 min (major enantiomer, **I-155b**).

Spectral data for **I-155b**: R_f = 0.27 (1:4 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 – 2.76 (m, 1H), 2.74 – 2.96 (m, 1H), 5.26 – 5.48 (m, 1H), 5.44 – 5.65 (m, 1H), 7.18 – 7.38 (d, *J* = 10 Hz, 2H), 7.46 (dd, *J* = 6.2, 2.8 Hz, 1H), 7.51 – 7.63 (d, *J* = 10 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 43.29, 80.31, 107.53, 122.90, 127.74, 132.01, 136.90, 162.98, 191.62. These spectral data match those previously reported for this compound[10].



(R)-2-(4-bromophenyl)-2,3-dihydro-4H-pyran-4-one ***I-155b***: Pyranone product **I-155b** was obtained in 96% yield following General Procedure E using (*S*)-BINOL ligand. The optical purity of **I-155b** was determined to be 91% *ee* by HPLC.

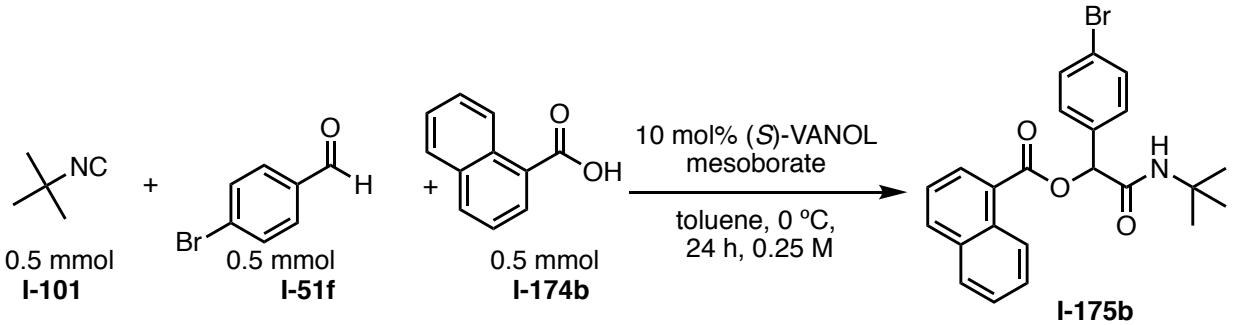
4.2.20 General procedure **F** for 3C Passerini reaction catalyzed by VANOL *meso*borate **I-118** (*Scheme 1.23*) -- illustrated for the reaction with 4-bromobenzaldehyde **I-51f**, and *t*butyl isocyanide **I-101** with benzoic acid **I-174a**



1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl benzoate ***I-175a***: To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a T-shaped high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*S*)-VANOL (43.8 mg, 0.100 mmol). Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (3 mL) was added through the top of the Teflon valve to effect dissolution. After the addition of the toluene, BH_3•Me_2S (25 µL, 0.050 mmol, 2 M in toluene) was added. The flask was sealed by closing the Teflon valve, and then placed in a 100 °C oil bath for 0.5 h. After 0.5 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 100 °C (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. To this Schlenk flask containing

precatalyst was added 4-bromobenzaldehdye **I-51f** (92.5 mg, 0.500 mmol) and *t*butyl isocyanide **I-101** (57 µL, 0.50 mmol) and toluene (2 mL) under a nitrogen flow through side-arm of the Schlenk flask. The mixture was cooled to 0 ºC for 10 min and then was added benzoic acid (61.1 mg, 0.500 mmol) in one portion. After stirred at 0 ºC for 24 h, to the reaction flask was added brine (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The conversion of aldehyde was determined using ^{1}H NMR analysis of crude product by integration of the CHO relative to the internal standard (Ph_3CH). The crude product was purified by flash column chromatography (silica gel, eluted with hexanes/EtOAc 9:1 to 4:1) to give the pure product **I-175a** as a white solid (102 mg, mp 183-185 ºC, 0.261 mmol) in 52% yield. The optical purity of **I-175a** was determined to be 35% *ee* by HPLC (Chiralcel OD-H column, 95:5 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 9.67 min (major enantiomer, **I-175a**) and R_t = 10.69 min (minor enantiomer, *ent*-**I-175a**).

Spectral data for **I-175a**: R_f = 0.14 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 6.01 (s, 1H), 6.14 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.41 – 7.53 (m, 4H), 7.56 – 7.63 (m, 1H), 8.05 (dd, J = 8.4, 1.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.68, 51.70, 75.30, 123.08, 128.73, 129.04, 129.08, 129.71, 131.92, 133.78, 135.00, 164.69, 166.85. HRMS (ESI-TOF) *m/z* 388.0553 [(M–H$^+$); calcd. for $C_{19}H_{19}{}^{79}BrNO_3$: 388.0548]; $[\alpha]_D^{20}$ +1.0 (*c* 1.0, CH_2Cl_2) on 35% *ee* material (HPLC).

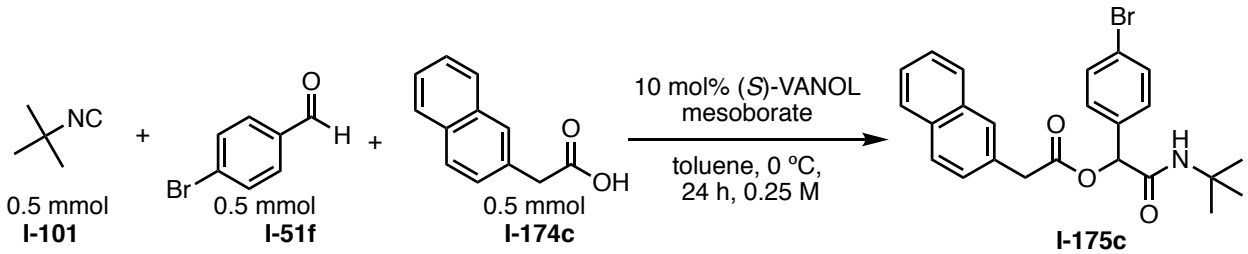


I-175b

69% conv., 43%, 37% ee

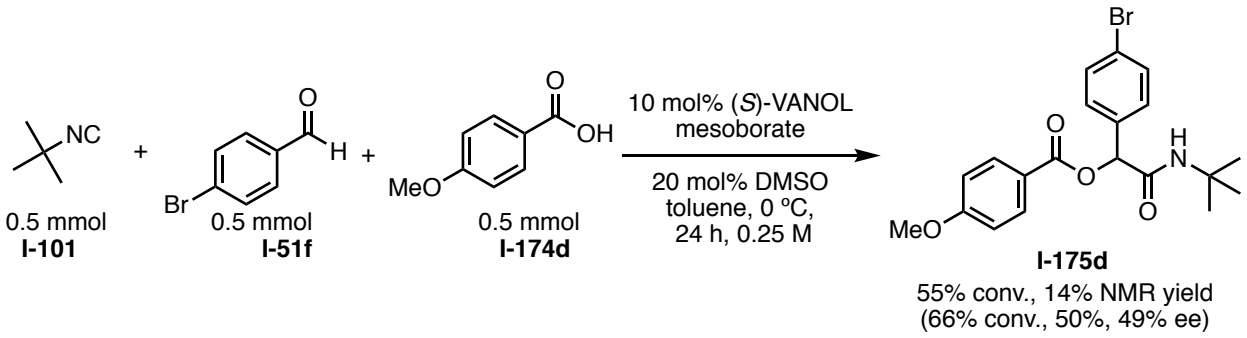
1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl 1-naphthoate ***I-175b****:* The α-acyloxyamides **I-175b** was prepared following the general procedure **C** with 1-naphthoic acid **I-174b** (86.1 mg, 0.500 mmol). The crude product was purified by flash column chromatography (silica gel, eluted with hexanes/EtOAc 9:1 to 4:1) to give the pure product **I-175b** as a white solid (95.4 mg, mp 128-131 ºC, 0.217 mmol) in 43% yield. The optical purity of **I-175b** was determined to be 37% *ee* by HPLC (Chiralcel OD-H column, 95:5 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 13.56 min (major enantiomer, **I-175b**) and R_t = 22.33 min (minor enantiomer, *ent*-**I-175b**).

Spectral data for **I-175b**: R_f = 0.15 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 6.20 (s, 1H), 6.31 (s, 1H), 7.41 – 7.78 (m, 7H), 7.92 (dd, *J* = 8.2, 4.6 Hz, 1H), 8.00 – 8.15 (m, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 8.89 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.71, 51.83, 75.60, 123.15, 124.53, 125.46, 126.57, 128.05, 128.23, 128.74, 129.19, 130.31, 131.70, 132.00, 133.86, 134.22, 134.46, 135.04, 165.56, 167.25, 172.57. HRMS (ESI-TOF) *m/z* 438.0713 [(M–H$^+$); calcd. for $C_{23}H_{21}{}^{79}BrNO_3$: 438.0705]; $[\alpha]_D^{20}$ +12.0 (*c* 1.0, CH_2Cl_2) on 37% *ee* material (HPLC).



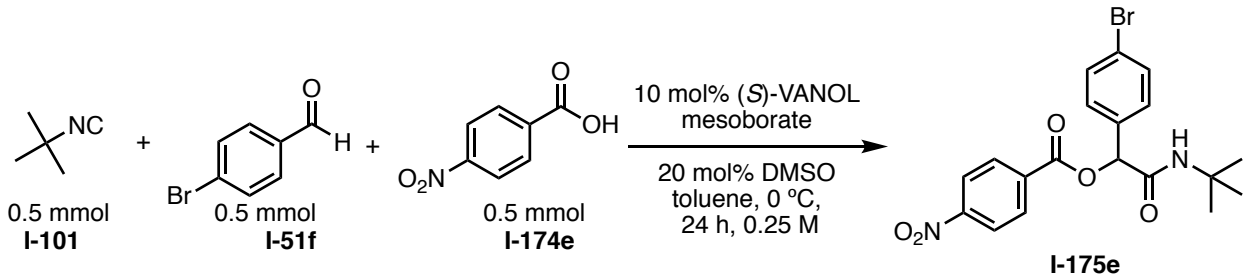
1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl 2-(naphthalen-2-yl)acetate ***I-175c****:* The α-acyloxyamides **I-175c** was prepared following the general procedure **C** with 2-(naphthalen-2-yl)acetic acid **I-174c** (93.1 mg, 0.500 mmol). The crude product was purified by flash column chromatography (silica gel, eluted with hexanes/EtOAc 9:1 to 4:1) to give the pure product **I-175c** as a white solid (89.7 mg, mp 120-122 ºC, 0.197 mmol) in 40% yield. The optical purity of **I-175c** was determined to be 35% *ee* by HPLC (Chiralcel OD-H column, 95:5 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 29.05 min (minor enantiomer, *ent*-**I-175c**) and R_t = 39.81 min (major enantiomer, **I-175c**).

Spectral data for **I-175c**: R_f = 0.15 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 3.88 (d, *J* = 2.5 Hz, 2H), 5.62 (s, 1H), 5.92 (s, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.59 (m, 5H), 7.61 – 7.94 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.29, 41.74, 51.30, 75.04, 123.01, 126.27, 126.61, 127.01, 127.62, 127.71, 128.03, 128.76, 128.97, 130.72, 131.82, 132.59, 133.47, 134.93, 166.63, 169.08. HRMS (ESI-TOF) *m/z* 458.0868 [(M–H$^+$); calcd. for $C_{24}H_{23}{}^{79}BrNO_3$: 452.0861]; $[\alpha]_D^{20}$ +1.3 (*c* 1.0, CH_2Cl_2) on 35% *ee* material (HPLC).



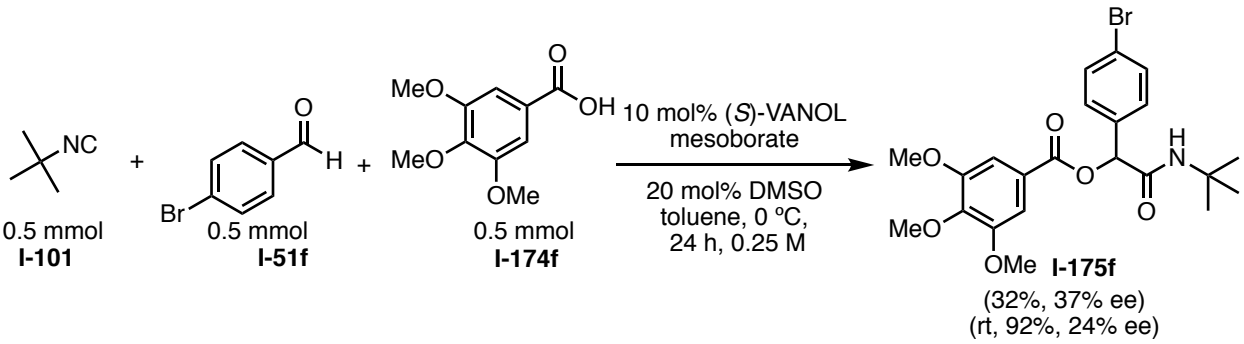
1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl 4-methoxybenzoate ***I-175d****:* The α-acyloxyamides **I-175d** was prepared following the general procedure **C** with 4-methoxybenzoic acid **I-174d** (76.1 mg, 0.500 mmol) with DMSO (7.0 µL, 0.10 mmol). The crude product was purified by flash column chromatography (silica gel, eluted with hexanes/EtOAc 9:1 to 4:1) to give the pure product **I-175d** as a white solid (105 mg, mp 159-162 ºC, 0.250 mmol) in 50% yield. The optical purity of **I-175d** was determined to be 49% *ee* by HPLC (Chiralcel OD-H column, 95:5 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 16.07 min (major enantiomer, **I-175d**) and R_t = 18.77 min (minor enantiomer, *ent*-**I-175d**).

Spectral data for **I-175d**: R_f = 0.17 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 9H), 3.86 (s, 3H), 6.16 (s, br, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.25 – 7.48 (m, 2H), 7.50 (d, J = 8.2 Hz, 2H), 8.03 (dd, J = 8.5, 3.3 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 28.66, 51.64, 55.54, 64.01, 69.19, 75.02, 113.99, 121.30, 122.93, 128.34, 129.04, 129.65, 131.84, 133.01, 135.22, 164.00, 164.45, 167.18. HRMS (ESI-TOF) *m/z* 418.0657 [(M–H^+); calcd. for $C_{20}H_{21}{}^{79}BrNO_4$: 418.0654]; $[\alpha]_D^{20}$ +6.8 (*c* 1.0, CH_2Cl_2) on 49% *ee* material (HPLC).



1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl 4-nitrobenzoate ***I-175e****:* The α-acyloxyamides **I-175e** was prepared following the general procedure **C** with 4-nitrobenzoic acid **I-174e** (76.1 mg, 0.500 mmol) with DMSO (7.0 µL, 0.10 mmol). The crude product was purified by flash column chromatography (silica gel, eluted with hexanes/EtOAc 9:1 to 4:1) to give the pure product **I-175e** as a yellow solid (70.4 mg, mp 172-174 ºC, 0.162 mmol) in 32% yield. The optical purity of **I-175e** was determined to be 3% *ee* by HPLC (Chiralcel OD-H column, 95:5 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 37.44 min (major enantiomer, **I-175e**) and R_t = 34.05 min (minor enantiomer, *ent*-**I-175e**).

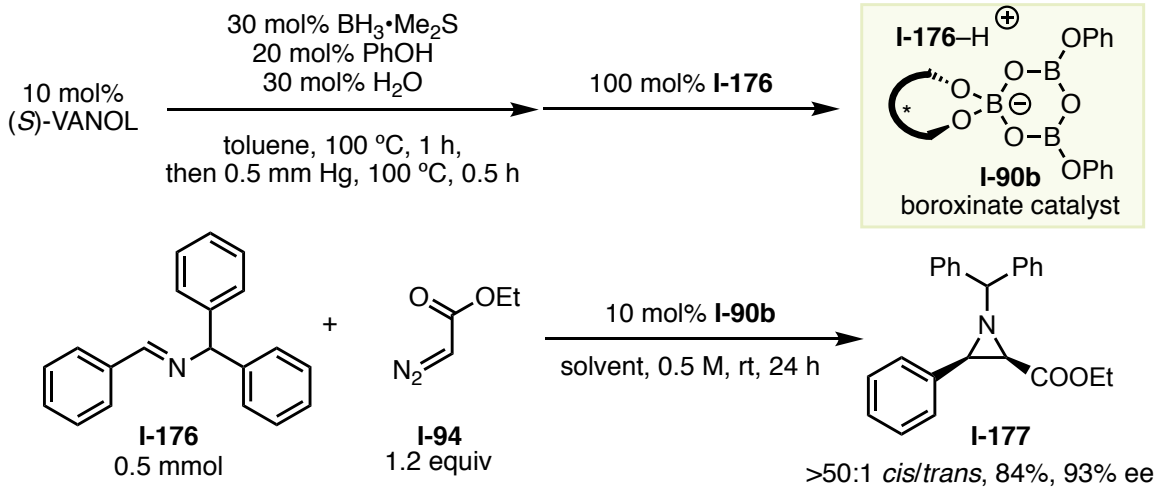
Spectral data for **I-175e**: R_f = 0.14 (1:9 EtOAc/hexane); HRMS (ESI-TOF) *m/z* 433.0417 [(M–H^+); calcd. for $C_{19}H_{18}{}^{79}BrN2O_5$: 433.0399];



1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl 3,4,5-trimethoxybenzoate ***I-175f****:* The α-acyloxyamides **I-175f** was prepared following the general procedure **C** with 3,4,5-trimethoxybenzoic acid **I-174f** (106.1 mg, 0.500 mmol) with DMSO (7.0 μL, 0.10 mmol). The crude product was purified by flash column chromatography (silica gel, eluted with hexanes/EtOAc 9:1 to 4:1) to give the pure product **I-175f** as a white solid (222 mg, mp 185-187°C, 0.461 mmol) in 92% yield. The optical purity of **I-175d** was determined to be 24% *ee* by HPLC (Chiralcel OD-H column, 95:5 hexane/2-propanol at 228 nm, flow-rate: 1 mL/min): retention times: R_t = 8.82 min (major enantiomer, **I-175d**) and R_t = 12.78 min (minor enantiomer, *ent*-**I-175d**).

Spectral data for **I-175d**: R_f = 0.20 (1:9 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.89 (d, *J* = 4.4 Hz, 9H), 5.95 (s, 1H), 6.09 (s, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.59 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.67, 51.72, 56.30, 61.01, 75.48, 107.02, 123.16, 123.91, 129.11, 131.97, 134.86, 143.00, 153.12, 164.48, 166.79. HRMS (ESI-TOF) *m/z* 478.0881 [(M–H$^+$); calcd. for $C_{22}H_{25}{}^{79}BrNO_6$: 478.0865]; $[\alpha]_D^{20}$ +0.3 (*c* 1.0, CH_2Cl_2) on 24% *ee* material (HPLC).

4.2.21 General procedure **G** for aziridination reaction of benzhydryl imine **I-176** and ethyl diazoacetate **I-94** (*Table 1.22*) -- illustrated by using VANOL boroxinate catalyst **I-90b**

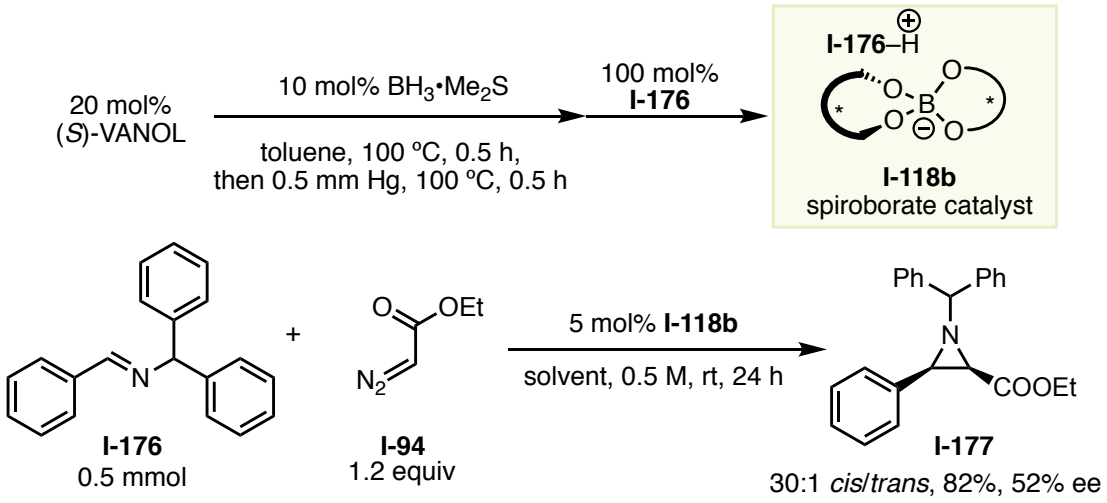


Preparation of the pre-catalyst solution: Precatalyst **I-90b** was prepared according to the General Procedure **B** (4.2.2) without adding DMSO.

*(2R,3R)-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate **I-177***: To the flask containing the precatalyst (made by General Procedure **B**) was first added the aldimine **I-176** (136 mg, 0.500 mmol) and then dry toluene (1 mL) under a nitrogen flow through side-arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light orange solution. To this solution was rapidly added ethyl diazoacetate (EDA) **I-94** (72 µL, 0.60 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow towards the end of the reaction. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then *trans*ferred to a 100 mL round bottom flask. The reaction flask was rinsed with

dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as an off-white solid. A measure of the extent to which the reaction went to completion was estimated from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methane protons relative to either the imine methine proton or the proton on the imine carbon. The *cis/trans* ratio was determined by comparing the ^{1}H NMR integration of the ring methine protons for each aziridine in the crude reaction mixture. The *cis* (J = 7-8 Hz) and the *trans* (J = 2-3 Hz) coupling constants were used to differentiate the two isomers. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 19:1 hexanes/EtOAc as eluent, under gravity) afforded pure *cis*-aziridine **I-177** as a white solid (mp 127.5-128.5 °C on 93% *ee* material) in 84% isolated yield (149 mg, 0.420 mmol); *cis/trans*: >50:1. The optical purity of **I-177** was determined to be 93% *ee* by HPLC analysis ((CHIRALCEL OD-H column, 90:10 hexanes/iPrOH at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.01 min (major enantiomer, **I-177**) and R_t = 4.67 min (minor enantiomer, *ent*-**I-177**).

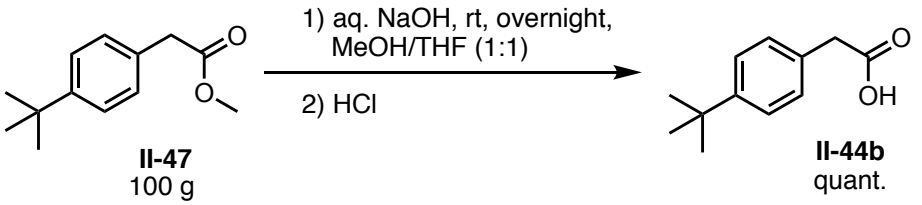
Spectral data for **I-177**: R_f = 0.3 (1:9 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, 3H, J = 7.3 Hz), 2.64 (d, J = 6.8 Hz, 1H), 3.19 (d, J = 6.8 Hz, 1H), 3.91 (q, J = 7.1 Hz, 2H), 3.93 (s, 1H), 7.16-7.38 (m, 11H), 7.47 (d, J = 7.1 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.93, 46.36, 48.01, 60.57, 77.68, 127.18, 127.31, 127.39, 127.52, 127.76, 127.78, 128.48, 135.00, 142.37, 142.49, 167.75. These spectral data match those previously reported for this compound[11].



(2R,3R)-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate ***I-177*****:** The General Procedure **G** was followed using precatalyst **I-118** (made by General Procedure **C**). Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 19:1 hexanes/EtOAc as eluent, under gravity) afforded pure *cis*-aziridine **I-177** as a white solid in 82% isolated yield (147 mg, 0.410 mmol); *cis/trans*: 30:1. The optical purity of **I-177** was determined to be 52% *ee* by HPLC analysis ((CHIRALCEL OD-H column, 90:10 hexanes/iPrOH at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.01 min (major enantiomer, **I-177**) and R_t = 4.67 min (minor enantiomer, *ent*-**I-177**).

4.3 Experimental for Chapter Two

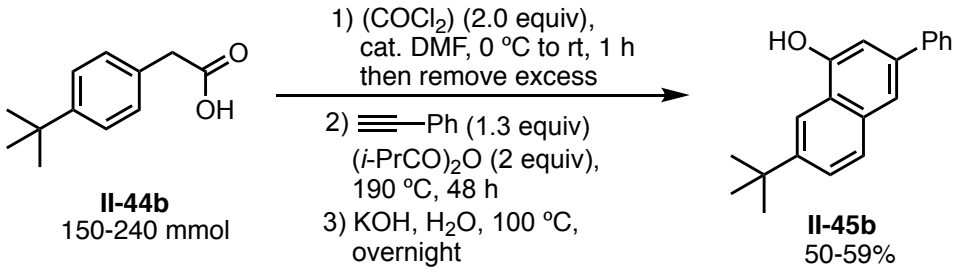
4.3.1 Synthesis of (±)-tBuVANOL **II-46b** (*Scheme 2.10*)



*2-(4-(tert-butyl)phenyl)acetic acid **II-44b***. An oven-dried 2 L round-bottomed flask equipped with an egg-shaped stirring bar (50 mm × 20 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, methyl 2-(4-(*tert*-butyl)phenyl)acetate **II-47** (100 g, 48.5 mmol, 1.00 equiv) is added followed by addition of methyl alcohol (500 mL) (Note), tetrahydrofuran (500 mL) and 6 M aq. NaOH solution (160 mL, 2.00 equiv). The mixture is stirred at room temperature (23 °C) for 12 h. The reaction mixture is concentrated in vacuo using a rotary evaporator (40 °C, 15 mm Hg) then cooled in the ice bath for 10 min. To the the reaction mixture 6N aq. HCl is added in portion (10×10 mL) and the white precipitate is then filtered and allowed to dry overnight. The white solid is put under high vacuum (23 °C, 0.2 mmHg) for 30 min to yield 93.23 g of the product **II-47** as a white solid at >99% purity (48.50 mmol, mp 80-82 ºC, 100% yield).

Spectral data for **II-47**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.61 (s, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.34 (m, J = 7.0 Hz, 2H) 10.2 (br s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.33, 34.54, 40.53, 125.61, 129.02, 130.24, 150.26, 177.67. These spectral data match those previously reported for this compound[11].

General Procedure **H'** for CAEC process with $(COCl)_2$ -- illustrated for synthesis of 7-(*tert*-butyl)-3-phenylnaphthalen-1-ol **II-45b** from 2-(4-(*tert*-butyl)phenyl)acetic acid **II-44b**:



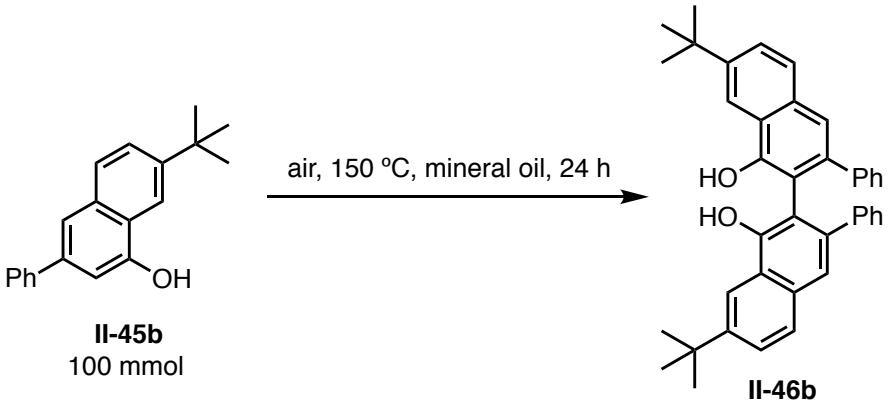
II-44b
150-240 mmol

II-45b
50-59%

*7-(*tert*-butyl)-3-phenyl-1-naphthol* ***II-45b***. An oven-dried 1 L round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, 2-(4-(*tert*-butyl)phenyl)acetic acid **II-44b** (46.34 g, 241.0 mmol, 1.000 equiv) is added followed by addition of anhydrous dichloromethane (241 mL) before cooling in the ice bath for 10 min. To the solution oxalyl chloride (50.0 mL, 600 mmol, 2.50 equiv) is added in one portion followed by addition of 10 drops of anhydrous DMF. The ice bath is removed. The mixture is stirred and allowed to warm up to room temperature (23 °C). After 2 h, the reaction mixture is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) then put under high vacuum (23 °C, 0.2 mmHg) for 30 min to completely remove excess $(COCl)_2$. The reaction flask containing the crude acid chloride is filled with N_2, and then phenylacetylene (34.0 mL, 313 mmol, 1.30 equiv) and $(i\text{-PrCO})_2O$ (80.0 mL, 482 mmol, 2.00 equiv) are added. The flask is fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal. The reaction mixture was heated and stirred in a 190 ºC oil bath for 48 h with a gentle nitrogen flow across the top of the

condenser. The brown reaction mixture is cooled to about 60 ºC (oil bath temperature), and aq KOH (80.0 g, 1.43 mol) in 320 mL of H_2O is slowly added. After stirring in a 100 ºC oil bath overnight (15 h), the orange solution is cooled to rt, ether (300 mL) is added, and the mixture stirred for 30 min before the organic layer is isolated in a 2 L separatory funnel. The water layer is extracted twice with ether (300 mL×2), and the combined organic layer is washed with brine (300 mL), dried over $MgSO_4$ and filtered. The dark-colored organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (23 °C, 0.2 mmHg) overnight to give 40 g of the dark brown crude product. Recrystallization from CH_2Cl_2/hexanes gave 26.46 g product **II-45b** (mp 135-136 °C) as solid crystals (95.70 mmol, 40%, first crop). Successive crystallization yields the product **II-45b** a combined yield of 59% (8.7%, 5.77 g, mp 137-138 °C, second crop; 10.1%, 6.72 g, mp 135-138°C, third crop).

Spectral data for **II-45b**: R_f = 0.34 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 5.36 (s, 1H), 7.06 (d, *J* = 1.6 Hz, 1H), 7.30 – 7.39 (m, 1H), 7.45 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.57 – 7.70 (m, 4H), 7.80 (d, *J* = 8.7 Hz, 1H), 8.09 (dd, *J* = 1.8, 0.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.30, 35.10, 108.34, 116.24, 118.34, 123.25, 125.82, 127.22, 127.29, 127.78, 128.78, 133.16, 138.13, 141.01, 148.25, 151.65. These spectral data match those previously reported for this compound[11].



II-45b
100 mmol

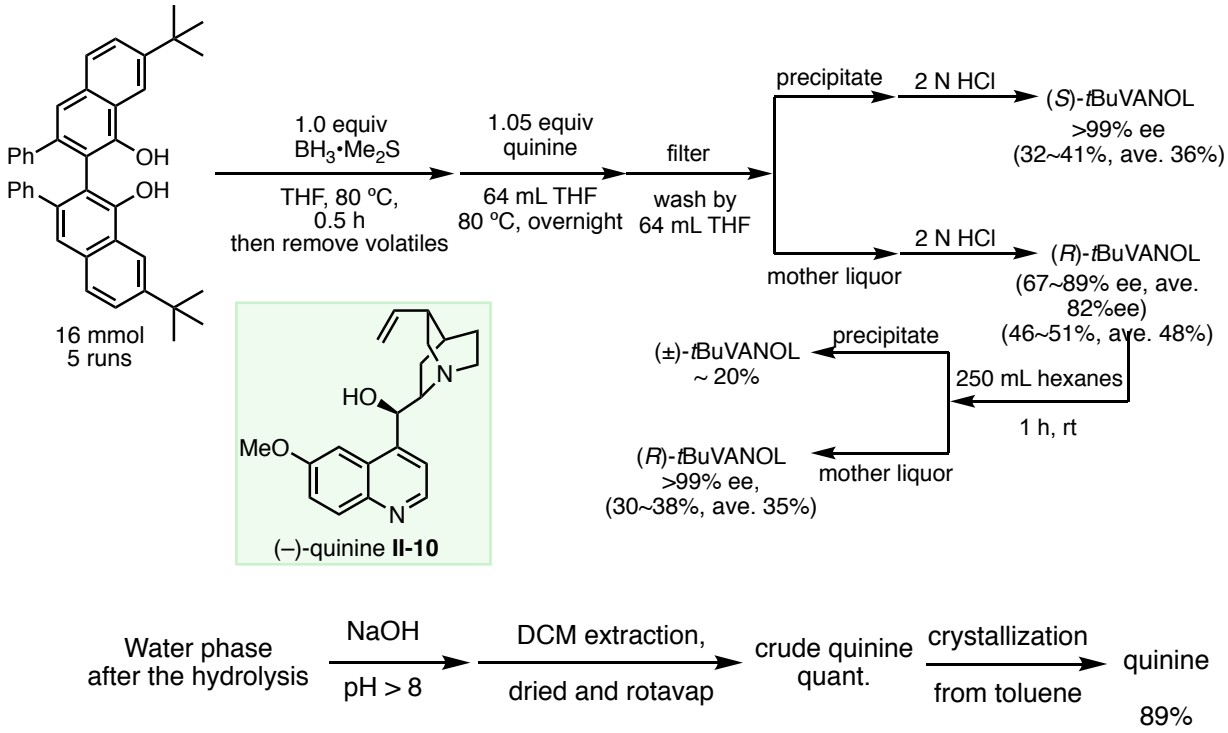
II-46b
71-76%

*7,7'-di-*tert*-butyl-3,3'-diphenyl-[2,2'-binaphthalene]-1,1'-diol (tBuVANOL)* ***II-46b***. An oven-dried 250 mL three-necked round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, naphthol **II-45b** (27.64 g, 100.0 mmol) is added by a funnel followed by the addition of 110 mL of light mineral oil through the same funnel and then an oven-dried reflux condenser is attached. A glass tube (6 mm id) is introduced into the flask via the second neck to about 5 cm above the surface of the naphthol solution and is used to provide a stream of house air which is maintained at a flow rate of 0.15 0.20 L/min. The third neck is sealed with a rubber septum. The stir bar in the oil bath was removed before the flask is introduced into the oil bath to warm it up for about 15 min until the solid was melted. Airflow is allowed to flow into the flask while the molten **II-45b** was stirred as fast as possible. The airflow is switched to N_2 after the reaction is kept at 150 ºC for 24 h. The flask is removed from the oil bath and cooled to rt before hexanes (500 mL) is added to the flask. The mixture was stirred for 30 min, and then it was cooled to –20 ºC overnight (12 h) before the solid is collected by suction filtration. The crude product is dried on high vacuum and crystallized from CH_2Cl_2. The dark-colored solution is cooled to room

temperature and then to –20 ºC overnight (12 h). The brown crystals are collected via suction filtration, washed with hexanes (3 x 30 mL), and dried under vacuum to give the first crop product of (±)-*t*BuVANOL (9.60 g, 17.4 mmol, 34.9%, 154-157 ºC). Successive crystallization from CH_2Cl_2 yield the product **II-46b** a combined yield of 71% (5.35 g, 9.70 mmol, 19.4%, mp 155-158 °C, second crop; 4.67 g, 8.50 mmol, 16.9%, mp 155-156°C, third crop).

Spectral data for **II-46b**: R_f = 0.39 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 18H), 5.82 (s, 2H), 6.60 (dt, *J* = 7.0, 1.3 Hz, 4H), 6.95 (t, *J* = 7.7 Hz, 4H), 6.98 – 7.09 (m, 2H), 7.27 (s, 2H), 7.60 – 7.75 (m, 4H), 8.29 (d, *J* = 1.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.32, 35.20, 112.67, 117.68, 121.61, 122.60, 126.38, 126.40, 127.42, 127.43, 128.87, 132.79, 139.98, 140.35, 148.54, 150.20. These spectral data match those previously reported for this compound[11].

4.3.2 Resolution of tBuVANOL and recovery of quinine (*Scheme 2.18*)



(S)-tBu$_2$VANOL ***(S)-II-46b*** and *(R)-tBu$_2$VANOL* ***(R)-II-46b***. An oven-dried 250 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, (±)-*t*BuVANOL **4** (8.81 g, 16.0 mmol) is added followed by addition of anhydrous tetrahydrofuran (65 mL) and BH_3•Me_2S (8.16 mL, 2 M solution in toluene, 16.3 mmol, 1.02 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture is stirred and refluxed in an 80 ºC oil bath for 30 min, and the evolution of gas ceases. After cooling to rt (23 ºC), the clear solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C, anhydrous tetrahydrofuran (65 mL) is added followed by addition of quinine (5.294 g, 16.32 mmol, 1.020 equiv). The reflux condenser

is reconnected and the mixture is stirred and refluxed in an 80 ºC oil bath for overnight (12 h). A white precipitate begins to crash out after 10 min of refluxing. The flask containing reaction mixture is cooled to rt then to –20 ºC for 30 min before the solid is collected by suction filtration, washed with ice-cold anhydrous tetrahydrofuran (60 mL).

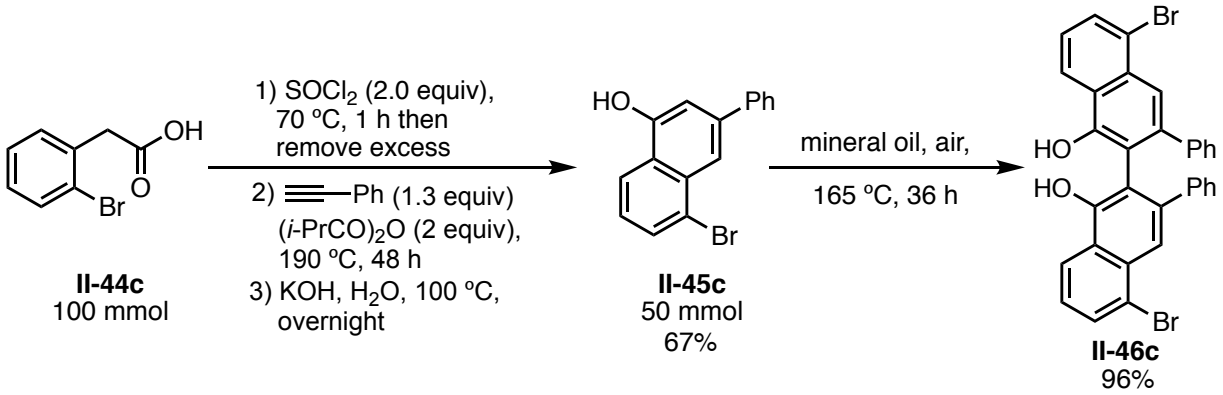
The solid is transferred to a 100 mL round-bottomed flask and CH_2Cl_2 (15 mL) is added followed by addition of aq. HCl (15 mL, 2 M) and an egg-shaped stirring bar (30 mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with CH_2Cl_2 (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of CH_2Cl_2 and hexanes (1:2) to afford (*S*)-tBu_2VANOL **(*S*)-II-46b** as a white solid (3.375 g, 6.128 mmol, 38%, >99% *ee*).

The mother liquor is transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). CH_2Cl_2 (15 mL) is added followed by addition of aq. HCl (15 mL, 2M) and an egg-shaped stirring bar (30 mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with CH_2Cl_2 (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The water layer containing chloride salt of protonated quinine is transferred to a

clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column wet loaded with hexanes. The column was eluted with a mixture of CH_2Cl_2 and hexanes (1:2) to afford crude (*R*)-*t*BuVANOL **(*R*)-II-46b** as a white solid (3.589 g, 6.517 mmol, 41%, 87% *ee*). The crude **(*R*)-II-46b** is transferred to a 500 mL round-bottomed flask and hexanes (250 mL) is added. The mixture was stirred for 60 min at rt before the precipitate (*t*BuVANOL racemate) is filtered by suction filtration. The mother liquor is transferred to a 250 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and dried under vacuum (23 °C, 0.2 mmHg) for 1 h to afford (*R*)-*t*Bu_2VANOL **(*R*)-II-46b** as a white solid (3.312 g, 6.014 mmol, 38%, >99% *ee*).

Recovery of quinine: The combined water phase after the extraction after the hydrolysis was transferred to a 500 mL Erlenmeyer flask. After cooling to 0 ºC for 10 min, NaOH solution (aq. 1 M) was added until pH > 8.0. The suspension was extract with DCM (50 mL x 3) and the combined organic layer is washed with brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) to give the crude quine (5.356 g, 101%). Purification by crystallization from toluene gave the recovered quinine (4.712 g, 14.50 mmol) in 89% yield (>98% pure based on ^{1}H NMR).

4.3.3 Synthesis of 5,5'-R_2VANOL (*Table 2.2*)



General Procedure **H** for CAEC process with $SOCl_2$ -- illustrated for synthesis of 5-bromo-3-phenyl-1-naphthol **II-45c** from 2-(2-bromophenyl)acetic acid **II-44c**:

*5-bromo-3-phenyl-1-naphthol **II-45c***: An oven-dried 500 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) and a condenser is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, 2-(2-bromophenyl)acetic acid **II-44c** (21.505 g, 100.00 mmol, 1.0000 equiv) is added followed by addition of $SOCl_2$ (15.0 mL, freshly distilled, 200 mmol, 2.00 equiv). The condenser is vented by an adaptor to a bubbler and then into a beaker filled with aq. NaOH to trap acid gases. The mixture is heated in a 70 °C oil bath until the gas evolution ceases (1 h). The excess of thionyl chloride was removed by distillation under aspirator pressure (60 °C oil bath, ~ 25 mm Hg). Anhydrous toluene (40 mL) is added, and the mixture is distilled under aspirator pressure again. The process is repeated twice to ensure complete removal of all excess thionyl chloride. The crude mixture is then vacuum-dried at rt for 1 h to remove the excess toluene. The reaction flask containing the crude acid chloride is filled with N_2, and then phenylacetylene (15.0 mL, 130 mmol, 1.30 equiv) and (*i*-PrCO)$_2$O (33.0 mL, 200 mmol, 2.00 equiv) are added. The flask is fitted with a condenser flushed with nitrogen

with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal. The reaction mixture was heated and stirred in a 190 ºC oil bath for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture is cooled to about 60 ºC (oil bath temperature), and aq KOH (33.4 g, 1.43 mol) in 120 mL of H_2O is slowly added. After stirring in a 100 ºC oil bath overnight (12 h), the orange solution is cooled to rt, ether (300 mL) is added, and the mixture stirred for 30 min before the organic layer is isolated in a 2 L separatory funnel. The water layer is extracted twice with ether (300 mL×2), and the combined organic layer is washed with brine (300 mL), dried over $MgSO_4$ and filtered. The dark-colored organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (23 °C, 0.2 mmHg) overnight to give 40 g of the dark brown crude product. Recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes 1:3 to 1:1) gave the product **II-45c** as an off-white solid in a combined yield of 67% (20.07 g, mp 133-134 ºC, 67.10 mmol).

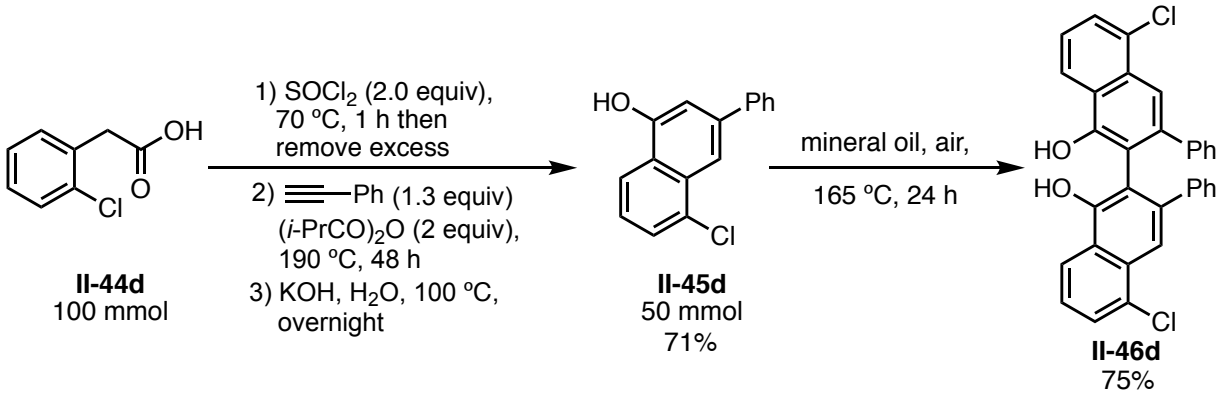
Spectral data for **II-45c**: R_f = 0.48 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (br, 1H), 7.12 (d, *J* = 1.5 Hz, 1H), 7.29 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.35 – 7.44 (m, 1H), 7.41 – 7.53 (m, 2H), 7.63 – 7.75 (m, 2H), 7.80 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.02 (dd, *J* = 1.5, 0.9 Hz, 1H), 8.18 (dt, *J* = 8.4, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 109.12, 118.11, 121.59, 122.95, 124.80, 125.41, 127.46, 127.79, 128.90, 131.07, 133.42, 140.24, 140.62, 151.85. These spectral data match those previously reported for this compound[11].

General Procedure **I** for oxidative coupling of VANOL monomer -- illustrated for synthesis of 5,5'-Br_2VANOL **II-46c** from 5-bromo-3-phenyl-1-naphthol **II-45c**:

*5,5'-Br_2VANOL **II-46c***: An oven-dried 250 mL three-necked round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, naphthol **II-45c** (29.92 g, 100.0 mmol) is added by a funnel followed by the addition of 110 mL of light mineral oil through the same funnel and then an oven-dried reflux condenser is attached. A needle is introduced into the flask via the second neck to about 5 cm above the surface of the naphthol solution and is used to provide a stream of house air which is maintained at a flow rate of 0.15-0.20 L/min. The third neck is sealed with a rubber septum. The stir bar in the oil bath was removed before the flask is introduced into the oil bath to warm it up for about 15 min until the solid was melted. Airflow is allowed to flow into the flask while the molten **II-45c** was stirred as fast as possible. The airflow is switched to N_2 after the reaction is kept at 165 ºC for 36 h. The flask is removed from the oil bath and cooled to rt before hexanes (100 mL) is added to the flask. The mixture was stirred for 30 min, and then it was cooled to –20 ºC overnight (12 h) before the solid is collected by suction filtration. The crude product is dried on high vacuum and crystallized from CH_2Cl_2. The dark-colored solution is cooled to room temperature and then to –20 ºC overnight (12 h). The brown crystals are collected via suction filtration, washed with hexanes, and dried under vacuum to give **II-46c** (27.49 g, mp > 260 ºC, 17.40 mmol, 92%).

Spectral data for **II-46c**: R_f = 0.40 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (s, 2H), 6.61 – 6.82 (m, 4H), 6.96 – 7.22 (m, 6H), 7.41 (dd, *J* = 8.4, 7.4 Hz, 2H),

7.73 (d, J = 0.8 Hz, 2H), 7.89 (dd, J = 7.5, 1.1 Hz, 2H), 8.36 (dt, J = 8.3, 1.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.29, 121.35, 122.67, 122.73, 124.13, 126.03, 127.07, 127.67, 128.87, 131.78, 133.17, 139.70, 141.90, 150.46. These spectral data match those previously reported for this compound[11].



II-44d
100 mmol

II-45d
50 mmol
71%

II-46d
75%

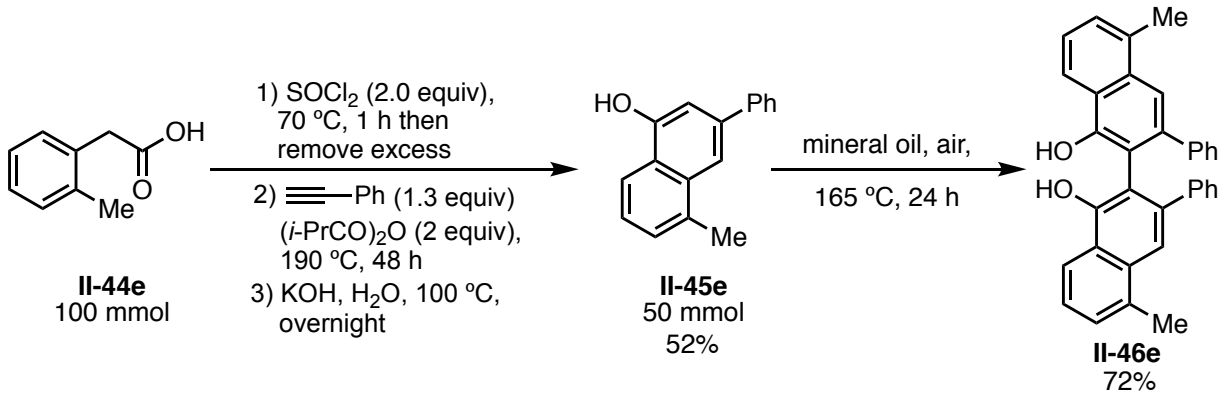
*5-chloro-3-phenyl-1-naphthol **II-45d***: 1-naphthol **II-45d** was prepared from 2-(2-chlorophenyl)acetic acid **II-44d** (17.06 g, 100.0 mmol) by the General Procedure **H**. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes 1:3 to 1:1) to give **II-45d** as a white crystal in 71% combined isolated yield (18.01 g, mp 127-128 ºC, 70.70 mmol).

Spectral data for **II-45d**: R_f = 0.28 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (br, 1H), 7.11 (d, J = 1.6 Hz, 1H), 7.29 – 7.44 (m, 2H), 7.42 – 7.56 (m, 2H), 7.60 (dd, J = 7.4, 1.1 Hz, 1H), 7.63 – 7.74 (m, 2H), 8.06 (dd, J = 1.5, 1.0 Hz, 1H), 8.13 (dt, J = 8.4, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 109.18, 115.34, 120.85, 124.77, 124.96, 127.29, 127.45, 127.78, 128.90, 132.08, 132.28, 140.04, 140.65, 151.88. HRMS (ESI^-) *m/z* 253.0430 [calcd. for $C_{16}H_{10}OCl$ (M–H): 253.0420].

*5,5'-Cl_2VANOL **II-46d***: VANOL derivative **II-46d** was prepared from 5-chloro-3-phenylnaphthalen-1-ol **II-45d** (12.74 g, 50.0 mmol) by the General Procedure **I** with

heating at 165 ºC for 24 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-46d** as an off-white solid in 75% combined isolated yield (9.500 g, mp 253-255 ºC 18.70 mmol).

Spectral data for **II-46d**: R_f = 0.40 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 2H), 6.63 – 6.74 (m, 4H), 6.96 – 7.07 (m, 4H), 7.13 (td, *J* = 7.3, 1.3 Hz, 2H), 7.47 (dd, *J* = 8.4, 7.5 Hz, 2H), 7.68 (dd, *J* = 7.5, 1.1 Hz, 2H), 7.76 (d, *J* = 1.0 Hz, 2H), 8.31 (dt, *J* = 8.4, 1.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.40, 118.63, 121.99, 124.13, 125.57, 127.04, 127.64, 127.97, 128.89, 131.89, 132.00, 139.77, 141.73, 150.53. HRMS (ESI^-) *m/z* 505.0805 [calcd. for $C_{32}H_{19}O_2Cl_2$ (M–H): 505.0762].



II-44e
100 mmol

II-45e
50 mmol
52%

II-46e
72%

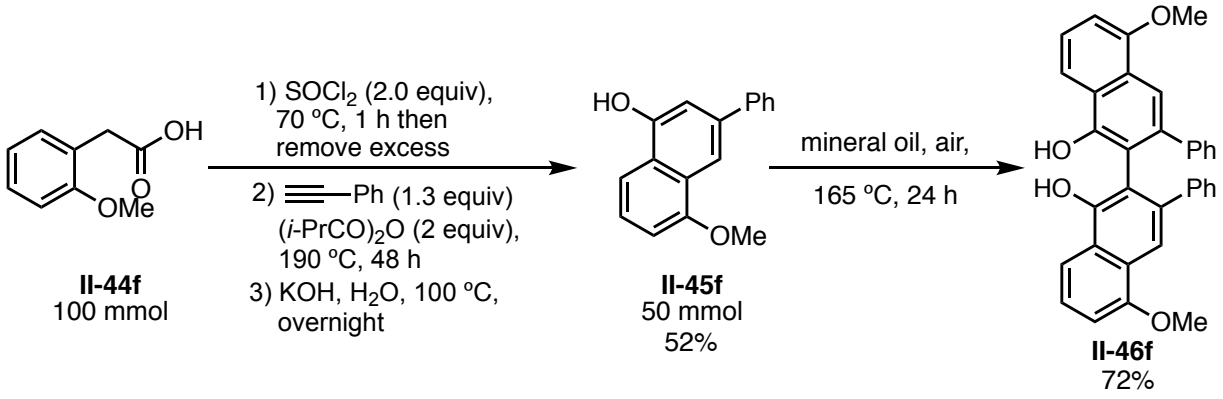
*5-methyl-3-phenyl-1-naphthol **II-45e***: 1-naphthol **II-45e** was prepared from 2-(2-methylphenyl)acetic acid **II-44e** (15.02 g, 100.0 mmol) by the General Procedure **H**.The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes 1:3 to 1:1) to give **II-45e** as a white crystal in 52% combined isolated yield (12.166 g, 51.90 mmol).

Spectral data for **II-46e**: R_f = 0.48 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71 (d, *J* = 0.9 Hz, 3H), 7.08 (d, *J* = 1.5 Hz, 1H), 7.33 – 7.40 (m, 2H), 7.44 – 7.51 (m,

3H), 7.59 – 7.71 (m, 2H), 7.71 – 7.89 (m, 1H), 8.01 – 8.13 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.94, 108.29, 115.30, 119.60, 123.50, 124.98, 127.41, 127.45, 127.68, 128.82, 134.12, 134.47, 138.70, 141.38, 152.08. HRMS (ESI^-) *m/z* 232.0890 [calcd. for $C_{17}H_{13}O$ (M–H): 232.0888].

*5,5'-Me$_2$VANOL **II-46e***: VANOL derivative **II-46e** was prepared from 5-methyl-3-phenyl-1-naphthol **II-45e** (11.72, 50.0 mmol) by the General Procedure **I** with heating at 165 ºC for 24 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes 1:3 to 1:1) to give **II-46e** as an off-white solid in 72% combined isolated yield (8.452 g, mp 248-251 ºC, 18.10 mmol).

Spectral data for **II-46e**: R_f = 0.53 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (s, 6H), 5.85 (dd, *J* = 2.6, 1.3 Hz, 2H), 6.63 – 6.82 (m, 4H), 6.97 – 7.18 (m, 6H), 7.40 – 7.55 (m, 7H), 8.27 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.67, 112.52, 118.58, 121.00, 122.96, 125.39, 126.59, 127.52, 128.25, 129.00, 133.83, 134.29, 140.41, 140.67, 150.72. HRMS (ESI^-) *m/z* 465.1839 [calcd. for $C_{34}H_{25}O_2$ (M–H): 465.1855].



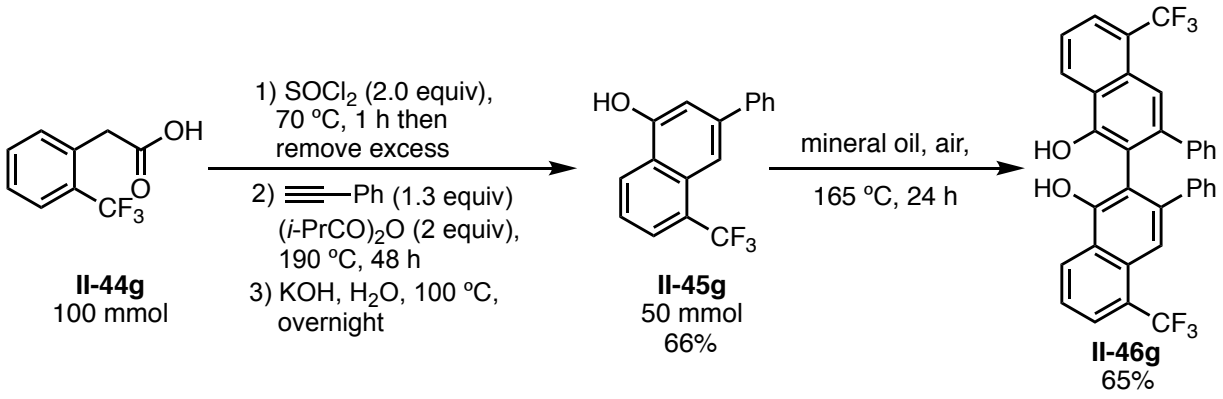
*5-methoxy-3-phenyl-1-naphthol **II-45f***: 1-naphthol **II-45f** was prepared from 2-(2-methylphenyl)acetic acid **II-44f** (16.618, 100.00 mmol) by the General Procedure **H**. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column

chromatography (silica gel, DCM/hexanes 1:3 to 1:1) to give **II-45f** as a white crystal in 52% combined isolated yield (3.884 g, mp 142-143 ºC, 51.60 mmol).

Spectral data for **II-46f**: R_f = 0.42 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (s, 3H), 6.86 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.12 (d, *J* = 1.6 Hz, 1H), 7.27 – 7.52 (m, 4H), 7.70 (ddt, *J* = 10.6, 7.8, 1.0 Hz, 3H), 8.07 (dd, *J* = 1.7, 0.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.58, 104.81, 109.02, 112.97, 113.47, 124.44, 125.36, 127.07, 127.29, 127.33, 128.74, 138.12, 141.13, 151.50, 155.64. HRMS (ESI^-) *m/z* 249.0937 [calcd. for $C_{17}H_{13}O_2$ (M–H): 249.0916].

*5,5'-OMe$_2$VANOL **II-46f***: VANOL derivative **II-46f** was prepared from 5-methoxy-3-phenyl-1-naphthol **II-45f** (12.520, 50.000 mmol) by the General Procedure **I** with heating at 165 ºC for 24 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-46f** as an off-white solid in 72% combined isolated yield (8.996 g, mp > 260 ºC 18.00 mmol).

Spectral data for **II-46f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 6H), 5.80 (s, 2H), 6.64 – 6.74 (m, 4H), 6.92 (dd, *J* = 7.8, 0.9 Hz, 2H), 6.94 – 7.01 (m, 4H), 7.03 – 7.11 (m, 2H), 7.47 (dd, *J* = 8.5, 7.7 Hz, 2H), 7.76 (d, *J* = 0.9 Hz, 2H), 7.93 (dt, *J* = 8.4, ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.70, 55.51, 76.75, 77.00, 77.25, 105.33, 113.39, 114.83, 116.20, 123.82, 125.72, 126.43, 126.70, 127.36, 128.93, 139.91, 140.45, 150.04, 155.31. HRMS (ESI^-) *m/z* 465.1649 [calcd. for $C_{34}H_{25}O_2$ (M–H): 465.1655].



*5-trifluoromethyl-3-phenyl-1-naphthol **II-45g***: 1-naphthol **II-45g** was prepared from 2-(2-methylphenyl)acetic acid **II-44g** (20.42 mL, 100.0 mmol) by the General Procedure **H.** The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes 1:3 to 1:1) to give **II-45g** as a white crystal in 66% combined isolated yield (19.21 g, mp 122-123 ºC 66.60 mmol).

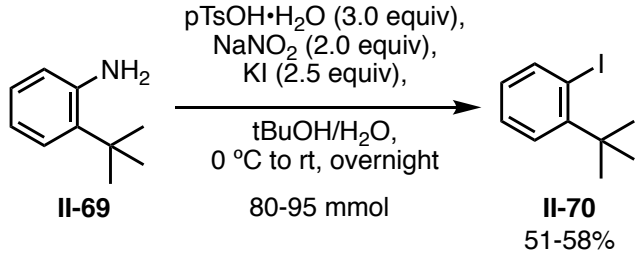
Spectral data for **II-46g**: R_f = 0.48 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 1H), 7.14 (d, *J* = 1.4 Hz, 1H), 7.32 – 7.55 (m, 4H), 7.61 – 7.73 (m, 2H), 7.78 – 8.03 (m, 2H), 8.43 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 109.08, 115.18, 115.20, 123.46, 124.19, 125.80 (q, *J* = 5 Hz), 125.86, 126.46, 127.52, 127.93, 128.96, 130.50, 140.63, 140.80, 152.04. HRMS (ESI^-) *m/z* 287.0682 [calcd. for $C_{17}H_{10}F_3O$ (M–H): 287.0684].

*5,5'-$(CF_3)_2$VANOL **II-46g***: VANOL derivative **II-46g** was prepared from 5-methyl-3-phenyl-1-naphthol **II-45g** (14.41, 50.0 mmol) by the General Procedure I with heating at 165 ºC for 24 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes 1:3 to 1:1) to give **II-46d** as an off-white solid in 65% combined isolated yield (9.382 g, mp > 260 ºC, 16.30 mmol).

Spectral data for **II-46g**: R_f = 0.32 (DCM/hexanes 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 18.0 Hz, 2H), 6.58 – 6.71 (m, 4H), 7.00 (td, *J* = 7.8, 2.8 Hz, 4H), 7.06 – 7.18 (m, 2H), 7.54 – 7.68 (m, 4H), 7.96 (d, *J* = 7.2 Hz, 2H), 8.58 (d, *J* = 8.4 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 113.18, δ 118.46, 123.55, 123.57, 124.13, 125.94 (q, J = 120 Hz), 126.47 (q, *J* = 5.8 Hz), 127.23, 127.45, 127.73, 128.80, 130.31, 139.54, 142.35, 150.71. ^{19}F NMR (470 MHz, $CDCl_3$) δ -59.76 (d, *J* = 3.9 Hz). HRMS (ESI^-) *m/z* 573.1265 [calcd. for $C_{34}H_{19}F_6O_2$ (M–H): 573.1289].

4.3.4 Synthesis of 5,5'-*t*Bu_2VANOL (*Scheme 2.23*)

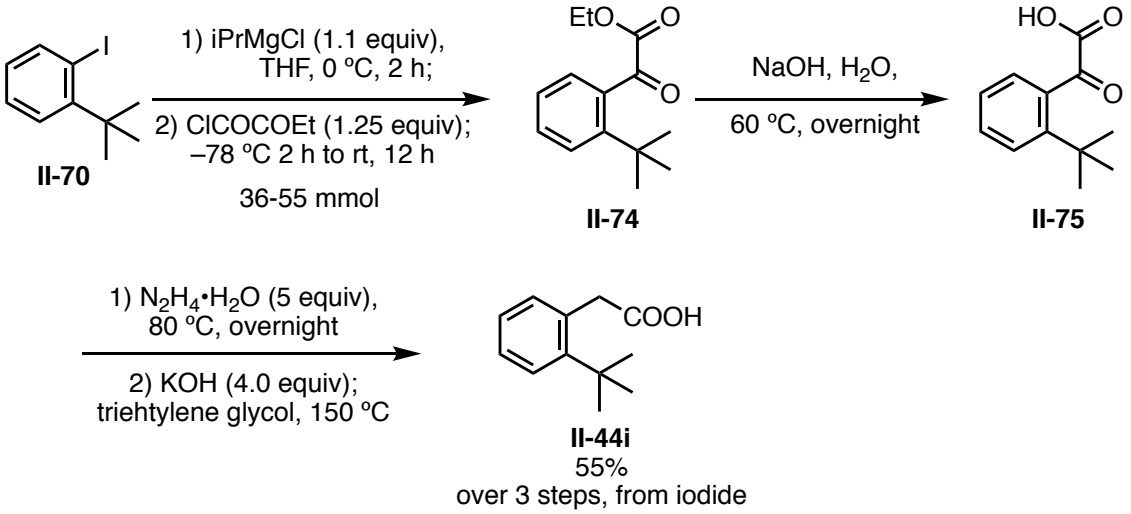
General Procedure **J** for preparation of aryl iodide by the Sandmeyer reaction -- illustrated for synthesis of 1-(tert-butyl)-2-iodobenzene **II-70**



II-69 80-95 mmol **II-70** 51-58%

*1-(tert-butyl)-2-iodobenzene **II-70***: To a solution of *p*-TsOH·H_2O (11.40 g, 60.00 mmol) in *t*BuOH (80 mL) was added the 2-(*tert*-butyl) aniline (3.19 mL, 20.0 mmol). The resulting suspension of amine salt was cooled to 0–10 °C and to this was added, gradually, a solution of $NaNO_2$ (2.76 g, 40.0 mmol) and KI (8.30 g, 50.0 mmol) in H_2O (12 mL). The reaction mixture was stirred for 10 min then allowed to come to 20 °C and stirred for 2 h. To the reaction mixture was then added H_2O (35 mL), $NaHCO_3$ (sat., 70 mL) and $Na_2S_2O_3$ (sat., 40 mL). The aromatic iodide was extracted with EtOAc (3 × 100 mL) and purified by flash chromatography (hexanes) to afford **II-70** as a as a colorless liquid (4.213 g, 16.20 mmol, 81%).

Spectral data for **II-70**: R_f = 0.72 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 6.81 (ddd, *J* = 7.8, 7.2, 1.7 Hz, 1H), 7.22 – 7.28 (m, 1H), 7.42 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.5 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 29.84, 36.71, 95.12, 127.50, 127.53, 127.89, 143.56, 150.14. These spectral data match those previously reported for this compound[12].



ethyl 2-(2-(tert-butyl)phenyl)-2-oxoacetate ***II-74***: An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, 1-(*tert*-butyl)-2-iodobenzene **II-70** (9.32 g, 35.8 mmol) and THF (30 ml) was added and the solution was cooled to 0 °C in an ice bath for 10 min. Isopropylmagnesium chloride (2 M in THF, 20.0 mL, 40 mmol) was added dropwise to the round-bottomed flask at 0 °C for 10 min and stirred for 2 h. The resulting reaction solution was added dropwise to another 250 mL round-bottomed flask containing ethyl chlorooxoacetate (5.0 mL, 50 mmol) in THF (30 mL) at –78 °C and warmed to room temperature for 12 h. The reaction was quenched with saturated NH_4Cl solution (75 mL), extracted with EtOAc (100 mL x 3), washed with

brine, dried (Na_2SO_4) and evaporated under reduced pressure to give **II-74** as a colourless liquid, which appeared pure by ^1H NMR analysis and was used without purification.

Spectral data for **II-74**: R_f = 0.32 (EtOAc/hexanes 1:4); ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.28 – 1.31 (m, 9H), 4.02 (q, *J* = 7.2 Hz, 2H), 7.11 – 7.20 (m, 2H), 7.34 (ddd, *J* = 8.2, 5.2, 3.6 Hz, 1H), 7.46 (dt, *J* = 8.1, 0.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.84, 21.31, 31.76, 62.50, 124.96, 127.35, 127.76, 130.70, 135.59, 149.33, 162.27, 191.49. HRMS (ESI-TOF) *m/z* 234.1249 [calcd. for $C_{14}H_{18}O_3$ (M^+): 234.1256];

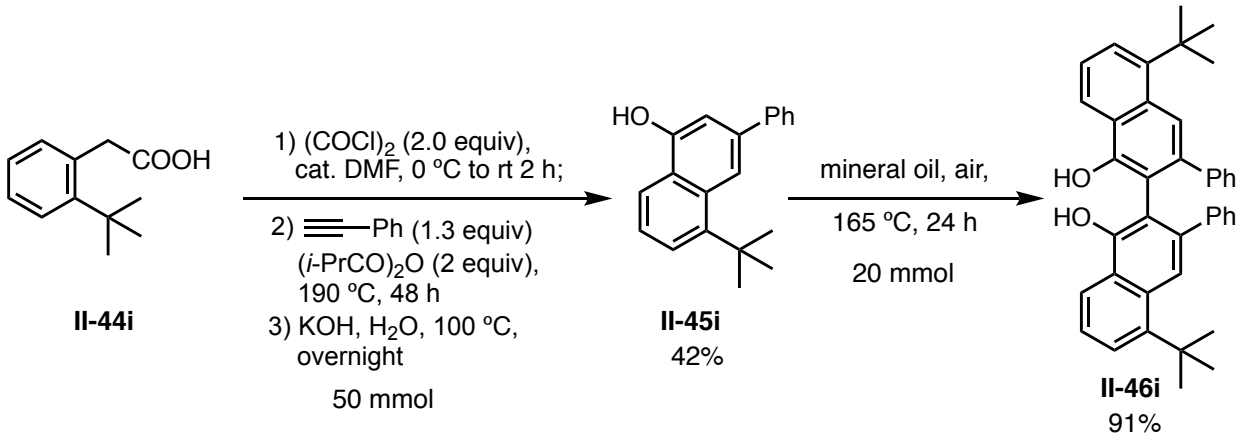
2-(2-(tert-butyl)phenyl)-2-oxoacetic acid ***II-75***: Crude ethyl 2-(2-(*tert*-butyl)phenyl)-2-oxoacetate **II-74** was transferred to an oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar. To the round-bottomed flask was added 2.5 M NaOH (aq) (30 mL). The resulting suspension was heated and maintained at 60 ºC with stirring for 12 h. The reaction mixture was quenched with 4 M HCl (aq) (~30 mL) and the resulting aqueous mixture was extracted with DCM (3 x 15 mL). The combined organic extract was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the **II-74** as a yellow liquid. This product appeared pure by ^1H NMR analysis and was used without purification.

Spectral data for **II-75**: R_f = 0.30 (EtOAc/hexanes 1:2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 – 1.41 (m, 9H), 7.21 – 7.32 (m, 2H), 7.41 – 7.49 (m, 1H), 7.55 (dt, *J* = 8.2, 0.9 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 32.06, 36.11, 125.06, 127.65, 127.93, 131.30, 131.32,

149.92, 191.91, 191.96. HRMS (ESI^-) *m/z* 205.0866 [calcd. for $C_{12}H_{13}O_3$ (M–H): 205.0865].

2-(2-(tert-butyl)phenyl) acetic acid ***II-44i***: Hydrazine hydrate (7.00 mL, 220 mmol) was added to an oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar. The hydrazine hydrate was cooled to 0 ºC and the crude 2-(2-(*tert*-butyl)phenyl)-2-oxoacetic acid **II-75** (8.673 g, 42.00 mmol) was added in one portion. The resulting suspension was then heated and maintained at 80 ºC with stirring for 12 h. The round-bottomed flask was removed from oil bath and cooled briefly. To the reaction mixture was added KOH (9.45 g, 168 mmol) in one portion and triethylene glycol (34 mL). The resulting reaction mixure was heated in oil bath and maintained at 150 ºC for 12 h after which time the round bottom flask was cooled to rt and diluted with water (20 mL). The aqueous mixture was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane 1:4 to 1:2) to provide the desired product ***II-44i*** (5.49 g, 68%) as a white solid.

Spectral data for **II-44i**: R_f = 0.33 (EtOAc/hexanes 1:2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 9H), 3.96 (s, 2H), 7.10 – 7.29 (m, 3H), 7.35 – 7.48 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.56, 35.47, 40.07, 126.10, 126.43, 127.41, 131.49, 133.07, 148.06, 178.70. HRMS (ESI^-) *m/z* 191.1075 [calcd. for $C_{12}H_{15}O_2$ (M–H): 191.1072].



II-44i

II-45i
42%

II-46i
91%

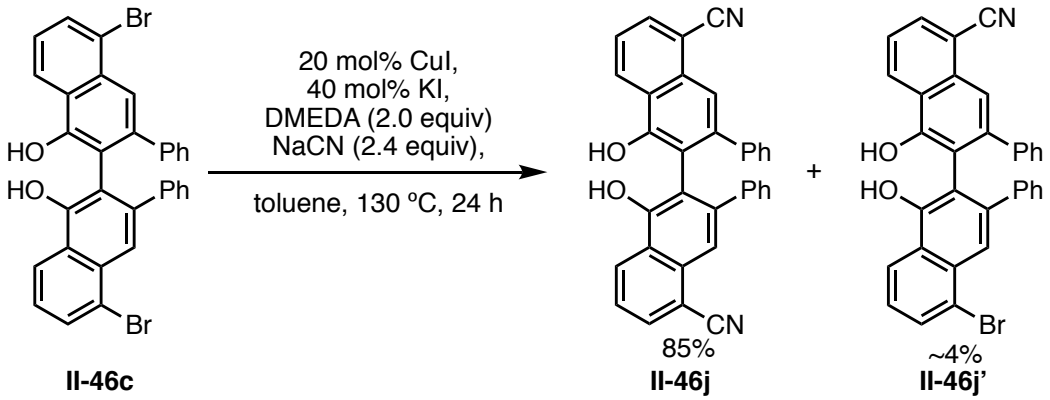
*5-tert-butyl-3-phenyl-1-naphthol **II-45i***: 1-naphthol **II-45i** was prepared from 2-(2-(*tert*-butyl)phenyl)acetic acid **II-44i** (9.610 g, 50.00 mmol, 1.000 equiv) by the General Procedure **H**. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-45i** as a white crystal in 42% combined isolated yield (5.845 g, mp 104-106 ºC, 21.10 mmol).

Spectral data for **II-45i**: R_f = 0.33 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (s, 9H), 5.57 (s, 1H), 7.04 (d, *J* = 1.4 Hz, 1H), 7.39 – 7.56 (m, 4H), 7.61 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.65 – 7.73 (m, 2H), 8.21 (dt, *J* = 8.3, 1.0 Hz, 1H), 8.31 (t, *J* = 1.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.07, 36.26, 107.48, 118.62, 120.39, 124.40, 124.88, 125.14, 127.39, 127.45, 128.96, 133.05, 137.30, 141.77, 146.27, 152.48. HRMS (ESI^-) *m/z* 275.1437 [calcd. for $C_{20}H_{19}O$ (M–H): 275.1436].

*5,5'-tBu$_2$VANOL **II-46i***: VANOL derivative **II-46i** was prepared from 5-*tert*-butyl-3-phenyl-1-naphthol **II-45i** (5.528 g, 20.00 mmol) by the general procedure with heating at 165 ºC for 24 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-46i** as an off-white solid in 91% combined isolated yield (5.031 g, mp 287-288 ºC, 9.140 mmol).

Spectral data for **II-46i**: R_f = 0.41 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 18H), 5.97 (s, 2H), 6.73 (d, *J* = 7.6 Hz, 4H), 7.04 (t, *J* = 7.8 Hz, 4H), 7.14 (t, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.9 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 2H), 8.02 (s, 2H), 8.41 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.99, 36.19, 111.76, 121.62, 121.72, 124.59, 124.88, 125.15, 126.50, 127.59, 128.99, 132.83, 139.03, 141.05, 146.07, 151.18. HRMS (ESI^-) *m/z* 549.2844 [calcd. for $C_{40}H_{37}O_2$ (M–H): 549.2794].

4.3.5 Synthesis of 5,5'-CN_2VANOL (*Scheme 2.24*)



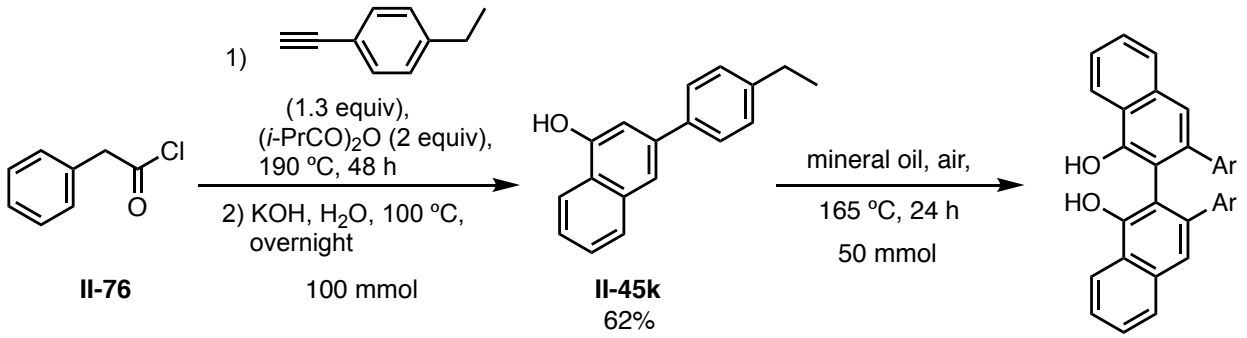
II-46c **II-46j** **II-46j'**

*5,5'-CN_2VANOL **II-46j***: VANOL derivative **II-46j** was synthesized from a modified procedure[13] by Buchwald et al. To a 50 mL Schlenk flask was charged with NaCN (118 mg, 2.40 mmol, 2.40 equiv), CuI (38.1 mg, purified, 0.200 mmol), 5,5'-Br_2VANOL **II-46c** (596 mg, 1.00 mmol), and KI (66.4 mg, 0.400 mmol). The flask was then briefly evacuated and backfilled with nitrogen three times. Anhydrous toluene (2 mL) and N,N -dimethylethylenediamine (216 μL, 2.00 mmol, 2.00 equiv) were added under argon. The Schlenk flask was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (3 mL), and extracted with EtOAc (4 × 2 mL). The water layer was discarded, and the suspension of **II-46j** in EtOAc was purified by filtration then wash with

cold DCM to afford **II-46j** as a yellow solid (416 mg, mp > 320 ºC (decomposed), 0.851 mmol) in 85% yield.

Spectral data for **II-46j**: R_f = 0.30 (DCM/hexanes 1:1); HRMS (ESI^-) *m/z* 487.1480 [calcd. for $C_{34}H_{19}N_2O_2$ (M–H): 487.1447].

4.3.6 Synthesis of 3,3'-R_2-phenyl VANOL (*Table 2.3*)



II-76 100 mmol **II-45k** 62%

II-46k, Ar =4-EtC_6H_4 63%

General Procedure **K** for CAEC process with 2-phenylacetyl chloride **II-76** -- illustrated for synthesis of 3-(4-ethylphenyl)-1-naphthol **II-45k** with 1-ethyl-4-ethynylbenzene:

*3-(4-ethylphenyl)-1-naphthol **II-45k***: An oven-dried 500 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) and a condenser is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, 2-phenylacetyl chloride **II-76** (13.22 mL, 100.0 mmol, 1.000 equiv) is added followed by 1-ethyl-4-ethynylbenzene (18.2 mL, 130 mmol, 1.30 equiv) and (*i*-PrCO)$_2$O (33.0 mL, 200 mmol, 2.00 equiv). The flask is fitted with a condenser flushed with nitrogen with a Teflon sleeve in the joint and Teflon tape wrapped around the joint to secure a tight seal. The reaction mixture was heated and stirred in a 190 ºC oil bath for 48 h with a gentle nitrogen flow

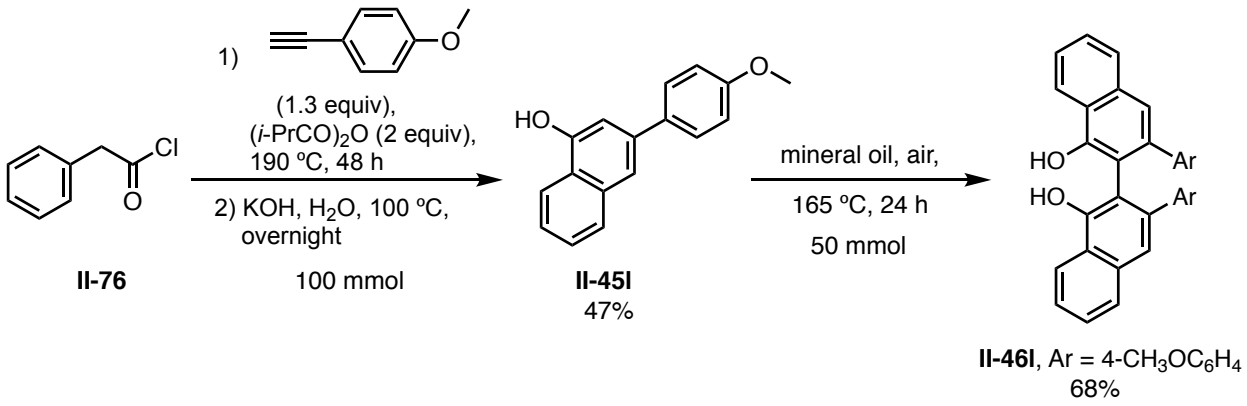
across the top of the condenser. The brown reaction mixture is cooled to about 60 ºC (oil bath temperature), and aq KOH (33.4 g, 1.43 mol) in 120 mL of H_2O is slowly added. After stirring in a 100 ºC oil bath overnight (12 h), the orange solution is cooled to rt, ether (300 mL) is added, and the mixture stirred for 30 min before the organic layer is isolated in a 2 L separatory funnel. The water layer is extracted twice with ether (300 mL×2), and the combined organic layer is washed with brine (300 mL), dried over $MgSO_4$ and filtered. The dark-colored organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (23 °C, 0.2 mmHg) overnight to give 40 g of the dark brown crude product. Recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) gave the product **II-45k** as an off-white solid (15.30 g, mp 117-120 ºC, 61.60 mmol) in a combined yield of 62%.

Spectral data for **II-45k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (td, *J* = 7.6, 1.2 Hz, 3H), 2.70 (q, *J* = 7.6 Hz, 2H), 5.26 (s, 1H), 7.07 (d, *J* = 1.7 Hz, 1H), 7.26 – 7.35 (m, 2H), 7.48 (dddd, *J* = 18.0, 8.1, 6.8, 1.4 Hz, 2H), 7.56 – 7.68 (m, 3H), 7.79 – 7.89 (m, 1H), 8.15 (ddd, *J* = 8.0, 1.6, 0.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.63, 28.56, 108.38, 118.51, 121.43, 123.40, 125.19, 126.86, 127.22, 127.99, 128.39, 134.99, 138.23, 138.86, 143.69, 151.62. HRMS (ESI^-) *m/z* 247.1138 [calcd. for $C_{18}H_{15}O$ (M–H): 247.1123].

3,3'-pEtPh$_2$VANOL ***II-46k***: VANOL derivative **II-46k** was prepared from 3-(4-ethylphenyl)-1-naphthol **II-45k** (12.42 g, 50.00 mmol, 1.000 equiv) by the General Procedure **I** with heating at 165 ºC for 36 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel,

DCM/hexanes: 1:3 to 1:1) to give **II-46k** as an off-white solid in 63% combined isolated yield (7.823 g, mp 178-180 ºC, 15.80 mmol).

Spectral data for **II-46k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (td, *J* = 7.6, 0.9 Hz, 6H), 2.51 (q, *J* = 7.6 Hz, 4H), 5.79 (d, *J* = 1.1 Hz, 2H), 6.51 – 6.63 (m, 4H), 6.79 (d, *J* = 8.0 Hz, 4H), 7.34 (s, 2H), 7.47 – 7.61 (m, 4H), 7.73 – 7.84 (m, 2H), 8.34 (ddd, *J* = 7.4, 2.2, 0.9 Hz, 2H). ^{13}C NMR (126 MHz $CDCl_3$) δ 15.64, 28.44, 112.86, 121.92, 122.84, 122.85, 125.49, 127.00, 127.42, 127.65, 128.77, 134.62, 137.52, 140.71, 142.64, 150.25. HRMS (ESI^-) *m/z* 493.2176 [calcd. for $C_{36}H_{29}O_2$ (M–H): 493.2168].



II-76 100 mmol **II-45l** 47%

II-46l, Ar = 4-$CH_3OC_6H_4$ 68%

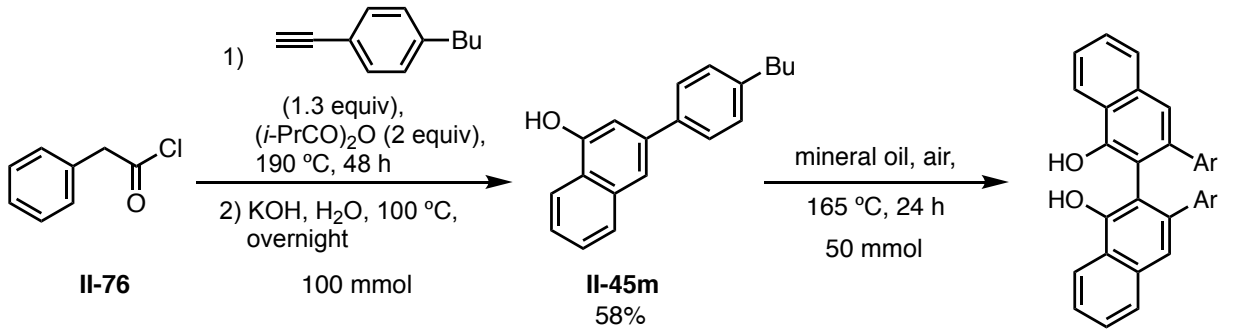
*3-(4-methoxyphenyl)-1-naphthol **II-45l***: 1-naphthol **II-45l** was prepared from 4-ethynylanisole (17.2 mL, 130 mmol, 1.30 equiv) by the General Procedure **K**. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-45l** as an off-white crystal in 47% combined isolated yield (11.85 g, mp 155-156 ºC, 47.40 mmol).

Spectral data for **II-45l**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.29 (s, 1H), 6.96 – 7.02 (m, 2H), 7.03 – 7.06 (m, 1H), 7.47 (dddd, *J* = 20.2, 8.1, 6.8, 1.4 Hz, 2H), 7.57 – 7.64 (m, 3H), 7.80 – 7.86 (m, 1H), 8.14 (ddd, *J* = 8.2, 1.5, 0.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.39, 108.24, 114.27, 118.05, 121.40, 123.20, 125.05, 126.86, 127.88,

128.31, 133.39, 135.02, 138.49, 151.64, 159.27. HRMS (ESI$^-$) *m/z* 249.0937 [calcd. for $C_{17}H_{13}O$ (M–H): 249.0916].

*3,3'-pOMePh$_2$VANOL **II-46l***: VANOL derivative **II-46l** was prepared from 5-methyl-3-phenylnaphthalen-1-ol **II-45l** (11.264 g, 45.00 mmol) by the General Procedure **I** with heating at 165 ºC for 36 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-46l** as an off-white solid in 68% (76% brsm) combined isolated yield (7.600 g, mp 243-244 ºC, 15.20 mmol).

Spectral data for **II-46l**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 3H), 5.79 (s,1H), 6.44 – 6.73 (m, 4H), 7.30 (s, 1H), 7.43 – 7.60 (m, 2H), 7.70 – 7.85 (m, 1H), 8.32 (dd, *J* = 7.4, 1.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.16, 112.89, 112.93, 121.81, 122.74, 122.80, 125.46, 127.45, 127.60, 129.96, 132.82, 134.62, 140.30, 150.27, 158.43. HRMS (ESI$^-$) *m/z* 497.1792 [calcd. for $C_{34}H_{25}O_4$ (M–H): 497.1753].



II-76 100 mmol **II-45m** 58%

II-46m, Ar = 4-BuC_6H_4 49%

*3-(4-butylphenyl)-1-naphthol **II-45m***: 1-naphthol **II-45m** was prepared from 1-butyl-4-ethynylbenzene (22.7 mL, 130 mmol, 1.30 equiv) by the General Procedure **K**. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column

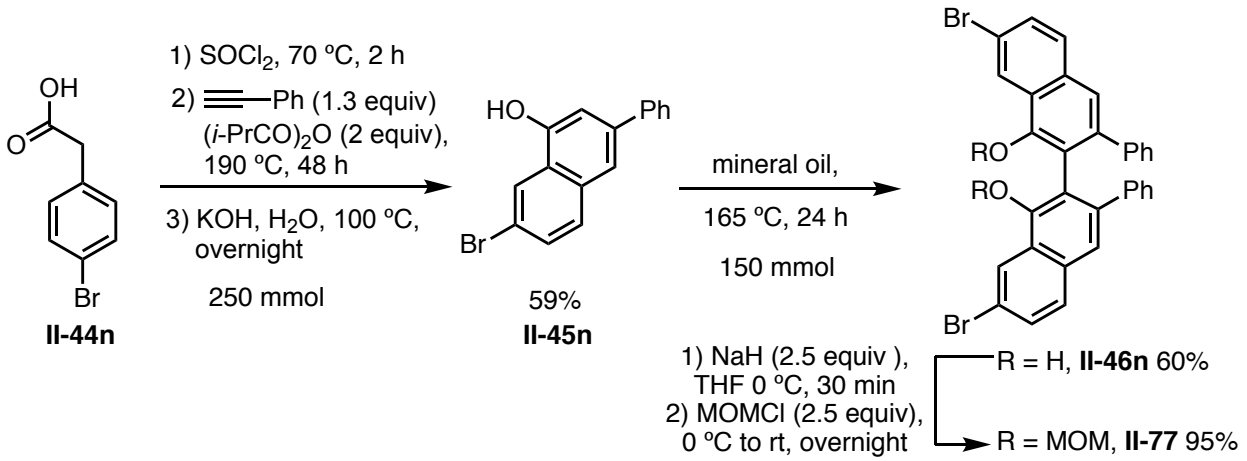
chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-45m** as a yellow crystal in 58% combined isolated yield (15.96 g, mp 110-111 ºC, 57.70 mmol).

Spectral data for **II-45m**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.27 – 1.52 (m, 2H), 1.54 – 1.78 (m, 2H), 2.53 – 2.77 (m, 2H), 5.24 (d, *J* = 1.4 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.22 – 7.30 (m, 2H), 7.48 (dddd, *J* = 18.1, 8.2, 6.8, 1.5 Hz, 2H), 7.55 – 7.61 (m, 2H), 7.63 (t, *J* = 1.1 Hz, 1H), 7.72 – 7.95 (m, 1H), 7.95 – 8.22 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.01, 22.43, 33.67, 35.33, 108.37, 118.49, 121.42, 123.38, 125.18, 126.85, 127.12, 127.98, 128.93, 134.99, 138.16, 138.87, 142.37, 151.61. HRMS (ESI^-) *m/z* 275.1458 [calcd. for $C_{20}H_{19}O$ (M–H): 275.1436].

*3,3'-pBuPh$_2$VANOL **II-46m***: VANOL derivative **II-46m** was prepared from 1-butyl-4-ethynylbenzene (13.82 g, 50.00 mmol, 1.300 equiv) by the General Procedure **I** with heating at 165 ºC for 36 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-46i** as a yellow solid in 49% combined isolated yield (6.798 g, mp 161-163 ºC, 12.30 mmol).

Spectral data for **II-46m**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (tt, *J* = 7.4, 1.5 Hz, 6H), 1.28 (dddd, *J* = 17.2, 7.3, 5.2, 3.7 Hz, 4H), 1.35 – 1.64 (m, 4H), 2.22 – 2.62 (m, 4H), 5.63 – 5.89 (m, 2H), 6.43 – 6.68 (m, 4H), 6.68 – 6.92 (m, 4H), 7.24 – 7.45 (m, 2H), 7.54 (qd, *J* = 7.4, 5.2 Hz, 4H), 7.78 (dd, *J* = 7.2, 2.1 Hz, 2H), 8.33 (dd, *J* = 7.8, 2.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.96, 22.25, 33.57, 35.15, 112.86, 121.85, 122.82, 122.83, 125.46, 127.39, 127.53, 127.63, 128.68, 134.62, 137.44, 140.69, 141.24, 150.22. HRMS (ESI^-) *m/z* 549.2801 [calcd. for $C_{40}H_{37}O_2$ (M–H): 549.2794].

4.3.7 Synthesis of 7,7'-R_2VANOL (*Scheme 2.25*)



7-bromo-3-phenyl-1-naphthol ***II-45n***: 1-naphthol **II-45n** was prepared from 2-(4-bromophenyl)acetic acid **II-44n** (53.76 g, 250.0 mmol) by the General Procedure **H**. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-45n** as an off-white solid in 59% combined isolated yield (44.35 g, mp 94-97 ºC, 148.0 mmol).

Spectral data for **II-45n**: R_f = 0.35 (DCM). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.24 (s, 1H), 7.08 (d, 1H, *J* = 1.7 Hz), 7.34-7.39 (m, 1H), 7.44-7.48 (m, 2H), 7.57 (dd, 1H, *J* = 8.5, 1.5 Hz), 7.59 (s, 1H), 7.62-7.65 (m, 2H), 7.71 (d, 1H, J = 9.0 Hz), 8.36 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125MHz) δ 109.28, 118.63, 119.32, 124.28, 124.66, 127.24, 127.71, 128.93, 129.61, 130.32, 133.37, 139.43, 140.51, 150.86. These spectral data match those previously reported for this compound[11].

5,5'-tBu$_2$VANOL ***II-46n***: VANOL derivative **II-46n** was prepared from 7-bromo-3-phenylnaphthalen-1-ol **II-45n** (44.88 g, 150.0 mmol) by the general procedure with heating at 165 ºC for 24 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to

give **II-46n** as a light brown solid in 60% combined isolated yield (26.88 g, mp 136-138 ºC, 45.10 mmol).

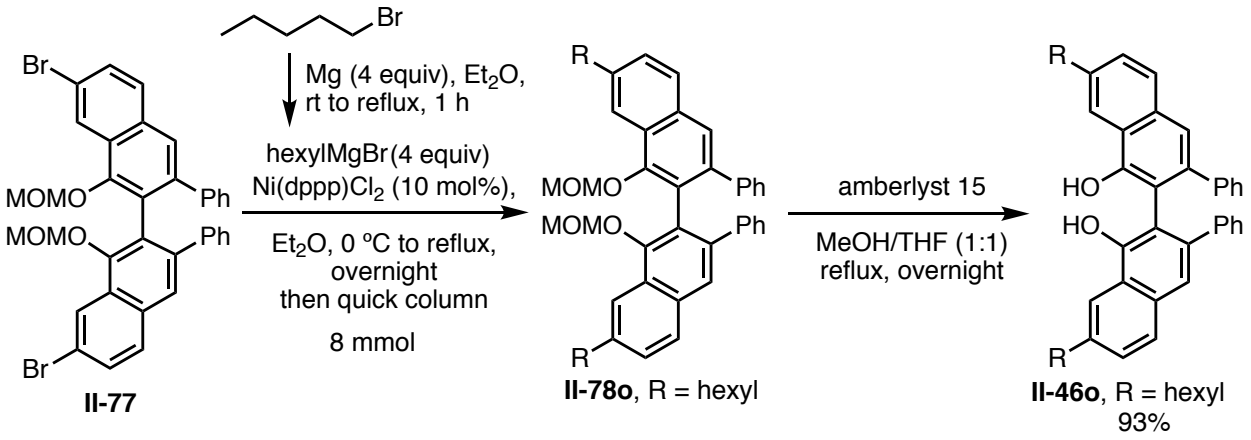
Spectral data for **II-46n**: Rf = 0.51 (DCM). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.76 (s, 2H), 6.59-6.61 (m, 4H), 6.95-6.98 (m, 4H), 7.05-7.10 (m, 2H), 7.28 (s, 2H), 7.62-7.63 (m, 4H), 8.49-8.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 113.57, 119.92, 121.94, 123.97, 125.30, 126.96, 127.57, 128.77, 129.37, 131.09, 133.13, 139.65, 141.08, 149.49; These spectral data match those previously reported for this compound[11].

7,7'-BrVANOL-MOM$_2$ ***II-77***: To a flame-dried 250 mL round bottom flask were added NaH (2.00 g, 60% in mineral oil, 50.0 mmol, 2.50 equiv) and THF (80 mL). The resulting mixture was cooled to 0 °C and a solution of 7,7'-Br_2VANOL **II-46n** (11.93 g, 20.00 mmol) in THF (20 mL) was added. The mixture was stirred at 0 °C for 30 min and then allowed to warm up to room temperature for 15 minutes. The mixture was re-cooled to 0 °C and MOMCl (3.80 mL, 50.0 mmol) was added. The mixture was warmed up to room temperature and stirred for an additional 12 h. NH_4Cl (sat. aq. 30 mL) was added to the mixture and the organic solvent was removed on a rotary evaporator. The residue was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (DCM:hexanes 1:2 to 3:4 to 1:1) gave **II-77** as a white solid (13.05 g, 19.10 mmol, mp 97-98 °C) in 95% yield.

Spectral data for **II-77**: Rf = 0.22 (DCM/hexanes 1:1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.77 (s, 6H), 5.05-5.09 (m, 4H), 6.71 (dd, 4H, *J* = 8.5, 1.0 Hz), 6.89-6.93 (m, 4H), 7.03-

7.09 (m, 2H), 7.46 (s, 2H), 7.57 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.68 (d, 2H, *J* = 9.0 Hz), 8.32-8.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 56.50, 99.51, 120.46, 125.18, 125.49, 126.31, 127.52, 127.55, 128.17, 129.04, 129.87, 130.02, 132.84, 140.42, 141.13, 151.52; These spectral data match those previously reported for this compound[11].

General Procedure **L** for synthesis of 7,7'-dialkyl VANOL by the Kumada coupling -- illustrated for synthesis of 7,7'-hexyl$_2$VANOL **II-45o**.



7,7'-hexyl$_2$VANOL-MOM$_2$ ***II-78o***: An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, 1-bromohexane (4.50 mL, 32.0 mmol, 4.00 equiv) and Et_2O (15 mL) was added. The solution was cooled to 0 °C in an ice bath for 10 min. To the round bottom flask magnesium (800 mg, 32.9 mmol) was added and activated with 1 drop of TMSCl under nitrogen. The reaction mixture was stirred at rt for 0.5 h then was refluxed for 1 h until most of the magnesium disappeared. To a separate oven-dried 250 mL round-bottomed flask was added **II-77** (5.476 g, 8.000 mmol), Ni(dppp)Cl_2 (432 mg, 0.800 mmol) and dry THF (40 mL) and then cooled to 0 ºC for 10 min. To this mixture was added dropwise the resulting solution of Grignard reagent

from the 100 mL round-bottomed flask at 0 ºC. The reaction mixture was then warmed to rt and heated to reflux (45 ºC) for 12 h. After cooling to room temperature, NH_4Cl (sat. aq. 20 mL) was added to the mixture. and the layers were separated. The aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. It was revealed by TLC and ^1H NMR analysis that the partial deproctection occurred (mono-MOM:di-MOM 1:4.7).Therefore the residue was purified by column chromatography (silica gel, DCM/hexanes 1:3) to give a mixture of **II-78o** and the partially deprotected procduct as a white solid (6.362 g). The crude mixture was used in the next step without further separation.

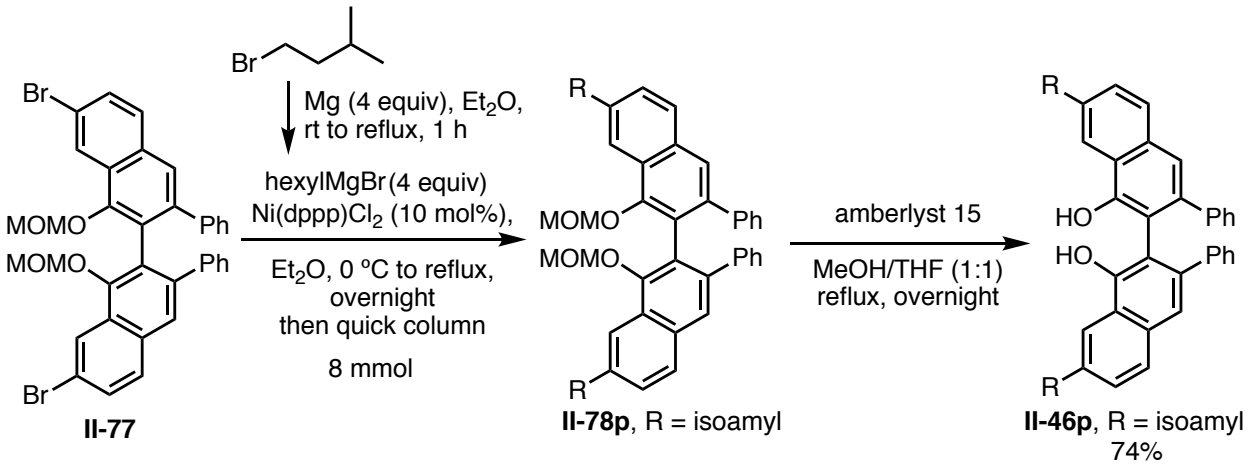
Spectral data for **II-78o**: Rf = 0.67 (DCM/hexanes 1:1). ^1H NMR (500 MHz, $CDCl_3$) δ 0.78 – 1.05 (m, 6H), 1.21 – 1.57 (m, 12H), 1.76 (q, *J* = 7.7 Hz, 4H), 2.68 (s, 6H), 2.84 (dd, *J* = 8.8, 6.6 Hz, 4H), 5.09 – 5.22 (m, 4H), 6.70 – 6.78 (m, 4H), 6.91 (t, *J* = 7.8 Hz, 4H), 6.99 – 7.10 (m, 2H), 7.38 (dd, *J* = 8.3, 1.7 Hz, 2H), 7.49 (s, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.92 – 8.05 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.17, 22.67, 29.10, 31.28, 31.81, 36.55, 56.28, 99.33, 121.04, 125.51, 125.74, 126.84, 126.99, 127.38, 128.02, 128.11, 129.15, 133.00, 139.71, 140.72, 141.12, 151.95.

Spectral data for mono-MOM-**II-78o**: R_f = 0.58 (DCM/hexanes 1:1). ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (td, *J* = 6.1, 5.2, 2.4 Hz, 6H), 1.30 – 1.53 (m, 12H), 1.77 (tdd, *J* = 11.6, 8.9, 5.5 Hz, 4H), 2.76 – 2.89 (m, 4H), 2.93 (s, 3H), 5.09 – 5.26 (m, 2H), 6.13 (s, 1H), 6.54 – 6.64 (m, 2H), 6.73 – 6.82 (m, 2H), 6.86 – 7.02 (m, 4H), 7.01 – 7.14 (m, 2H), 7.26 (s, 1H), 7.40 (ddd, *J* = 28.5, 8.4, 1.7 Hz, 2H), 7.49 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.96 (d, *J* = 1.7 Hz, 1H), 8.09 – 8.27 (m, 1H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 14.14, 14.15, 22.66, 29.09, 29.23, 31.44, 31.48, 31.78, 31.80, 36.49, 36.54, 56.96, 99.28, 117.73, 120.93, 121.10, 121.49, 123.79, 124.73, 126.01, 126.21, 126.51, 127.25, 127.30, 127.34, 127.40, 128.21, 128.24, 128.61, 128.97, 129.32, 132.52, 133.29, 139.27, 139.99, 140.42, 140.52, 141.16, 141.33, 149.08, 151.29.

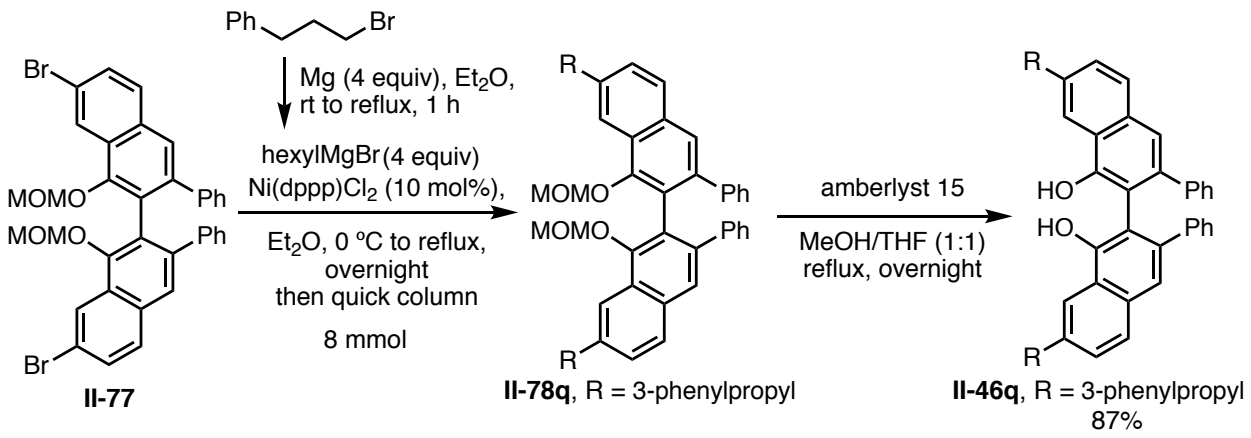
7,7'-hexyl$_2$VANOL **II-46o**: To a 500 mL round-bottomed flask, the purified mixture obtained above was dissolved in a mixture of THF and MeOH (160 mL, 1:1) and Amberlyst 15 (4.00 g) was added. The mixture was stirred at 65 ºC for 15 h under N_2. After cooling down to rt, the mixture was filtered through filter paper and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (DCM:hexanes 2:1) gave **II-46o** as a white solid (4.525 g, mp 107-108 ºC, 7.450 mmol) in 93% yield over two steps.

Spectral data for **II-46o**: R_f = 0.38 (DCM/hexanes 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 – 1.04 (m, 6H), 1.19 – 1.57 (m, 12H), 1.66 – 1.93 (m, 4H), 2.85 (t, *J* = 7.8 Hz, 4H), 5.82 (d, *J* = 1.4 Hz, 2H), 6.64 (dt, *J* = 8.3, 1.2 Hz, 4H), 6.97 (t, *J* = 7.6 Hz, 4H), 7.07 (t, *J* = 7.4 Hz, 2H), 7.30 (s, 2H), 7.44 (dd, *J* = 8.4, 1.7 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 8.13 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.16, 22.66, 29.18, 31.55, 31.80, 36.43, 112.72, 121.12, 121.83, 122.94, 126.43, 127.42, 127.61, 128.89, 129.05, 133.05, 139.74, 140.34, 140.61, 149.91. HRMS (ESI$^-$) *m/z* 607.3593 [calcd. for $C_{44}H_{47}O_2$ (M–H): 607.3576].



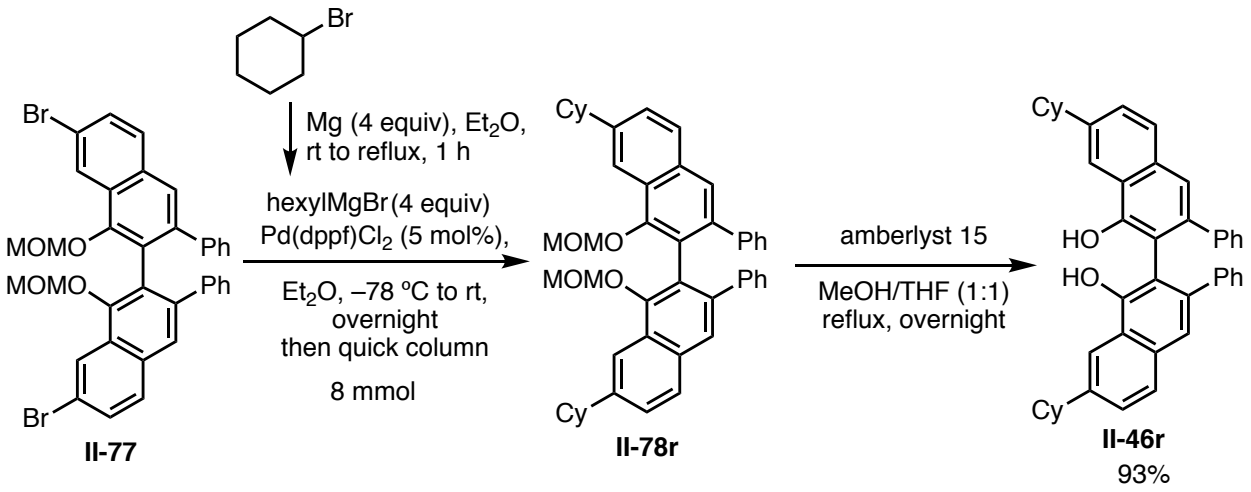
7,7'-isopentyl$_2$VANOL **II-46p**: VANOL derivatives **II-46p** was obtained by following General Procedure **L** with 1-bromo-3-methylbutane (3.84 mL, 32.0 mmol, 4.00 equiv). Crude mixture (4.5750 g) of **II-78p** and the mono-deprocteced compound was used for the next step to give **II-46p** as a white solid (3.898 g, mp 192-193 ºC, 6.730 mmol) in 84% yield over two steps.

Spectral data for **II-46p**: R_f = 0.36 (DCM/hexanes 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (dd, *J* = 6.2, 1.9 Hz, 12H), 1.60 – 1.87 (m, 6H), 2.86 (dd, *J* = 9.1, 6.5 Hz, 4H), 5.82 (s, 2H), 6.54 – 6.70 (m, 4H), 6.97 (t, *J* = 7.7 Hz, 4H), 7.04 – 7.15 (m, 2H), 7.30 (s, 2H), 7.44 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 8.06 – 8.19 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.60, 22.67, 27.91, 34.26, 40.88, 112.72, 121.04, 121.84, 122.96, 126.44, 127.42, 127.65, 128.88, 129.04, 133.04, 139.74, 140.34, 140.77, 149.89. HRMS (ESI^-) *m/z* 577.3130 [calcd. for $C_{42}H_{41}O_2$ (M–H): 577.3107].



7,7'-(3-phenylpropyl)$_2$VANOL **II-46q**: VANOL derivatives **II-46q** was obtained by following General Procedure **L** with (3-bromopropyl)benzene (4.9 mL, 32 mmol, 4.0 equiv). Crude mixture (6.752 g) of **II-78q** and the mono-deprocteced compound was used for the next step to give **II-46q** as a white solid (4.686 g, mp 129-131 ºC, 6.940 mmol) in 87 % yield over two steps.

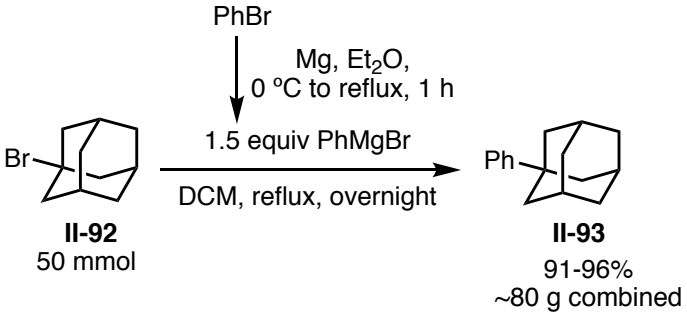
Spectral data for **II-46q**: R_f = 0.39 (DCM/hexanes 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 – 2.20 (m, 4H), 2.72 – 2.81 (m, 4H), 2.88 – 2.95 (m, 4H), δ 5.82 (s, 2H), 6.61 – 6.66 (m, 4H), 6.97 (t, *J* = 7.7 Hz, 4H), 7.04 – 7.11 (m, 2H), 7.19 – 7.28 (m, 6H), 7.28 – 7.36 (m, 6H), 7.44 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 8.05 – 8.30 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.03, 35.62, 35.88, 112.77, 121.28, 121.83, 122.94, 125.81, 126.48, 127.43, 127.73, 128.37, 128.52, 128.88, 128.99, 133.12, 139.85, 139.92, 140.30, 142.26, 149.94. HRMS (ESI$^-$) *m/z* 675.3296 [calcd. for $C_{50}H_{43}O_2$ (M–H): 675.3263].



7,7'-Cy$_2$VANOL **II-46r**: VANOL derivatives **II-46r** was obtained by following General Procedure **L** with bromocyclohexane (4.0 mL, 32 mmol, 4.0 equiv) using 5 mol% Pd(dppf)$_2$Cl$_2$ as catalyst instead of Ni(dppp)Cl$_2$. Crude mixture of **II-78r** and the mono-deprocteced compound was used for the next step to give **II-46r** as a white solid (4.503 g, mp 135-137 °C, 7.470 mmol) in 93% yield over two steps.

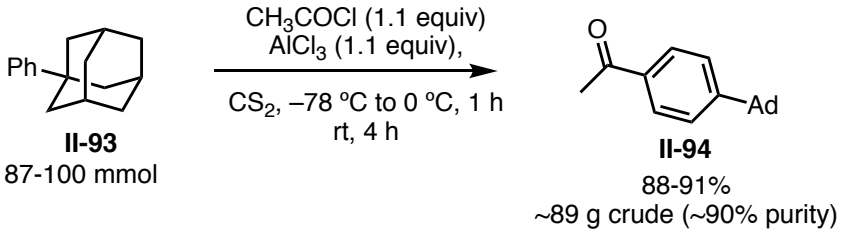
Spectral data for **II-46q**: R_f = 0.38 (DCM/hexanes 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 – 1.38 (m, 2H), 1.40 – 1.66 (m, 8H), 1.75 – 1.83 (m, 2H), 1.89 (d, *J* =12.1 Hz, 4H), 2.02 (d, *J* = 12.1 Hz, 4H), 2.74 (tt, *J* = 12.0, 3.4 Hz, 2H), 5.79 (s, 2H), 6.56 – 6.65 (m, 4H), 6.94 (t, *J* = 7.7 Hz, 4H), 7.00 – 7.10 (m, 2H), 7.27 (s, 2H), 7.45 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 1.8 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 26.20, 26.96, 34.42, 34.48, 44.95, 112.65, 119.46, 121.79, 122.94, 126.40, 127.42, 127.62, 127.75, 128.88, 133.23, 139.79, 140.37, 145.63, 150.04. HRMS (ESI$^-$) *m/z* 603.3262 [calcd. for $C_{44}H_{43}O_2$ (M–H): 603.3263].

4.3.8 Synthesis of 7,7'-Ad_2VANOL (*Scheme 2.27*)



1-phenyladamantane ***II-93***: An oven-dried 250 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, bromobenzene (7.9 mL, 75 mmol) and Et_2O (75 mL) was added. The solution was cooled to 0 °C in an ice bath for 10 min. To the round bottom flask magnesium (1.82 g, 75.0 mmol) was added and activated with 1 drop of TMSCl under nitrogen. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the Et_2O solution of Grignard reagent was transferred to another oven-dried 250 mL round-bottomed flask to remove the residual magnesium. Et_2O was removed in vacuo to give a solid. A solution of 1-bromoadamantane **II-92** (9.832 g, 50.00 mmol) in CH_2Cl_2 (40 mL) was added to the solidified Grignard reagent diluted with CH_2Cl_2 (60 mL) at room temperature under nitrogen, and then the mixture was refluxed for 12 h. After cooling, the reaction system was carefully poured into 2 N HCl at 0ºC and the layers were separated. The aqueous layer was extracted with hexanes (100 mL x 3). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography (silica gel, hexanes) to give **II-93** (9.615 g, 91%, 45.30 mmol, m.p. 76-78 ºC) as a white solid.

Spectral data for **II-93**: R_f = 0.24 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 – 1.86 (m, 6H), 1.91 (d, *J* = 3.0 Hz, 6H), 2.01 – 2.13 (m, 3H), 7.12 – 7.20 (m, 1H), 7.25 – 7.40 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.95, 36.16, 36.80, 43.14, 124.83, 125.48, 128.07, 151.30. These spectral data match those previously reported for this compound[14].



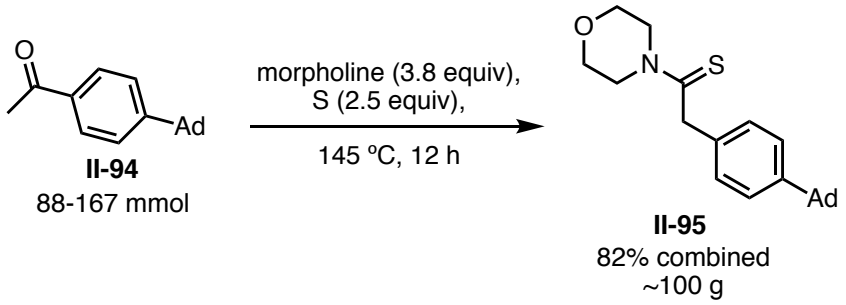
II-93
87-100 mmol

II-94
88-91%
~89 g crude (~90% purity)

*4-adamantylacetophenone **II-93***: To a flame-dried 100 mL round bottom flask was added $AlCl_3$ (14.7 g, 110 mmol) and CS_2 (30 mL). The solution was cooled to –78 °C for 10 min. To the stirred mixture at –78 °C was added a solution of 1-phenyladamantane **II-93** (21.23 g, 100.0 mmol), acetyl chloride (7.85 mL, 110 mmol) in CS_2 (20 mL). The reaction mixture was warmed up to 0 °C and maintained for 1 h, after which time the ice bath was removed to stir at rt for 4 h. The mixture was poured into a mixture of ice (300 g) and 2 M H_2SO_4. The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc 10:1) to give **II-94** (22.70 g, 89%, 89.20 mmol, m.p. 97-100 ºC) as a white solid.

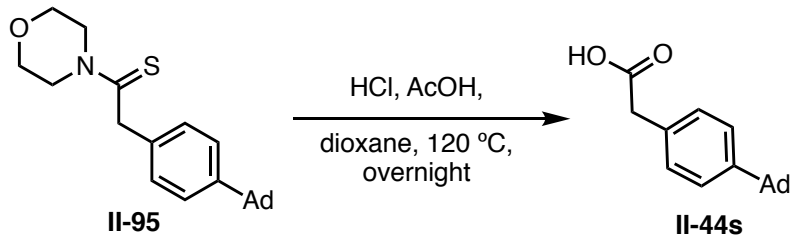
Spectral data for **II-94**: R_f = 0.52 (EtOAc/hexanes 1:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 – 1.79 (m, 6H), 1.85 (d, *J* = 3.6 Hz, 6H), 2.04 (p, *J* = 3.0 Hz, 3H), 2.48 (s, 3H), 7.31

– 7.43 (m, 2H), 7.80 – 7.87 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.76, 31.57, 36.55, 36.58, 42.80, 124.97, 128.23, 134.58, 156.65, 197.37. These spectral data match those previously reported for this compound[15].



1-morpholino-2-(4-adamantylphenyl) ethane-1-thione ***II-95***: To a flame-dried 250 mL round bottom flask was added 4-adamantylacetophenone **II-93** (22.33 g, 87.80 mmol) sulfur (7.04 g, 220 mmol) and morpholine (29.0 mL, 330 mmol). The mixtrure was heated to 145 ºC for 12 h. After being cooled to rt, the mixture was refluxed with EtOH (50 mL) for 1 h. The mixture was cooled to –20 ºC for 1 h then the precipitated solid was collected by suction filtration and wash by EtOH. This crude **II-95** (26.53 g, 85%, 74.60 mmol, m.p. 171-174 ºC) appeared pure by ^{1}H NMR analysis and was used in the next step without further purification.

Spectral data for **II-95**: R_f = 0.19 (EtOAc/hexanes 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (q, *J* = 10 Hz, 6H), 1.87 (d, *J* = 2.9 Hz, 6H), 2.07 (p, *J* = 3.2 Hz, 3H), 3.31 – 3.43 (m, 2H), 3.56 – 3.66 (m, 2H), 3.66 – 3.78 (m, 2H), 4.31 (s, 2H), 4.32 – 4.38 (m, 2H), 7.19 – 7.24 (m, 2H), 7.26 – 7.32 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.89, 35.98, 36.73, 43.14, 50.14, 50.19, 50.79, 66.11, 66.35, 125.41, 127.41, 132.59, 150.31, 200.31. HRMS (ESI-TOF) m/z 356.2053 [calcd. for C18H26NO4 ($M+H^+$): 356.2048].

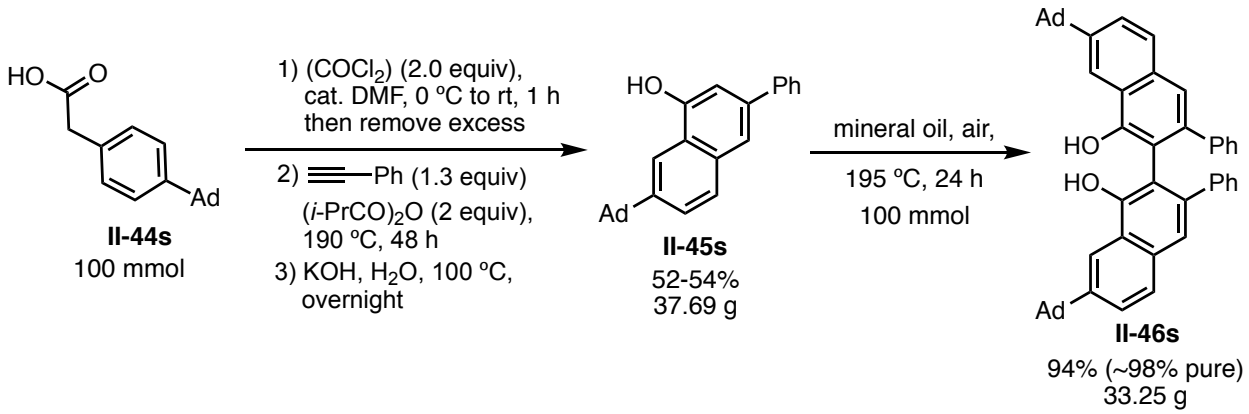


II-95
96 mmol, 107 mmol

II-44s
86% combined
~50 g

*2-(4-adamantylphenyl)acetic acid **II-44s***: To a flame-dried 500 mL round bottom flask was added morpholinyl ethanethione **II-95** (37.98 g, 106.8 mmol), dioxane (100 mL), HCl (12 N, 50 mL) and acetic acid (25 mL). The resulting mixtrure was heated to reflux at 120 ºC for 12 h. After being cooled to rt, the solvent was evaporated. The mixture was stirred with 1N HCl and cooled to 0 ºC for 1 h. The precipitated solid was collected by suction filtration and wash by cold 1 N HCl followed by exposure to high vacuum overnight. This crude product can be purified by recrystallization from EtOAc/hexanes (1:3) to afford **II-44s** (24.71 g, 86% combined yield from 3 crops, 91.40 mmol, m.p. 186-187 ºC) as a yellow solid.

Spectral data for **II-44s**: R_f = 0.21 (DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (q, *J* = 10 Hz, 6H), 1.91 (d, *J* = 2.9 Hz, 6H), 2.01 – 2.20 (m, 3H), 3.63 (s, 2H), 7.20 – 7.30 (m, 2H), 7.31 – 7.36 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.91, 36.00, 36.76, 40.50, 43.13, 125.20, 129.05, 130.23, 150.47, 177.57. HRMS (ESI^-) *m/z* 269.1544 [calcd. for $C_{18}H_{21}O_2$ (M–H): 269.1542].



*7-adamantyl3-phenyl-1-naphthol **II-45s***: 1-naphthol **II-45s** was prepared from 2-(4-adamantylphenyl)acetic acid **II-44s** (27.04 g, 100.0 mmol) by the General Procedure **H'**.The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-45s** as a white crystal in 54% combined isolated yield (19.13 g, mp 201-203 ºC, 53.90 mmol).

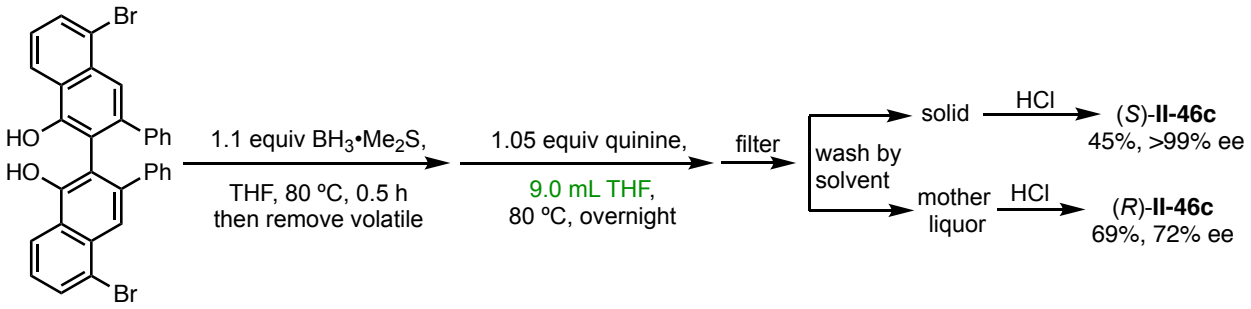
Spectral data for **II-45s**: R_f = 0.35 (DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 – 1.87 (m, 6H), 2.03 (d, *J* = 2.8 Hz, 6H), 2.14 (p, *J* = 3.1 Hz, 3H), 5.31 (s, 1H), 7.06 (d, *J* = 1.5 Hz, 1H), 7.26 – 7.39 (m, 1H), 7.40 – 7.53 (m, 2H), 7.51 – 7.71 (m, 4H), 7.80 (d, *J* = 8.7 Hz, 1H), 8.03 (dd, *J* = 1.9, 0.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.96, 36.60, 36.84, 43.11, 108.23, 116.18, 118.35, 123.35, 125.16, 127.22, 127.26, 127.74, 128.77, 133.27, 138.08, 141.04, 148.52, 151.69. HRMS (ESI^-) *m/z* 353.1917 [calcd. for $C_{26}H_{25}O$ (M–H): 353.1905].

*7,7'-Ad$_2$VANOL **II-46s***: VANOL derivative **II-46s** was prepared from 7-adamantyl3-phenyl-1-naphthol **II-45s** (35.45 g, 100.0 mmol) by the General Procedure **I** with heating at 195 ºC for 24 h. The crude product was purified by recrystallization from CH_2Cl_2/hexanes and column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to

give **II-46s** as an off-white solid in 94% combined isolated yield (33.25 g, mp 360 ºC (decomposed), 47.00 mmol).

Spectral data for **II-46s**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77 – 1.88 (m, 12H), 2.08 (d, *J* = 2.9 Hz, 12H), 2.09 – 2.25 (m, 6H), 5.83 (s, 2H), 6.52 – 6.70 (m, 4H), 6.94 (t, *J* = 7.7 Hz, 4H), 6.98 – 7.11 (m, 2H), 7.27 (s, 2H), 7.56 – 7.84 (m, 4H), 8.23 (d, *J* = 1.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.98, 36.71, 36.85, 43.12, 112.61, 117.65, 121.61, 122.74, 125.76, 126.37, 127.41, 127.42, 128.89, 132.91, 139.97, 140.40, 148.80, 150.30. HRMS (ESI^-) *m/z* 705.3748 [calcd. for $C_{52}H_{49}O_2$ (M–H): 705.3733].

4.3.9 General Procedure **M** for chiral resolution of VANOL derivatives with quinine borates (*Table 2.4*) -- illustrated for resolution of (±)-5,5'-Br_2VANOL *rac*-**II-46c**



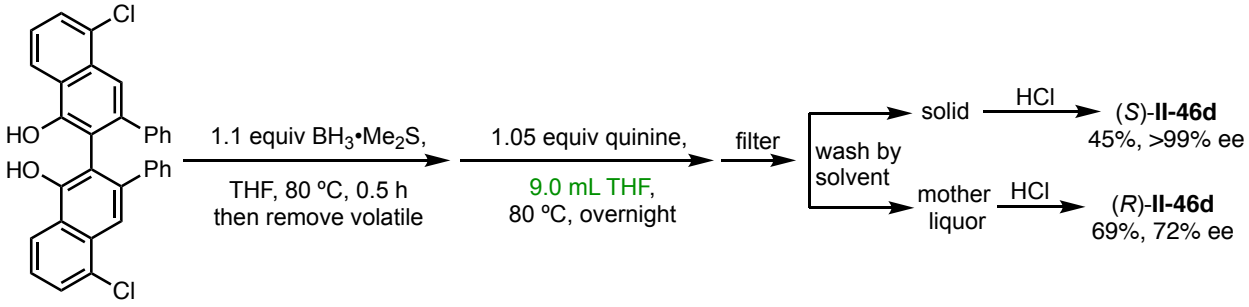
rac-**II-46c**
2.0 mmol

*(S)-5,5'-Br$_2$VANOL (S)-**II-46c***: An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, (±)-5,5'-Br_2VANOL **II-46c** (1.192 g, 2.000 mmol) is added followed by addition of anhydrous tetrahydrofuran (10 mL) and BH_3•Me_2S (1.10 mL, 2 M solution in toluene, 2.20 mmol, 1.10 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture is stirred and refluxed in an 80 ºC oil bath for 30 min, and the evolution of gas ceases. After

cooling to rt (23 ºC), the clear solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C, anhydrous tetrahydrofuran (9 mL) is added followed by addition of quinine (681 mg, 2.10 mmol, 1.05 equiv). The reflux condenser is reconnected and the mixture is stirred and refluxed in an 80 ºC oil bath for overnight (12 h). The flask containing reaction mixture is cooled to rt then to –20 ºC for 30 min before the solid is collected by suction filtration, washed with ice-cold anhydrous tetrahydrofuran (9 mL).

The solid is transferred to a 100 mL round-bottomed flask and EtOAc (10 mL) is added followed by addition of aq. HCl (10 mL, 2M) and an egg-shaped stirring bar (30 mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with EtOAc (15 mL×2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue is dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of CH_2Cl_2 and hexanes (1:2) to afford (*S*)-5,5'-Br_2VANOL (*S*)-**II-46c** as a white solid (0.549 g, 0.921 mmol, 46%). The optical purity of (*S*)-**II-46c** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 24.99 min for (*R*)-**II-46c** (minor) and R_t = 27.43 min for (*S*)-**II-46c** (major). $[\alpha]^{20}_D$ = –148.7 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46c** (HPLC).

*(R)-5,5'-Br_2VANOL (R)-**II-46c***: The mother liquor is transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). CH_2Cl_2 (15 mL) is added followed by addition of aq. HCl (15 mL, 2M) and an egg-shaped stirring bar (30 mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with CH_2Cl_2 (15 mL×2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of CH_2Cl_2 and hexanes (1:2) to afford (*R*)-5,5'-Br_2VANOL (*R*)-**II-46c** as a white solid (825 mg, 1.38 mmol, 69%). The optical purity of (*R*)-**II-46c** is determined to be 72% *ee* by HPLC analysis.

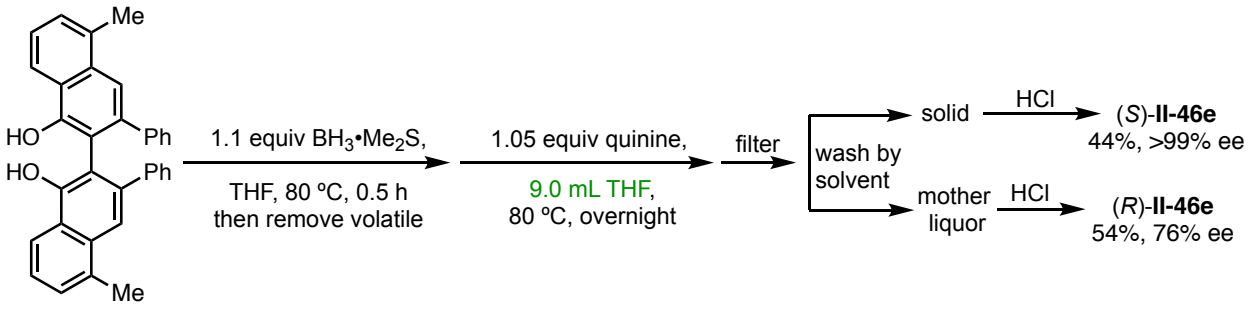


rac-**II-46d**
2.0 mmol

*(S)-5,5'-Cl_2VANOL (S)-**II-46d***: VANOL derivative (±)-**II-46d** (1.015 g, 2.000 mmol) was resolved by the General Procedure **M** with 9 mL refluxing THF to afford (*S*)-5,5'-Cl_2VANOL (*S*)-**II-46d** as a white solid (452 mg, 0.890 mmol, 45%). The optical purity of (*S*)-**II-46d** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine

column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 21.73 min for (*R*)-**II-46d** (minor) and R_t = 24.79 min for (*S*)-**II-46d** (major). $[\alpha]^{20}_D$ ND.

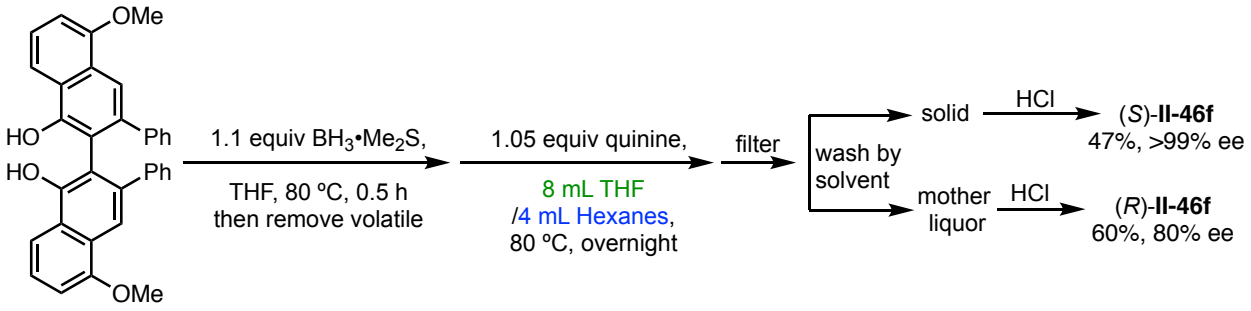
*(R)-5,5'-Cl$_2$VANOL (R)-**II-46d***: VANOL derivatives (*R*)-**II-46d** was obtained by following General Procedure **M**. Its optical purity is determined to be 72% *ee* by HPLC analysis.



rac-**II-46e**
2.0 mmol

*(S)-5,5'-Me$_2$VANOL (S)-**II-46e***: VANOL derivative (±)-**II-46e** (933.2 mg, 2.000 mmol) was resolved by the General Procedure **M** with 9 mL refluxing THF to afford (*S*)-5,5'-Me$_2$VANOL (*S*)-**II-46e** as a white solid (412 mg, 0.882 mmol, 44%). The optical purity of (*S*)-**II-46e** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.28 min for (*R*)-**II-46e** (minor) and R_t = 20.72 min for (*S*)-**II-46e** (major). $[\alpha]^{20}_D$ ND

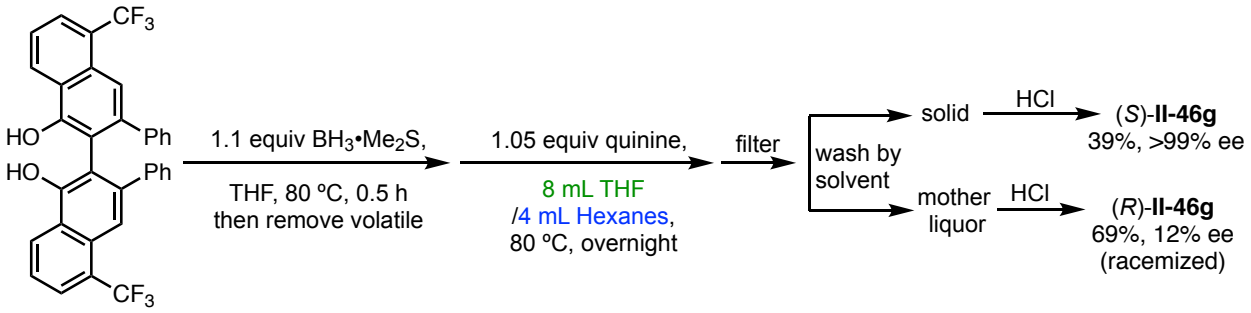
*(R)-5,5'-Me$_2$VANOL (R)-**II-46e***: VANOL derivatives (*R*)-**II-46e** was obtained by following General Procedure **M**. Its optical purity is determined to be 76% *ee* by HPLC analysis.



rac-**II-46f**
2.0 mmol

*(S)-5,5'-OMe$_2$VANOL (S)-**II-46f***: VANOL derivative (±)-**II-46f** (997.2 mg, 2.000 mmol) was resolved by the General Procedure M refluxing with 8 mL THF and 4 mL hexanes to afford (*S*)-5,5'-OMe$_2$VANOL (*S*)-**II-46f** as a white solid (469 mg, 0.941 mmol, 47%). The optical purity of (*S*)-**II-46f** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 32.05 min for (*R*)-**II-46f** (minor) and R_t = 36.45 min for (*S*)-**II-46f** (major). $[\alpha]^{20}_D$ = –178.6 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46f** (HPLC).

*(R)-5,5'-OMe$_2$VANOL (R)-**II-46f***: VANOL derivatives (*R*)-**II-46f** was obtained by following General Procedure **M**. Its optical purity is determined to be 80% *ee* by HPLC analysis.

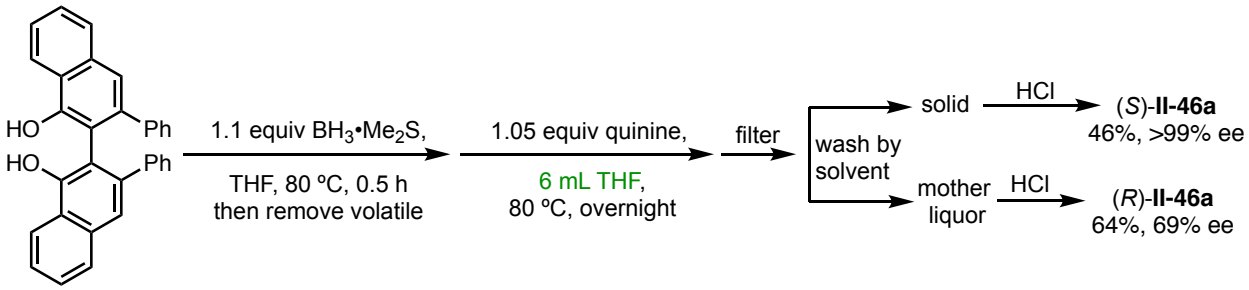


rac-**II-46g**
8.0 mmol

*(S)-5,5'-(CF$_3$)$_2$VANOL (S)-**II-46g***: VANOL derivative (±)-**II-46g** (1.149 g, 2.000 mmol) was resolved by the General Procedure M refluxing with 8 mL THF and 4 mL

hexanes to afford (*S*)-5,5'-$(CF_3)_2$VANOL (*S*)-**II-46g** as a white solid (0.449 g, 0.783 mmol, 39%). The optical purity of (*S*)-**II-46g** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 11.65 min for (*R*)-**II-46g** (minor) and R_t = 12.93 min for (*S*)-**II-46g** (major). $[\alpha]^{20}_D$ ND

*(R)-5,5'--$(CF_3)_2$VANOL (R)-**II-46g***: VANOL derivatives (*R*)-**II-46g** was obtained by following General Procedure **M**. Its optical purity is determined to be 12% *ee* by HPLC analysis.



rac-**II-46a**
2.0 mmol

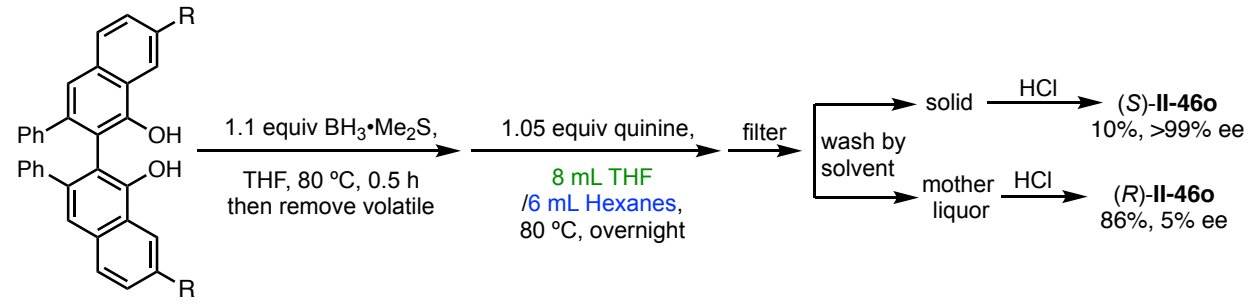
*(S)-VANOL (S)-**II-46a***: VANOL (±)-**II-46a** (877.0 mg, 2.000 mmol) was resolved by the General Procedure **M** with 6 mL refluxing THF to afford (*S*)-VANOL (*S*)-**II-46a** as a white solid (0.407 g, 0.928 mmol, 46%). The optical purity of (*S*)-**II-46a** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 16.93 min for (*R*)-**II-46a** (minor) and R_t = 19.70 min for (*S*)-**II-46a** (major). $[\alpha]^{20}_D$ = –310 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46a** (HPLC).

*(R)-VANOL (R)-**II-46a***: VANOL derivatives (*R*)-**II-46a** was obtained by following General Procedure **M**. Its optical purity is determined to be 69% *ee* by HPLC analysis.

rac-**II-46b**
2.0 mmol

*(S)-tBuVANOL (S)-**II-46b***: VANOL derivative (±)-**II-46b** (1.102 g, 2.000 mmol) was resolved by the General Procedure **M** with 8 mL refluxing THF to afford (*S*)-*t*BuVANOL (*S*)-**II-46b** as a white solid (0.389 g, 0.706 mmol, 35%). The optical purity of (*S*)-**II-46b** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 8.50 min for (*R*)-**II-46b** (minor) and R_t = 9.50 min for (*S*)-**II-46b** (major). $[\alpha]^{20}_D$ = –210.9 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46b** (HPLC).

*(R)-tBuVANOL (R)-**II-46b***: VANOL derivatives (*R*)-**II-46b** was obtained by following General Procedure **M**. Its optical purity is determined to be 77% *ee* by HPLC analysis.

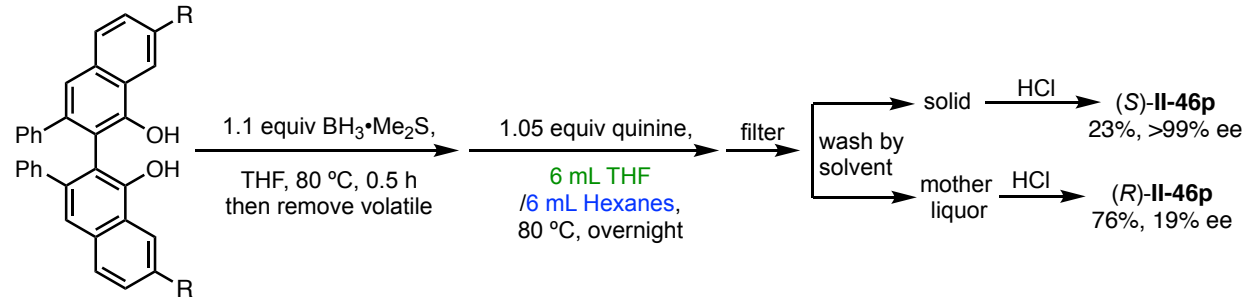


rac-**II-46o**, R = n-hexyl
2.0 mmol

*(S)-7,7'-hexyl$_2$VANOL (S)-**II-46o***: VANOL derivative (±)-**II-46o** (1.214 g, 2.000 mmol) was resolved by the General Procedure **M** refluxing with 8 mL THF and 6 mL hexanes to afford (*S*)- *7,7'-hexyl$_2$VANOL* (*S*)-**II-46o** as a white solid (0.130 g, 0.214 mmol,

10%). The optical purity of (*S*)-**II-46o** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 6.16 min for (*R*)-**II-46o** (minor) and R_t = 6.51 min for (*S*)-**II-46o** (major).

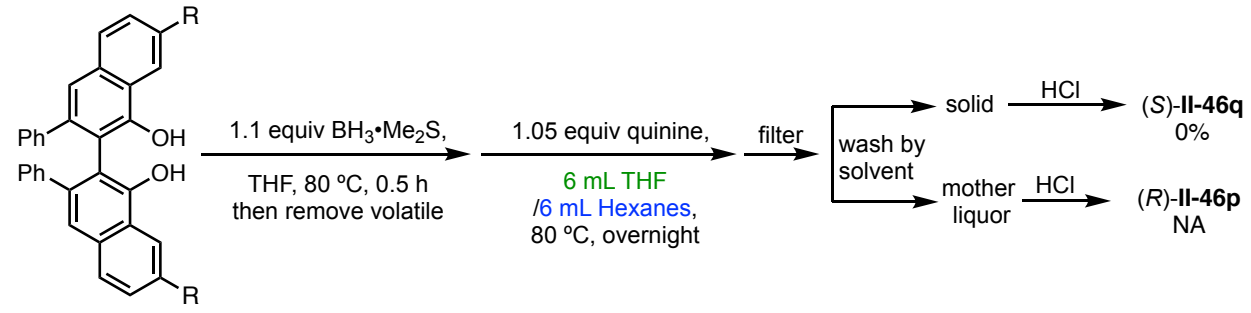
*(R)-7,7'-hexyl$_2$VANOL (R)-**II-46o***: VANOL derivatives (*R*)-**II-46o** was obtained by following General Procedure **M**. Its optical purity is determined to be 5% *ee* by HPLC analysis.



rac-**II-46p**, R = isopentyl
2.0 mmol

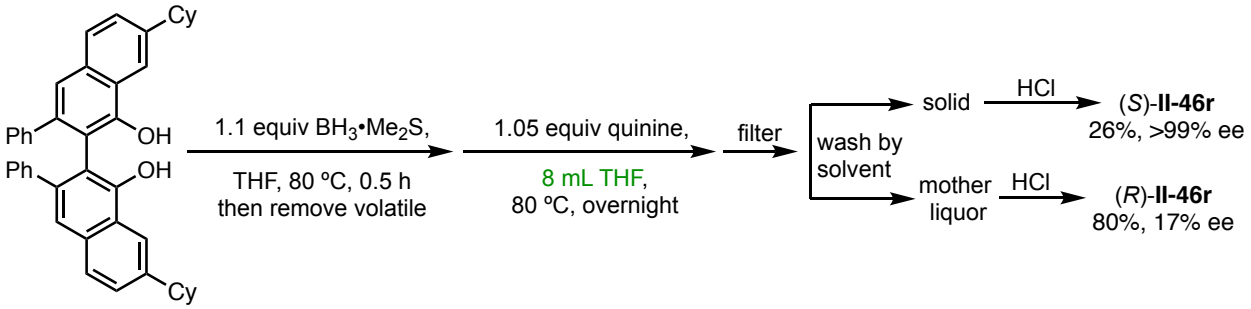
*(S)-7,7'-isopentyl$_2$VANOL (S)-**II-46p***: VANOL derivative (±)-**II-46p** (1.158 g, 2.000 mmol) was resolved by the General Procedure **M** refluxing with 6 mL THF and 6 mL hexanes to afford (*S*)-7,7'-isopentyl$_2$VANOL (*S*)-**II-46p** as a white solid (0.268 g, 0.463 mmol, 23%). The optical purity of (*S*)-**II-46p** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 6.75 min for (*R*)-**II-46p** (minor) and R_t = 7.25 min for (*S*)-**II-46p** (major). $[\alpha]^{20}_D$ = –235.9 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46p** (HPLC).

*(R)-7,7'-isopentyl$_2$VANOL (R)-**II-46p***: VANOL derivatives (*R*)-**II-46p** was obtained by following General Procedure **M**. Its optical purity is determined to be 19% *ee* by HPLC analysis.



rac-**II-46q**, R = 3-phenylpropyl
2.0 mmol

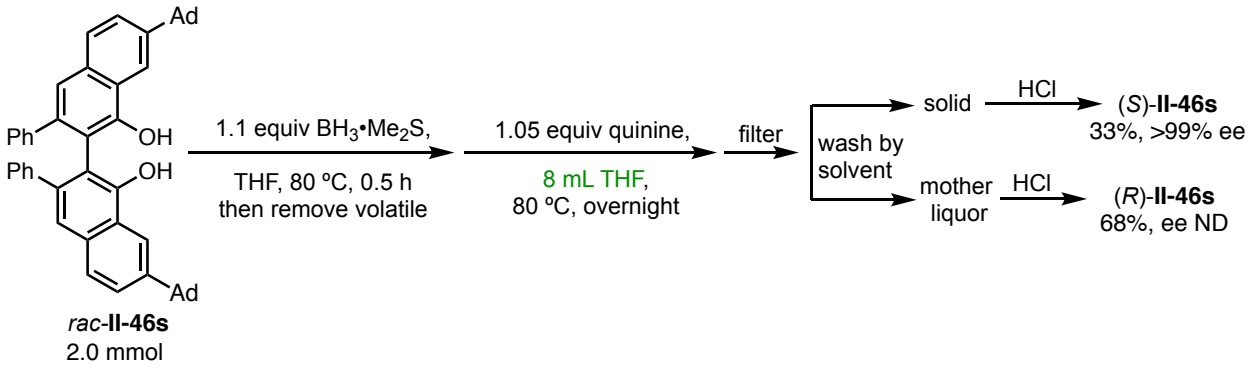
*(S)-7,7'-(3-phenylpropyl)$_2$VANOL (S)-**II-46q***: No precipitate formed when VANOL derivative (±)-**II-46q** (1.350 g, 2.000 mmol) was attempted to be resolved by the General Procedure **M** refluxing with 6 mL THF and 6 mL hexanes.



rac-**II-46r**
2.0 mmol

*(S)-7,7'-Cy$_2$VANOL (S)-**II-46r***: VANOL derivative (±)-**II-46r** (1.206 g, 2.000 mmol) was resolved by the General Procedure **M** with 8 mL refluxing THF to afford *(S)*-7,7'-Cy$_2$VANOL (*S*)-**II-46r** as a white solid (0.313 g, 0.519 mmol, 26%). The optical purity of (*S*)-**II-46r** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 7.70 min for (*R*)-**II-46r** (minor) and R_t = 8.65 min for (*S*)-**II-46r** (major). $[\alpha]^{20}_D$ = –206.1 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46r** (HPLC).

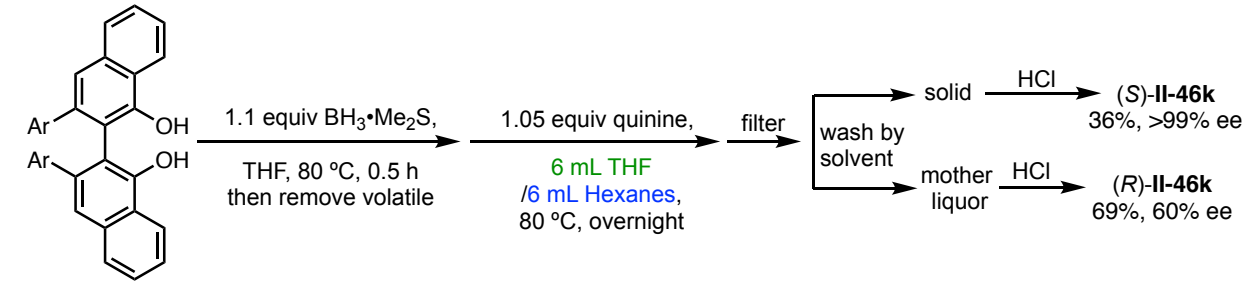
*(R)-7,7'-Cy$_2$VANOL (R)-**II-46r***: VANOL derivatives (*R*)-**II-46r** was obtained by following General Procedure **M**. Its optical purity is determined to be 17% *ee* by HPLC analysis.



rac-**II-46s**
2.0 mmol

*(S)-7,7'-Ad$_2$VANOL (S)-**II-46s***: VANOL derivative (±)-**II-46s** (1.414 g, 2.000 mmol) was resolved by the General Procedure **M** with 8 mL refluxing THF to afford (*S*)-7,7'-Ad$_2$VANOL (*S*)-**II-46s** as a white solid (0.470 g, 0.665 mmol, 33%). The optical purity of (*S*)-**II-46s** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 8.52 min for (*R*)-**II-46s** (minor) and R_t = 9.58 min for (*S*)-**II-46s** (major). $[\alpha]^{20}_D$ = –160.6 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46s** (HPLC).

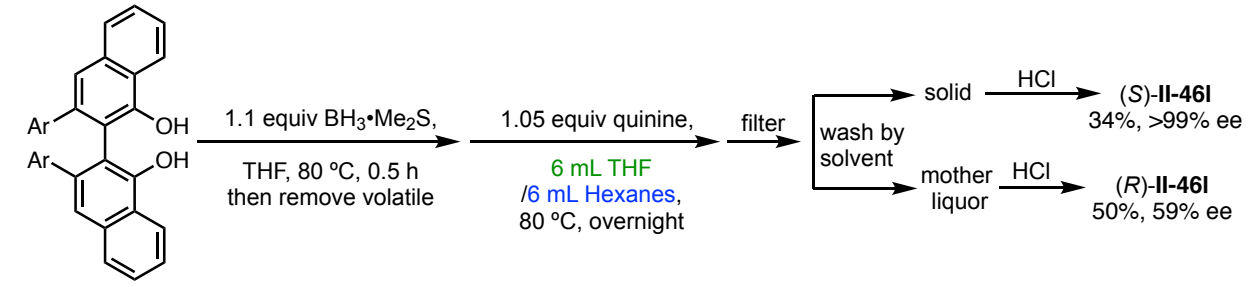
*(R)-7,7'-Ad$_2$VANOL (R)-**II-46s***: VANOL derivatives (*R*)-**II-46s** was obtained by following General Procedure **M**. Its optical purity was not determined due to overlapping peaks.



rac-**II-46k**, Ar = *p*-EtC_6H_4
2.0 mmol

*(S)-3,3'-pEtPh$_2$VANOL (S)-**II-46k***: VANOL derivative (±)-**II-46k** (989.3 mg, 2.000 mmol) was resolved by the General Procedure **M** refluxing with 6 mL THF and 6 mL hexanes to afford (*S*)-*3,3'-pEtPh$_2$VANOL* (*S*)-**II-46k** as a white solid (0.358 g, 0.724 mmol, 36%). The optical purity of (*S*)-**II-46k** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 14.83 min for (*R*)-**II-46k** (minor) and R_t = 16.42 min for (*S*)-**II-46k** (major).

*(R)-3,3'-pEtPh$_2$VANOL (R)-**II-46k***: VANOL derivatives (*R*)-**II-46k** was obtained by following General Procedure **M**. Its optical purity is determined to be 60% *ee* by HPLC analysis.

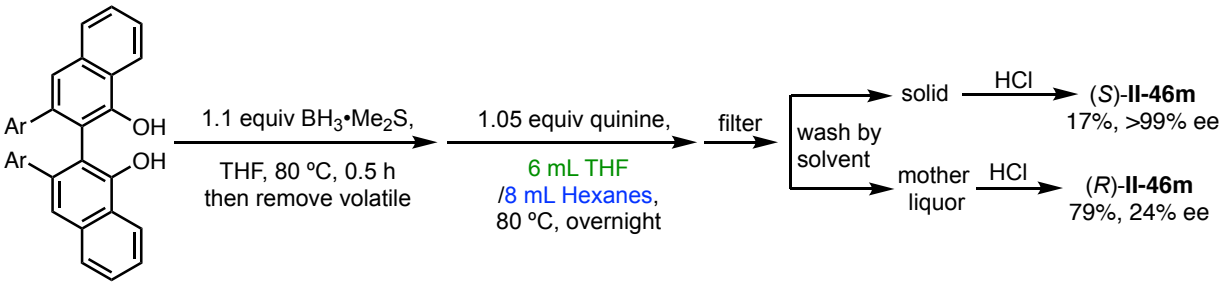


rac-**II-46l**, Ar = *p*-$MeOC_6H_4$
2.0 mmol

*(S)-3,3'-pOMePh$_2$VANOL (S)-**II-46l***: VANOL derivative (±)-**II-46l** (997.2 mg, 2.000 mmol) was resolved by the General Procedure **M** refluxing with 6 mL THF and 6 mL

hexanes to afford (*S*)-3,3'-*p*OMePh$_2$VANOL (*S*)-**II-46l** as a white solid (0.342 g, 0.686 mmol, 34%). The optical purity of (*S*)-**II-46l** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 6.31 min for (*R*)-**II-46l** (minor) and R_t = 7.02 min for (*S*)-**II-46l** (major). $[\alpha]^{20}_D$ ND.

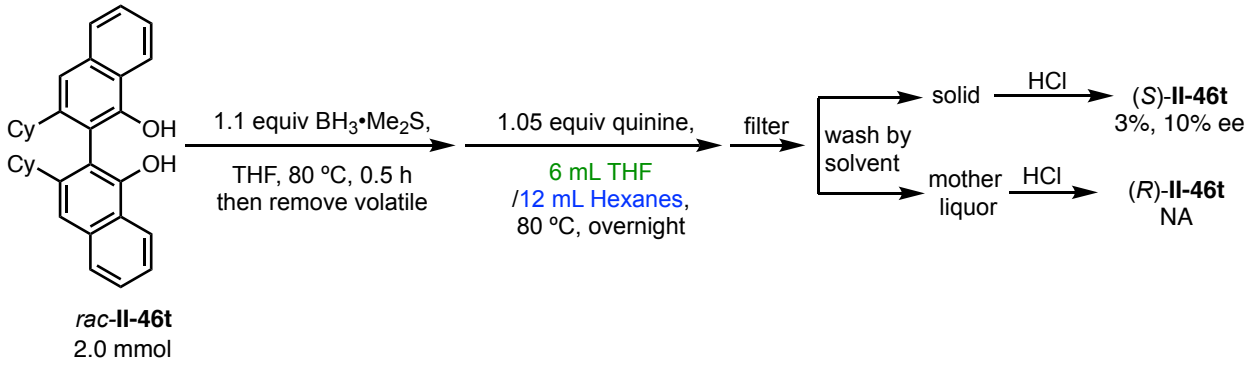
*(R)-3,3'-pOMePh$_2$VANOL (R)-**II-46l***: VANOL derivatives (*R*)-**II-46l** was obtained by following General Procedure **M**. Its optical purity is determined to be 59% *ee* by HPLC analysis.



rac-**II-46m**, Ar = *p*-BuC_6H_4
2.0 mmol

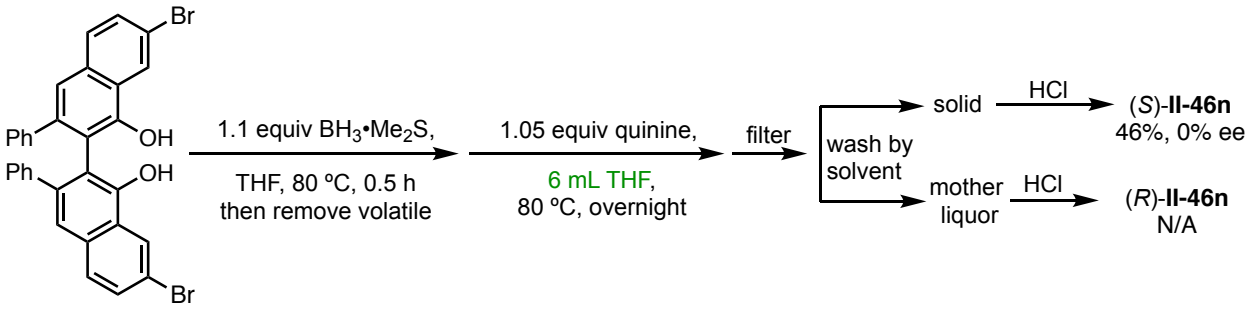
*(S)-3,3'-pOMePh$_2$VANOL (S)-**II-46m***: VANOL derivative (±)-**II-46m** (1.101 g, 2.000 mmol) was resolved by the General Procedure **M** with refluxing with 6 mL THF and 8 mL hexanes to afford (S)-3,3'-*p*OMePh$_2$VANOL (*S*)-**II-46m** as a white solid (191 mg, 0.346 mmol, 17%). The optical purity of (*S*)-**II-46m** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 13.01 min for (*R*)-**II-46m** (minor) and R_t = 15.06 min for (*S*)-**II-46m** (major). $[\alpha]^{20}_D$ ND.

*(S)-3,3'-pOMePh$_2$VANOL (S)-**II-46m***: VANOL derivatives (*R*)-**II-46m** was obtained by following General Procedure **M**. Its optical purity is determined to be 24% *ee* by HPLC analysis.



rac-**II-46t**
2.0 mmol

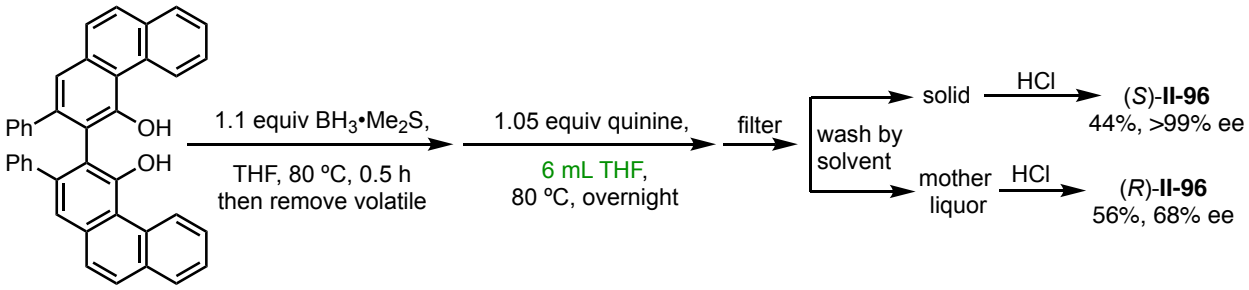
*(S)-3,3'-Cy$_2$VANOL (S)-**II-46t***: VANOL derivative (±)-**II-46t** (901.2 mg, 2.000 mmol) was resolved by the General Procedure **M** with refluxing with 6 mL THF and 12 mL hexanes to afford (*S*)-3,3'-Cy$_2$VANOL (*S*)-**II-46t** as a white foamy solid (27 mg, 0.060 mmol, 3%). The optical purity of (*S*)-**II-46t** is determined to be 10% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 8.36 min for (*R*)-**II-46t** (minor) and R_t = 9.16 min for (*S*)-**II-46t** (major).



rac-**II-46n**
2.0 mmol

*(S)-7,7'-Br$_2$VANOL (S)-**II-46n***: VANOL derivative (±)-**II-46n** (1.192 g, 2.000 mmol) was attempted to be resolved by the General Procedure **M** with 6 mL refluxing THF to

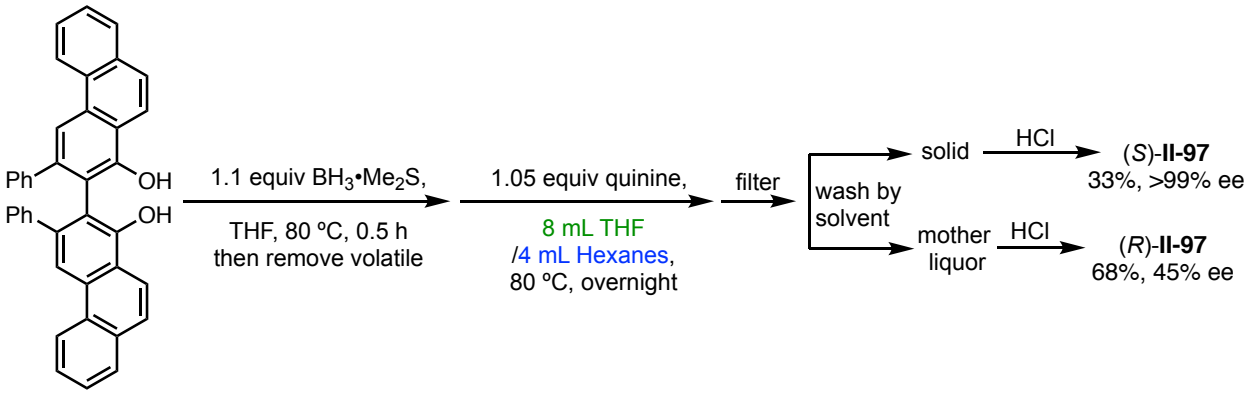
afford (±)-7,7'-Br_2VANOL (*S*)-**II-46n** as a white solid (0.549 g, 0.921 mmol, 46%). The optical purity of (*S*)-**II-46n** is determined to be 1% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 26.90 min for (*R*)-**II-46n** and R_t = 31.17 min for (*S*)-**II-46n**.



rac-**II-96**
2.0 mmol

*(S)-VAPOL (S)-**II-96***: VAPOL (±)-**II-96** (1.077 g, 2.000 mmol) was resolved by the General Procedure **M** with 6 mL refluxing THF to afford (*S*)-VAPOL (*S*)-**II-96** as a white solid (476 mg, 0.884 mmol, 44%). The optical purity of (*S*)-**II-96** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 14.69 min for (*R*)-**II-96** (minor) and R_t = 21.96 min for (*S*)-**II-96** (major). $[\alpha]^{20}_D$ ND.

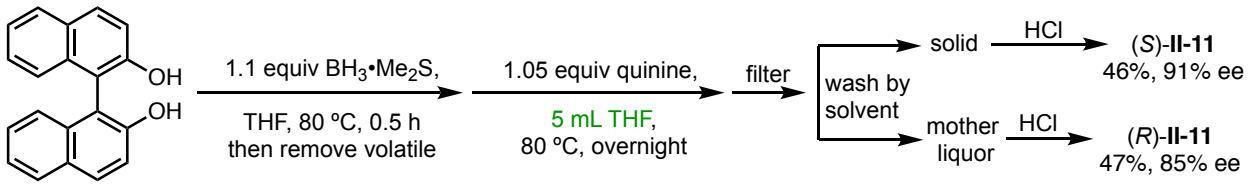
*(R)-VAPOL (R)-**II-96***: VANOL derivatives (*R*)-**II-96** was obtained by following General Procedure **M**. Its optical purity is determined to be 68% *ee* by HPLC analysis.



rac-**II-97**
2.0 mmol

*(S)-isoVAPOL (S)-**II-97***: *iso*VAPOL (±)-**II-97** (1.077 g, 2.000 mmol) was resolved by the General Procedure **M** with 6 mL refluxing THF to afford (*S*)-*iso*VAPOL (*S*)-**II-97** as a white solid (359 mg, 0.666 mmol, 33%). The optical purity of (*S*)-**II-97** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.69 min for (*R*)-**II-97** (minor) and R_t = 21.68 min for (*S*)-**II-97** (major). $[\alpha]^{20}_D$ ND.

*(R)-isoVAPOL (R)-**II-97***: VANOL derivatives (*R*)-**II-97** was obtained by following General Procedure **M**. Its optical purity is determined to be 45% *ee* by HPLC analysis.

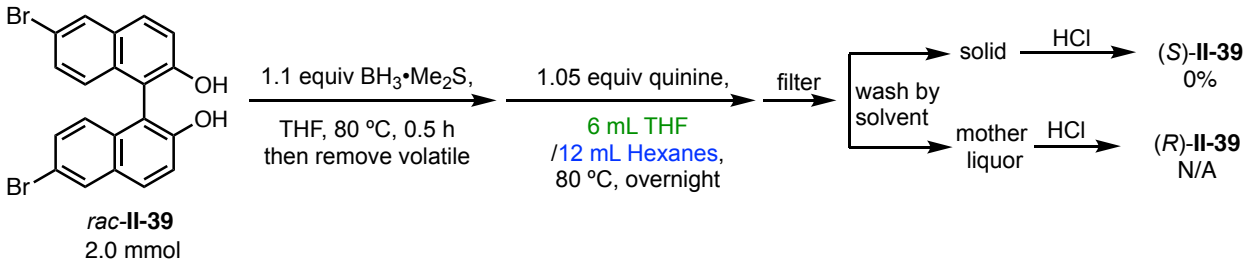


rac-**II-11**
2.0 mmol

*(S)-BINOL (S)-**II-11***: BINOL (±)-**II-11** (572.7 g, 2.000 mmol) was resolved by the General Procedure **M** with 5 mL refluxing THF to afford (*S*)-BINOL (*S*)-**II-11** as a white solid (264 mg, 0.461 mmol, 46%). The optical purity of (*S*)-**II-11** is determined to be 91% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm,

flow-rate: 1.0 mL/min). Retention times: R_t = 3.70 min for (*R*)-**II-11** (minor) and R_t = 3.12 min for (*S*)-**II-11** (major). $[\alpha]^{20}_D$ ND.

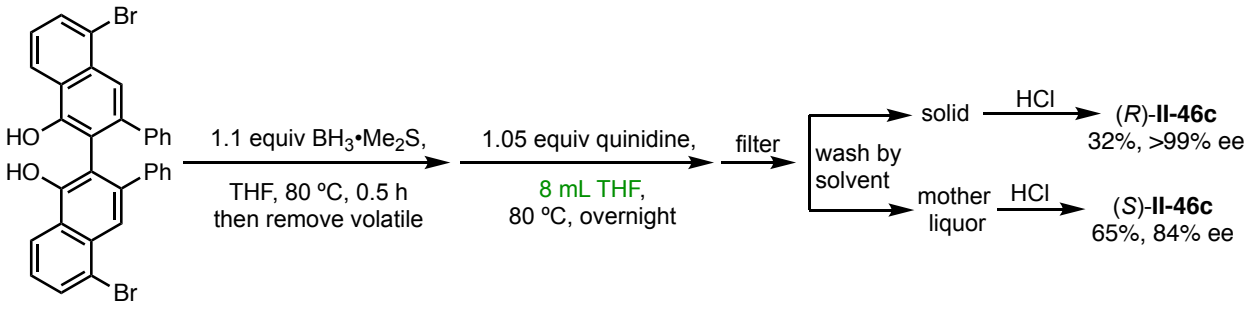
*(R)-BINOL (R)-**II-11***: VANOL derivatives (*R*)-**II-11** was obtained by following General Procedure **M**. Its optical purity is determined to be 85% *ee* by HPLC analysis.



rac-**II-39**
2.0 mmol

*(S)-6,6'-Br_2BINOL (S)-**II-39***: No precipitate formed when BINOL derivative (±)-**II-39** (888.2 mg, 2.000 mmol) was attempted to be resolved by the General Procedure **M** refluxing with 6 mL THF and 12 mL hexanes.

4.3.10 General Procedure **N** for chiral resolution of VANOL derivatives with quinidine borates (*Table 2.5*) -- illustrated for resolution of (±)-5,5'-Br_2VANOL *rac*-**II-46c**



rac-**II-46c**
2.0 mmol

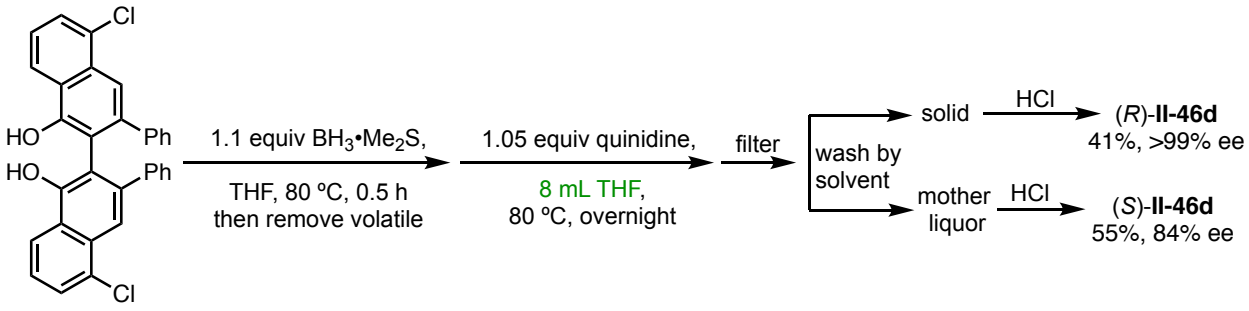
*(R)-5,5'-Br_2VANOL (R)-**II-46c***: An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, (±)-Br_2VANOL **II-46c** (1.192 g, 2.000 mmol) is added followed by addition of anhydrous tetrahydrofuran (10 mL) and

BH_3•Me_2S (1.10 mL, 2 M solution in toluene, 2.20 mmol, 1.10 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture is stirred and refluxed in an 80 ºC oil bath for 30 min, and the evolution of gas ceases. After cooling to rt (23 ºC), the clear solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C, anhydrous tetrahydrofuran (8 mL) is added followed by addition of quinidine (681 mg, 2.10 mmol, 1.05 equiv). The reflux condenser is reconnected and the mixture is stirred and refluxed in an 80 ºC oil bath for overnight (12 h). The flask containing reaction mixture is cooled to rt then to –20 ºC for 30 min before the solid is collected by suction filtration, washed with ice-cold anhydrous tetrahydrofuran (8 mL).

The solid is transferred to a 100 mL round-bottomed flask and EtOAc (10 mL) is added followed by addition of aq. HCl (10 mL, 2M) and an egg-shaped stirring bar (30 mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with EtOAc (15 mL×2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue is dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of CH_2Cl_2 and hexanes (1:2) to afford (*R*)-5,5'-Br_2VANOL (*S*)-**II-46c** as a white solid (386 mg, 0.648 mmol, 32%). The optical purity of (*R*)-**II-46c** is determined to be

>99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 24.99 min for (*R*)-**II-46c** (major) and R_t = 27.43 min for (*S*)-**II-46c** (minor). $[\alpha]^{20}_D$ = –148.7 (*c* 1.0, CH_2Cl_2) on >99% ee (*S*)-**II-46c** (HPLC).

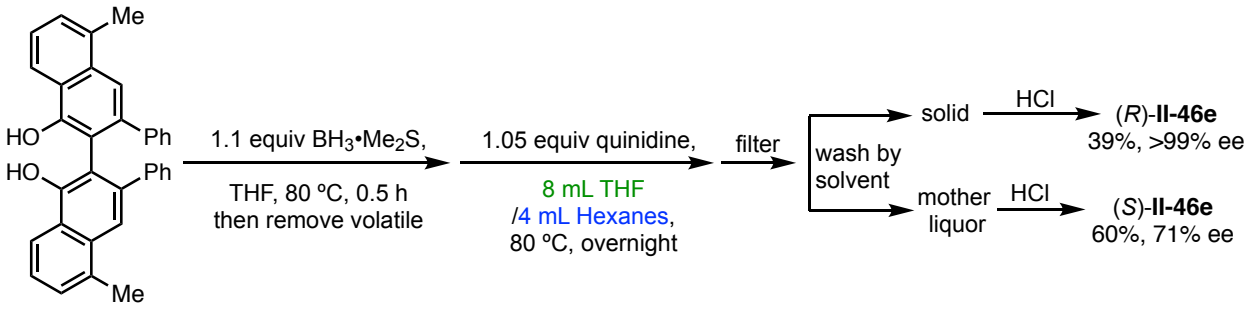
*(S)-5,5'-Br_2VANOL (R)-**II-46c***: The mother liquor is transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). CH_2Cl_2 (15 mL) is added followed by addition of aq. HCl (15 mL, 2 M) and an egg-shaped stirring bar (30 mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with CH_2Cl_2 (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of CH_2Cl_2 and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of CH_2Cl_2 and hexanes (1:2) to afford (*S*)-5,5'-Br_2VANOL (*S)*-**II-46c** as a white solid (775 mg, 1.30 mmol, 65%). The optical purity of (*S*)-**II-46c** is determined to be 84% *ee* by HPLC analysis.



rac-**II-46d**
2.0 mmol

*(R)-5,5'-Cl$_2$VANOL (S)-**II-46d***: VANOL derivative (±)-**II-46d** (1.015 g, 2.000 mmol) was resolved by the General Procedure **N** with 8 mL refluxing THF to afford (*R*)-5,5'-Cl$_2$VANOL (*R*)-**II-46d** as a white solid (416 mg, 0.820 mmol, 41%). The optical purity of (*S*)-**II-46d** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 21.73 min for (*R*)-**II-46d** (major) and R_t = 24.79 min for (*S*)-**II-46d** (minor). $[\alpha]^{20}_D$ = +178.3 (*c* 1.0, CH_2Cl_2) on >99% ee (*R*)-**II-46d** (HPLC).

*(S)-5,5'-Cl$_2$VANOL (S)-**II-46d***: VANOL derivatives (*S*)-**II-46d** was obtained by following General Procedure **N**. Its optical purity is determined to be 84% *ee* by HPLC analysis.

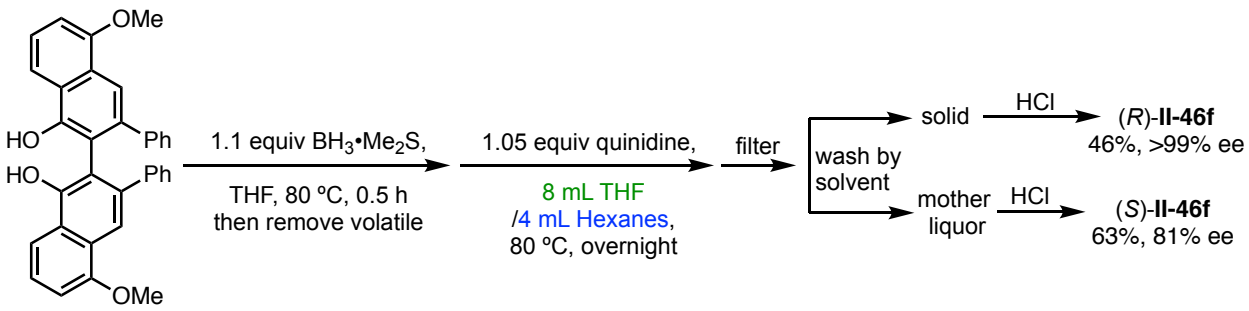


rac-**II-46e**
2.0 mmol

*(R)-5,5'-Me$_2$VANOL (R)-**II-46e***: VANOL derivative (±)-**II-46e** (933.2 mg, 2.000 mmol) was resolved by the General Procedure **N** refluxing with 8 mL THF and 4 mL

hexanes to afford (*R*)-5,5'-Me_2VANOL (*R*)-**II-46e** as a white solid (364 mg, 0.781 mmol, 39%). The optical purity of (*R*)-**II-46e** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.28 min for (*R*)-**II-46e** (major) and R_t = 20.72 min for (*S*)-**II-46e** (minor). $[\alpha]^{20}_D$ = +105.2 (*c* 1.0, CH_2Cl_2) on >99% ee (*R*)-**II-46e** (HPLC).

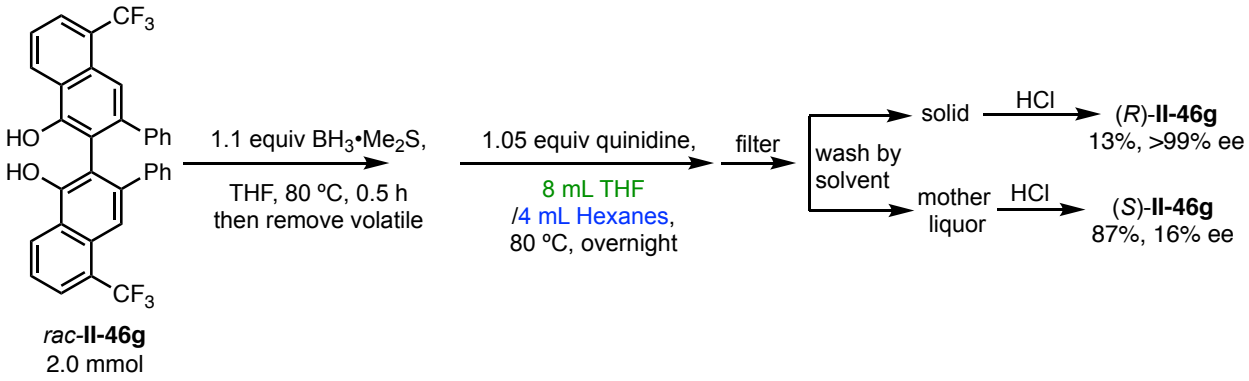
*(S)-5,5'-Me_2VANOL (S)-**II-46e***: VANOL derivatives (*R*)-**II-46e** was obtained by following General Procedure **N**. Its optical purity is determined to be 76% *ee* by HPLC analysis.



rac-**II-46f**
2.0 mmol

*(R)-5,5'-OMe_2VANOL (R)-**II-46f***: VANOL derivative (±)-**II-46f** (997.2 mg, 2.000 mmol) was resolved by the General Procedure **N** refluxing with 8 mL THF and 4 mL hexanes to afford (*R*)-5,5'-OMe_2VANOL (*R*)-**II-46f** as a white solid (463 mg, 0.928 mmol, 46%). The optical purity of (*S*)-**II-46f** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 32.05 min for (*R*)-**II-46f** (major) and R_t = 36.45 min for (*S*)-**II-46f** (minor). $[\alpha]^{20}_D$ ND.

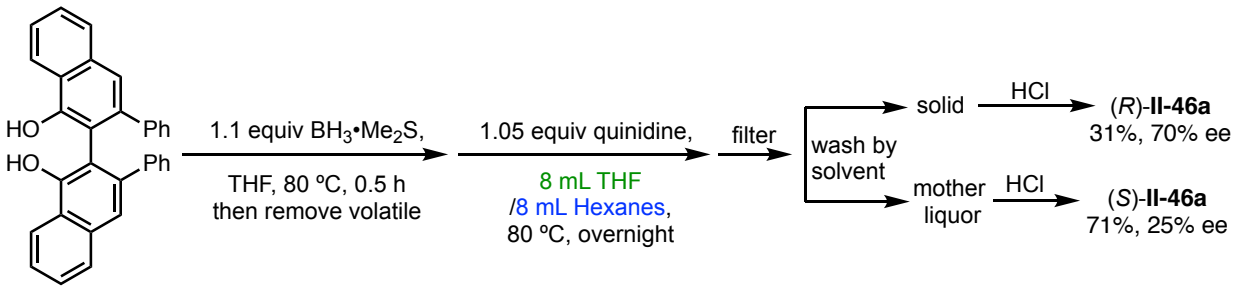
*(S)-5,5'-OMe$_2$VANOL (S)-**II-46f***: VANOL derivatives (*S*)-**II-46f** was obtained by following General Procedure **N**. Its optical purity is determined to be 81% *ee* by HPLC analysis.



rac-**II-46g**
2.0 mmol

*(R)-5,5'-(CF$_3$)$_2$VANOL (R)-**II-46g***: VANOL derivative (±)-**II-46g** (1.149 g, 2.000 mmol) was resolved by the General Procedure **N** refluxing with 8 mL THF and 4 mL hexanes to afford (*R*)-5,5'-(CF$_3$)$_2$VANOL (*R*)-**II-46g** as a white solid (0.152 g, 0.264 mmol, 13%). The optical purity of (*R*)-**II-46g** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 11.65 min for (*R*)-**II-46g** (major) and R_t = 12.93 min for (*S*)-**II-46g** (minor). $[\alpha]^{20}_D$ = +163.4 (*c* 1.0, CH_2Cl_2) on >99% ee (*R*)-**II-46g** (HPLC).

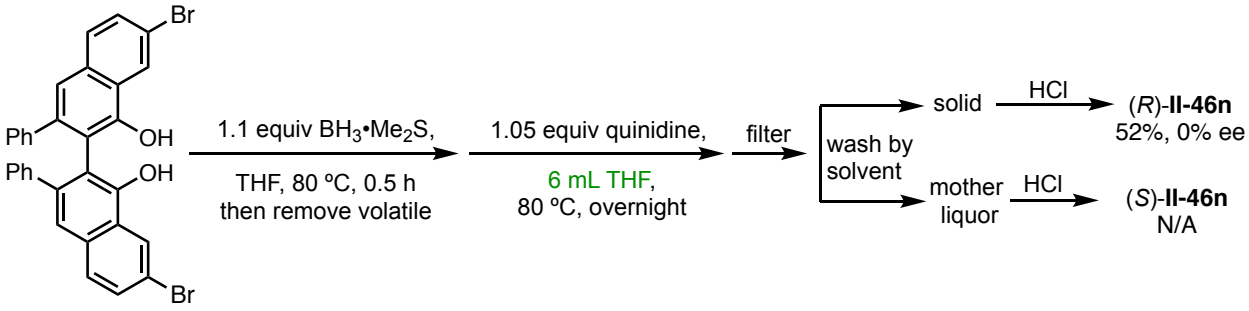
*(S)-5,5'--(CF$_3$)$_2$VANOL (R)-**II-46g***: VANOL derivatives (*S*)-**II-46g** was obtained by following General Procedure **N**. Its optical purity is determined to be 16% *ee* by HPLC analysis.



rac-**II-46a**
2.0 mmol

*(R)-VANOL (R)-**II-46a***: VANOL (±)-**II-46a** (877.0 mg, 2.000 mmol) was resolved by the General Procedure **N** refluxing with 8 mL THF and 8 mL hexanes to afford (*R*)-VANOL (*S*)-**II-46a** as a white solid (0.274 g, 0.624 mmol, 31%). The optical purity of (*R*)-**II-46a** is determined to be 70% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 16.93 min for (*R*)-**II-46a** (major) and R_t = 19.70 min for (*S*)-**II-46a** (minor). $[\alpha]^{20}_D$ ND.

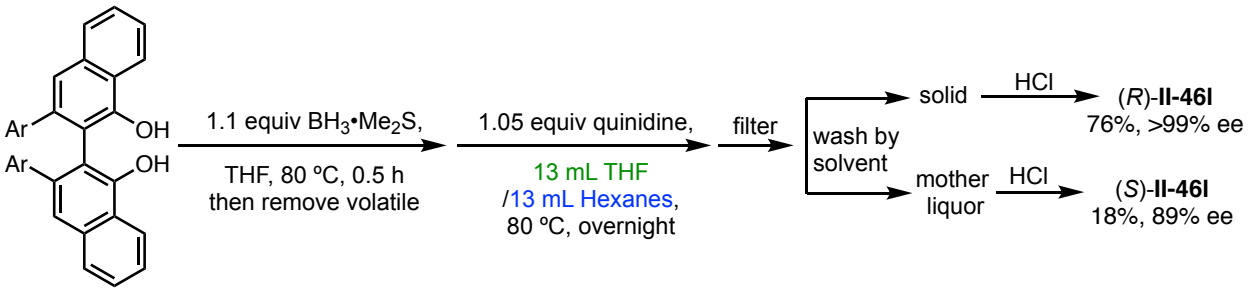
*(S)-VANOL (S)-**II-46a***: VANOL derivatives (*S*)-**II-46a** was obtained by following General Procedure **N**. Its optical purity is determined to be 25% *ee* by HPLC analysis.



rac-**II-46n**
2.0 mmol

*(S)-7,7'-Br_2VANOL (S)-**II-46n***: VANOL derivative (±)-**II-46n** (1.192 g, 2.000 mmol) was attempted to be resolved by the General Procedure **N** with 6 mL refluxing THF to afford (±)-7,7'-Br_2VANOL (±)-**II-46n** as a white solid (0.621 g, 1.042 mmol, 52%). The optical purity of (*S*)-**II-46n** is determined to be 0% *ee* by HPLC analysis. (Pirkle D-

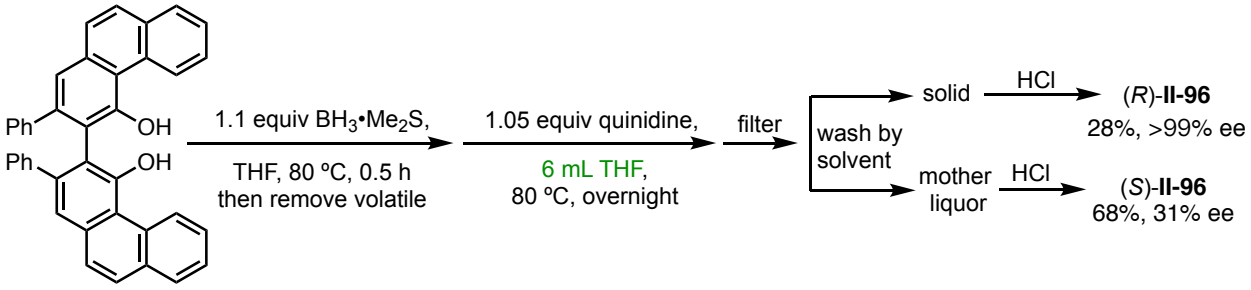
Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 26.90 min for (*R*)-**II-46n** and R_t = 31.17 min for (*S*)-**II-46n**



(R)-**II-46l**, 79% ee,
Ar = *p*-$MeOC_6H_4$
4.17 mmol

*(R)-3,3'-pOMePh₂VANOL (R)-**II-46l***: VANOL derivative (*R*)-**II-46l** (2.079 g, 4.170 mmol, 79% ee) was resolved by the General Procedure **N** refluxing with 13 mL THF and 13 mL hexanes to afford (*R*)-3,3'-*p*$OMePh_2$VANOL (*S*)-**II-46l** as a white solid (1.585 g, 3.178 mmol, 76%). The optical purity of (*S*)-**II-46l** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 6.31 min for (*R*)-**II-46l** (major) and R_t = 7.02 min for (*S*)-**II-46l** (minor). $[\alpha]^{20}_D$ = +271.3 (*c* 1.0, CH_2Cl_2) on >99% ee (*R*)-**II-46l** (HPLC).

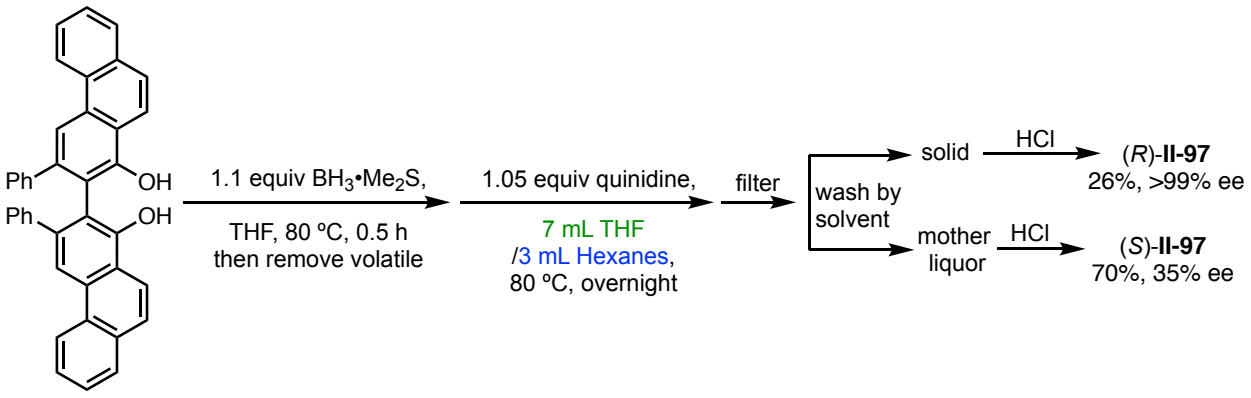
*(R)-3,3'-pOMePh₂VANOL (R)-**II-46l***: VANOL derivatives (*R*)-**II-46l** was obtained by following General Procedure **N**. Its optical purity is determined to be 89% *ee* by HPLC analysis.



rac-**II-96**
2.0 mmol

*(R)-VAPOL (R)-**II-96***: VAPOL (±)-**II-96** (1.077 g, 2.000 mmol) was resolved by the General Procedure **N** with 6 mL refluxing THF to afford (*R*)-VAPOL (*R*)-**II-96** as a white solid (302 mg, 0.560 mmol, 28%). The optical purity of (*R*)-**II-96** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 14.69 min for (*R*)-**II-96** (major) and R_t = 21.96 min for (*S*)-**II-96** (minor). $[\alpha]^{20}_D$ ND.

*(S)-VAPOL (S)-**II-96***: VANOL derivatives (*S*)-**II-96** was obtained by following General Procedure **N**. Its optical purity is determined to be 31% *ee* by HPLC analysis.

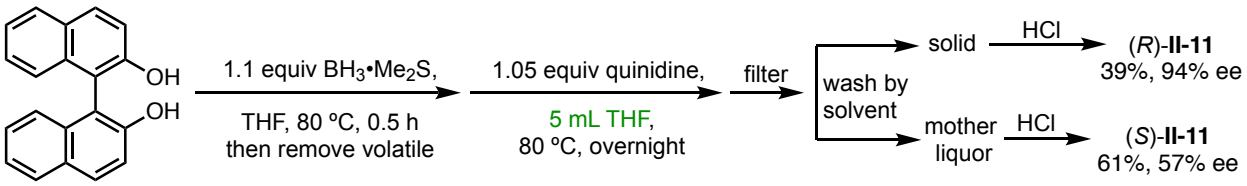


rac-**II-97**
2.0 mmol

*(R)-isoVAPOL (R)-**II-97***: *iso*VAPOL (±)-**II-97** (1.077 g, 2.000 mmol) was resolved by the General Procedure **N** refluxing with 7 mL THF and 3 mL hexanes to afford (*R*)-*iso*VAPOL (*R*)-**II-97** as a white solid (284 mg, 0.528 mmol, 26%). The optical purity of (*R*)-

II-97 is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 17.69 min for (*R*)-**II-97** (major) and R_t = 21.68 min for (*S*)-**II-97** (minor). $[\alpha]^{20}_D$ ND.

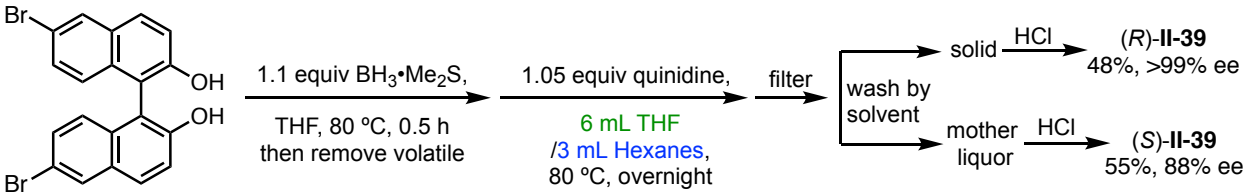
*(S)-isoVAPOL (S)-**II-97***: VANOL derivatives (*S*)-**II-97** was obtained by following General Procedure **N**. Its optical purity is determined to be 35% *ee* by HPLC analysis.



rac-**II-11**
2.0 mmol

*(R)-BINOL (R)-**II-11***: BINOL (±)-**II-11** (572.7 g, 2.000 mmol) was resolved by the General Procedure **N** with 5 mL refluxing THF to afford (*R*)-BINOL (*R*)-**II-11** as a white solid (225 mg, 0.786 mmol, 39%). The optical purity of (*S*)-**II-11** is determined to be 94% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 3.70 min for (*R*)-**II-11** (major) and R_t = 3.12 min for (*S*)-**II-11** (minor). $[\alpha]^{20}_D$ = –6.0 (*c* 1.0, CH_2Cl_2) on 94% ee (*R*)-**II-11** (HPLC).

*(S)-BINOL (S)-**II-11***: VANOL derivatives (*S*)-**II-11** was obtained by following General Procedure **N**. Its optical purity is determined to be 57% *ee* by HPLC analysis.



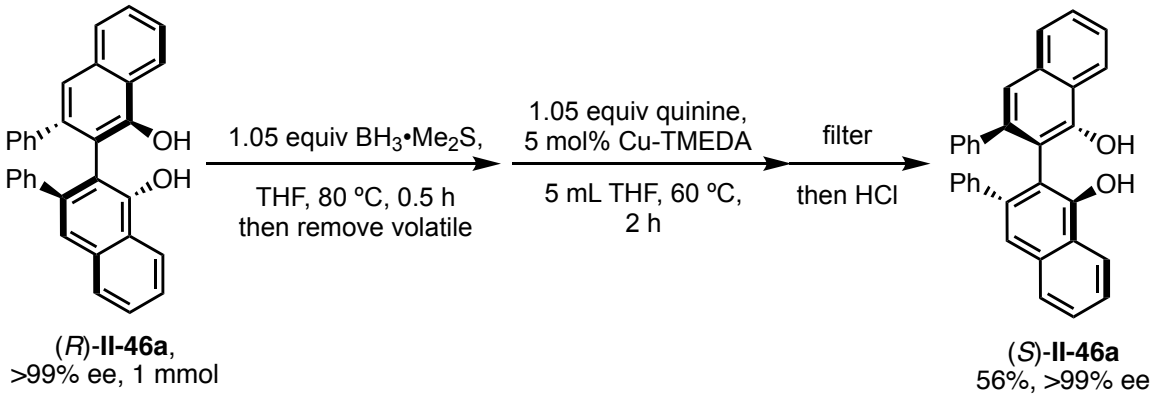
rac-**II-39**
2.0 mmol

*(R)-6,6'-Br_2BINOL (R)-**II-39***: BINOL (±)-**II-39** (888.2 mg, 2.000 mmol) was resolved by the General Procedure **N** refluxing with 6 mL THF and 3 mL hexanes to afford

(*R*)-BINOL (*R*)-**II-39** as a white solid (427 mg, 0.962 mmol, 48%). The optical purity of (*R*)-**II-39** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 75:25 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 2.832 min for (*R*)-**II-39** (major) and R_t = 3.31 min for (*S*)-**II-39** (minor). $[\alpha]^{20}_D$ = +129.6 (*c* 1.0, CH_2Cl_2) on >99% ee (*R*)-**II-39** (HPLC).

*(S)-BINOL (S)-**II-39***: VANOL derivatives (*S*)-**II-39** was obtained by following General Procedure **N**. Its optical purity is determined to be 88% *ee* by HPLC analysis.

4.3.11 Crystallization-induced dynamic resolution of VANOL (*Table 2.7*)



(*R*)-**II-46a**,
>99% ee, 1 mmol

(*S*)-**II-46a**
56%, >99% ee

*(S)-VANOL (S)-**II-46a***: An oven-dried 100 mL round-bottomed flask equipped with an egg-shaped stirring bar (30 mm × 15 mm) is placed under an N_2 atmosphere through a gas inlet. After cooling to 23 °C, (*R*)-VANOL (438 mg, 1.00 mmol) is added followed by addition of anhydrous tetrahydrofuran (5 mL) and BH_3•Me_2S (0.550 mL, 2 M solution in toluene, 1.10 mmol, 1.10 equiv). An oven-dried reflux condenser with an outlet connected to a bubbler is attached to the flask. The mixture is stirred and refluxed in an 80 ºC oil bath for 30 min, and the evolution of gas ceases. After cooling to rt (23 ºC), the clear solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg) and the residue is dried under high vacuum (60 °C, 0.2 mmHg) for 30 min. After cooling to 23 °C,

anhydrous tetrahydrofuran (5 mL) is added followed by addition of quinine (681 mg, 2.10 mmol, 1.05 equiv) and Cu-TMEDA (11.6 mg, 0.0500 mmol). The reflux condenser is reconnected and the mixture is stirred and refluxed in an 80 ºC oil bath for 2 h. The flask containing reaction mixture is cooled to rt then to –20 ºC for 30 min before the solid is collected by suction filtration, washed with ice-cold anhydrous tetrahydrofuran (5 mL).

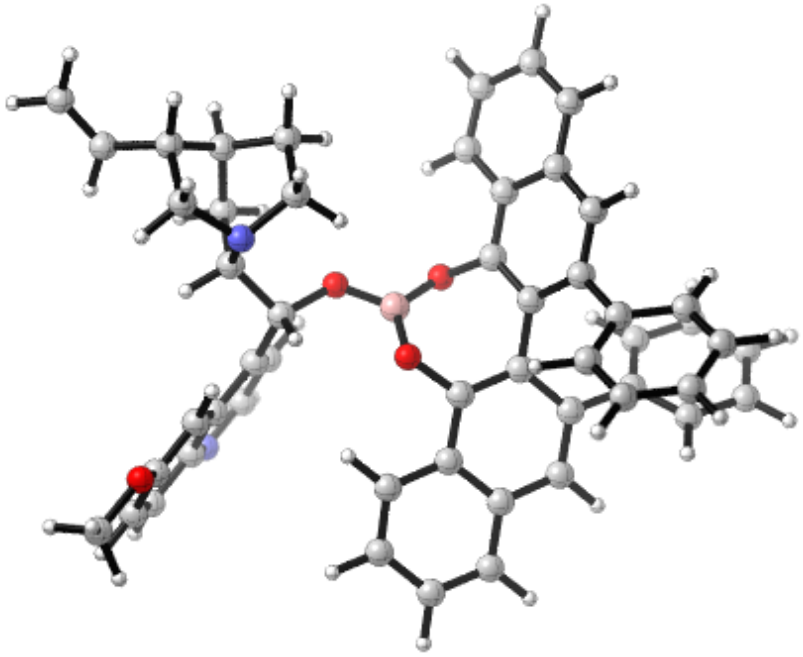
The solid is transferred to a 100 mL round-bottomed flask and EtOAc (10 mL) is added followed by addition of aq. HCl (5 mL, 2 M) and an egg-shaped stirring bar (30 mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with EtOAc (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The water layer containing chloride salt of protonated quinine is transferred to a clean container for recovery. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue is dissolved in a minimum amount of DCM and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of DCM and hexanes (1:2) to afford (*S*)-VANOL (*S*)-**II-46a** as a white solid (246 mg, 0.561 mmol, 56%). The optical purity of (*S*)-**II-46a** is determined to be >99% *ee* by HPLC analysis. (Pirkle D-Phenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 16.93 min for (*R*)-**II-46a** (minor) and R_t = 19.70 min for (*S*)-**II-46a** (major).

The mother liquor is transferred to a 100 mL round-bottomed flask and concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). DCM (15 mL) is added followed by addition of aq. HCl (15 mL, 2 M) and an egg-shaped stirring bar (30

mm × 15 mm). The mixture was stirred for 30 min at rt before the organic layer is isolated in a 60 mL separatory funnel. The water layer is extracted twice with DCM (15 mL × 2), and the combined organic layer is washed with brine (10 mL), dried over $MgSO_4$ and filtered. The organic solution is concentrated in vacuo using a rotary evaporator (40 °C, 15 mmHg). The residue was dissolved in a minimum amount of DCM and loaded onto a silica gel column wet loaded with hexanes. The column is eluted with a mixture of DCM and hexanes (1:2) to afford (*S*)-VANOL (*S*)-**II-46a** as a white solid (159 mg, 0.364 mmol, 36%). The optical purity of (*S*)-**II-46a** is determined to be 21% *ee* by HPLC analysis.

4.3.12 Computational Model of VANOL borates with quinine/quinidine

(*R*)-VANOL-quinine-borate complex at the B3LYP/6-31G(d) level[8]



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C	2.667002	0.659543	-0.048817	C	3.525679	-1.693968	-0.604134
C	3.949871	2.533096	0.837427	C	0.928362	-2.749944	-0.100023
C	1.875335	1.569656	-0.731144	C	3.300362	-3.056389	-0.624473
C	3.695592	1.174461	0.823345	H	4.108770	-3.721007	-0.915965
C	1.179457	-1.347277	-0.090998	H	4.706549	2.921465	1.513232
C	1.810162	-5.024100	-0.348128				

H	2.652308	-5.684309	-0.541092
C	-0.357466	-3.305591	0.130284
H	-1.195820	-2.645002	0.315147
H	-1.525538	-5.084850	0.305318
C	-0.536818	-4.671603	0.126633
H	0.397770	-6.614713	-0.119055
C	0.554841	-5.539429	-0.114873
C	1.344518	3.886690	-1.487701
H	0.523265	3.504640	-2.083602
C	3.488343	4.847850	0.052492
H	4.315414	5.216515	0.654486
H	1.045106	5.927417	-2.052052
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H	8.182503	-1.913345	-0.699760
C	7.285310	-1.429786	-1.077612
C	4.974071	-0.191636	-2.020754
H	4.077121	0.280329	-2.408743
C	6.222325	0.197493	-2.504946
H	6.285368	0.978844	-3.257854
H	8.356213	-0.116135	-2.414731
C	7.383721	-0.419390	-2.035832
C	4.436504	0.317229	1.791924
C	5.820333	0.478316	1.972281
H	6.362128	1.164503	1.327942
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H	2.689944	-0.730014	2.505723
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C	-3.873398	2.553377	-0.891314
C	-4.616140	2.658947	1.930679
C	-4.931468	3.895603	1.007682
H	-2.301928	-0.174168	0.635536
H	-2.321663	0.165982	-3.000938
H	-3.353934	-1.488444	-4.544962
H	-4.018122	-1.262318	1.367000
H	-6.379860	-4.687419	0.318291
H	-5.819235	-4.365687	-2.070442
H	-6.360430	-3.980279	3.872185
H	-7.312306	-4.040568	2.364236
H	-5.883050	-5.099504	2.567517
H	-4.613312	0.842503	0.232116
H	-2.162493	3.201756	2.555462
H	-1.359890	2.296364	1.283386
H	-2.417052	5.006494	1.071952
H	-1.692704	4.058373	-0.226682
H	-4.048943	4.720176	-0.807747
H	-4.812265	2.424438	-1.440571
H	-3.066666	2.562403	-1.629968
H	-5.459550	1.958382	1.937838
H	-4.461090	2.983890	2.965470
H	-4.792444	4.819741	1.584465
C	-6.346199	3.884370	0.498843
H	-6.653742	2.994163	-0.053417
C	-7.237044	4.860239	0.685278
H	-8.250180	4.794319	0.297389
H	-6.986172	5.765391	1.235498
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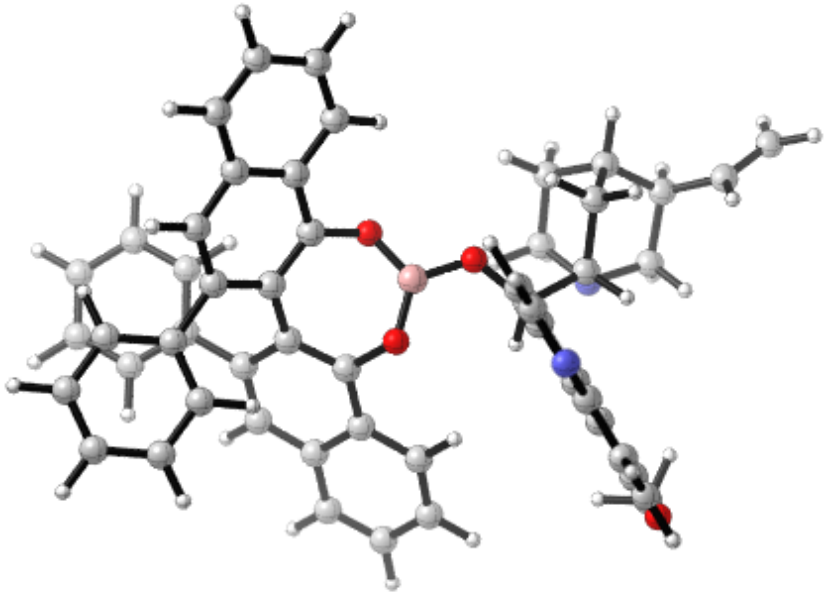
(*S*)-VANOL-quinine-borate complex at the B3LYP/6-31G(d) level



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C	-3.747432	4.230749	2.419429
H	-4.675985	4.259300	2.984411
C	-1.342487	4.139415	0.970787
H	-0.417301	4.096649	0.407100
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H	-6.926818	-3.587480	2.285271
C	-6.309883	-2.729212	2.032294
C	-4.586983	-0.328947	-1.875438
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H	-5.717759	2.728487	-2.889548
C	-5.746307	1.672104	-2.635466
H	-7.844483	1.450521	-3.091574

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C	3.649147	-1.321095	1.839523	H	4.250966	-3.888605	-1.406943
C	2.445260	0.610180	2.630756	H	5.771485	-2.950725	-1.366309
C	2.700181	0.173838	3.951588	H	4.795896	0.421413	-0.047291
C	3.840246	-1.669343	3.214681	H	3.230917	1.368729	-3.740151
C	4.189412	-2.166283	0.827248	H	2.058130	1.187085	-2.444571
C	4.882692	-3.311648	1.173214	H	3.310750	3.669999	-3.260102
C	5.066534	-3.659294	2.539577	H	2.276061	3.439177	-1.847637
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O	5.438072	-4.183779	0.286728	H	4.942073	2.624845	0.608611
C	5.305177	-3.908024	-1.100047	H	3.219507	2.888032	0.357398
C	3.953977	0.980955	-0.467186	H	6.130398	0.579438	-1.800540
N	4.051703	0.757676	-1.929815	H	5.514205	0.910758	-3.418379
O	1.573605	1.216955	0.031626	H	5.709648	3.206722	-3.121408
C	3.058140	1.559563	-2.674996	C	6.944770	2.976939	-1.421065
C	3.183011	3.077818	-2.345401	H	7.057234	2.503173	-0.443855
C	4.396730	3.266885	-1.413949	C	7.946251	3.724714	-1.888404
C	4.125405	2.490159	-0.108819	H	8.860374	3.878733	-1.321132
C	5.397377	1.172657	-2.360701	H	7.889692	4.213569	-2.859355
C	5.653619	2.710069	-2.143525	B	0.280013	0.807761	-0.032479
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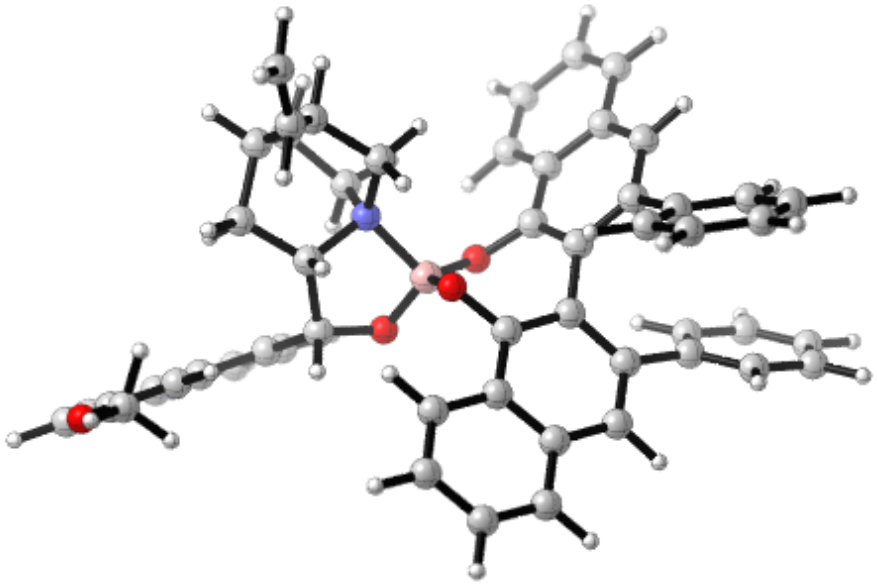
(*R*)-VANOL-quinine-cyclicborate complex at the B3LYP/6-31G(d) level



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H	-4.552679	1.594142	0.555386
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H	-0.113096	2.437022	1.919104
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H	-2.666117	1.089848	6.166497
H	-2.159761	2.794617	5.659724
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C	1.577684	-3.706289	-0.427181
C	2.216421	-0.938756	-0.304065
C	2.797478	-3.213738	-0.952050
C	0.970858	-1.393805	0.107024
C	3.128075	-1.871748	-0.915529

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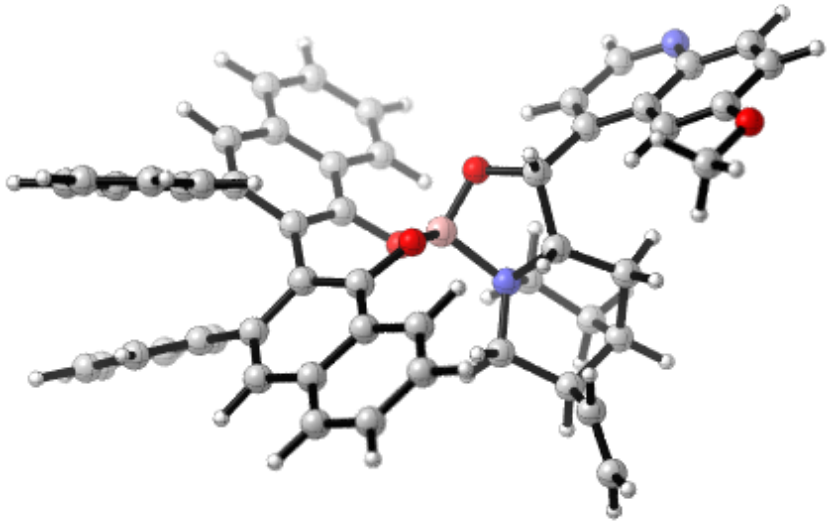
C	1.870988	5.160009	-1.384007	H	3.466194	0.166815	-2.700507
H	3.422692	6.554310	-0.783470	C	6.735006	-1.822176	-2.106767
C	3.080347	5.523542	-0.744902	H	7.650026	-2.383288	-1.934265
C	-0.605917	-3.264220	0.603369	H	5.515868	0.770869	-3.935573
H	-1.311639	-2.553197	1.018334	C	5.540501	-0.048981	-3.222282
C	1.249130	-5.088350	-0.437983	H	7.623066	-0.502612	-3.566520
H	1.971329	-5.791811	-0.845783	C	6.721706	-0.765497	-3.018826
H	-1.834999	-4.974394	0.986572	O	0.502128	1.217336	-1.096416
C	-0.889840	-4.612453	0.589844	O	0.052153	-0.503552	0.590350
H	-0.191058	-6.594815	0.047867	B	-0.475939	0.467189	-0.361559
C	0.044853	-5.533982	0.059424	H	-2.817072	-1.304846	-0.384917
C	4.587217	-0.082272	1.397166	H	-2.672726	1.201713	-2.918962
C	5.990106	-0.062687	1.329487				

(*S*)-VANOL-quinine-cyclicborate complex at the B3LYP/6-31G(d) level



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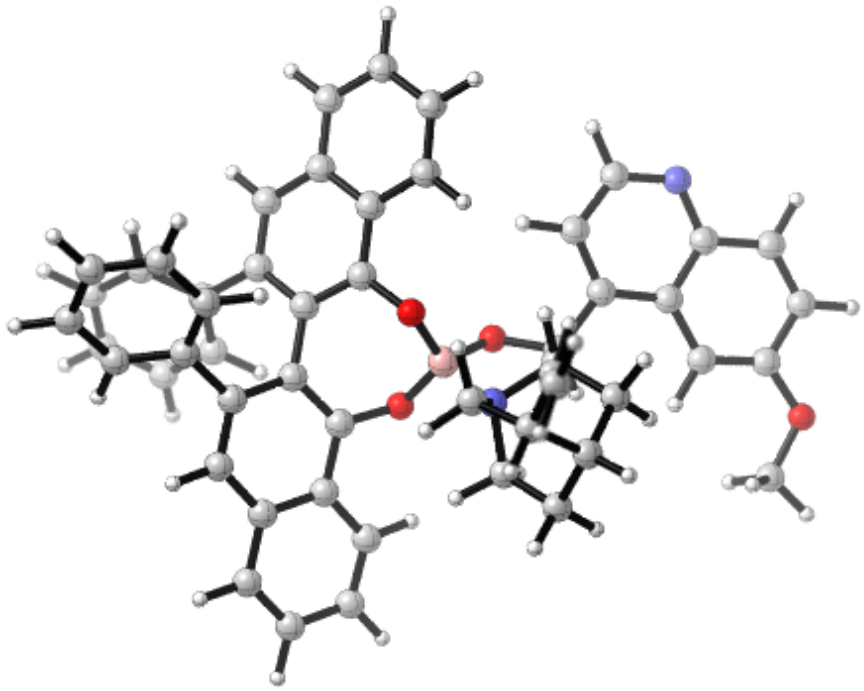
C	-2.623323	3.688742	0.140867
C	-2.439355	0.848515	0.151299
C	-3.505723	2.900703	0.919975
C	-1.503777	1.617088	-0.526525
C	-3.428440	1.520848	0.957085
C	-1.212455	-1.325574	0.303179
C	-2.393722	-0.639011	0.023993
C	-2.398711	-3.480510	0.214003
C	-3.561126	-1.401721	-0.344396
C	-1.203858	-2.746563	0.483408
C	-3.540029	-2.780020	-0.245105
H	-4.410646	-3.350333	-0.556324
H	-4.234161	3.407034	1.547291
C	-2.389207	-4.890729	0.384527
H	-3.297842	-5.446549	0.165007
C	-0.058926	-3.444315	0.951872
H	0.827117	-2.872475	1.205955
C	-0.087674	-4.811858	1.125692
H	-1.272598	-6.623253	0.961843
C	-1.261374	-5.544695	0.828893
C	-0.660748	3.822807	-1.330682
H	0.126039	3.316701	-1.878419
C	-2.713703	5.105311	0.087021
H	-3.507951	5.598482	0.642642
C	-0.781855	5.194908	-1.370216
H	-1.899507	6.926074	-0.687903
C	-1.816608	5.842930	-0.653013
C	-4.777599	-0.768125	-0.929837
C	-6.059793	-1.179629	-0.530001
H	-6.156758	-1.893197	0.282914
H	-8.184119	-0.988298	-0.804147
C	-7.202546	-0.659894	-1.136452
C	-4.677428	0.184491	-1.957772
H	-3.696614	0.506476	-2.292725
C	-5.819712	0.705909	-2.563579
H	-5.717369	1.438035	-3.360534
H	-7.977676	0.693800	-2.628993
C	-7.087754	0.286160	-2.156429
C	-4.318643	0.802698	1.913851
C	-5.680913	1.132860	2.006130
H	-6.100500	1.848160	1.304685
C	-3.804903	-0.149627	2.809989
H	-2.751410	-0.406849	2.768528
C	-6.502150	0.533767	2.960420
H	-7.554907	0.800890	3.007751
H	-4.204251	-1.478895	4.451235
C	-4.625808	-0.749957	3.763775
H	-6.617032	-0.879755	4.588355
C	-5.978163	-0.411449	3.843994
O	-0.028998	-0.682507	0.498405
O	-0.488192	1.002237	-1.211980
C	2.670927	0.540340	0.478016
C	3.813655	1.542560	0.452884
N	5.906331	3.465541	0.384172

C	5.107476	1.210705	0.966158	H	5.309592	-2.170403	3.399594
C	3.616212	2.821986	-0.023918	H	5.778575	-2.852137	1.812200
C	4.689643	3.741525	-0.041476	H	0.994703	0.823824	-3.102449
C	6.120983	2.220260	0.893995	H	2.268018	1.493345	-2.089976
C	5.427988	-0.049640	1.547982	H	2.582481	-0.242177	-4.503988
C	6.700622	-0.294598	2.028845	H	3.807306	0.715487	-3.672897
C	7.710060	0.702515	1.937960	H	4.399858	-1.681681	-3.429456
C	7.422810	1.922793	1.386835	H	4.585893	-1.719001	-0.974240
O	7.106877	-1.456020	2.614878	H	4.650383	-0.038079	-1.476153
C	6.155975	-2.495096	2.780214	H	0.776787	-2.339879	-1.357240
C	2.740367	-0.640526	-0.581921	H	0.360782	-1.468979	-2.832567
N	1.562151	-0.393767	-1.494734	H	2.134348	-2.521681	-3.902128
C	1.924375	0.586498	-2.585005	C	2.797445	-3.658995	-2.247753
C	3.002461	-0.011444	-3.518065	H	2.949389	-3.676921	-1.167649
C	3.551827	-1.287250	-2.860892	C	2.963134	-4.787237	-2.938658
C	3.998800	-0.916266	-1.429832	H	3.254309	-5.716291	-2.456654
C	1.173551	-1.688434	-2.135648	H	2.808719	-4.826964	-4.015297
C	2.403426	-2.336352	-2.854981	B	0.490197	0.330382	-0.407341
H	2.629242	3.123411	-0.356624	O	1.437468	1.182637	0.262770
H	4.527518	4.747840	-0.426607	H	2.467447	-1.550497	-0.042801
H	4.661210	-0.809886	1.626986	H	-0.079801	5.786402	-1.952233
H	8.696557	0.467017	2.324707	H	0.791086	-5.331437	1.499120
H	8.173220	2.703718	1.316136	H	2.668103	0.066567	1.471047
H	6.683086	-3.307627	3.283093				

(*R*)-VANOL-quinidine-cyclicborate complex at the B3LYP/6-31G(d) level



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C	3.261236	2.492203	-0.506116
C	4.092378	3.632822	-0.527754
C	5.956575	2.368269	-0.929198
C	5.899299	-0.072268	-1.228407
C	7.259812	-0.070055	-1.470336
C	7.999861	1.142194	-1.425034
C	7.359821	2.323928	-1.165074
O	8.004587	-1.173303	-1.769264
C	7.345059	-2.422859	-1.877437
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C	1.734330	-2.667839	0.227382
C	2.751046	-3.473086	1.074906
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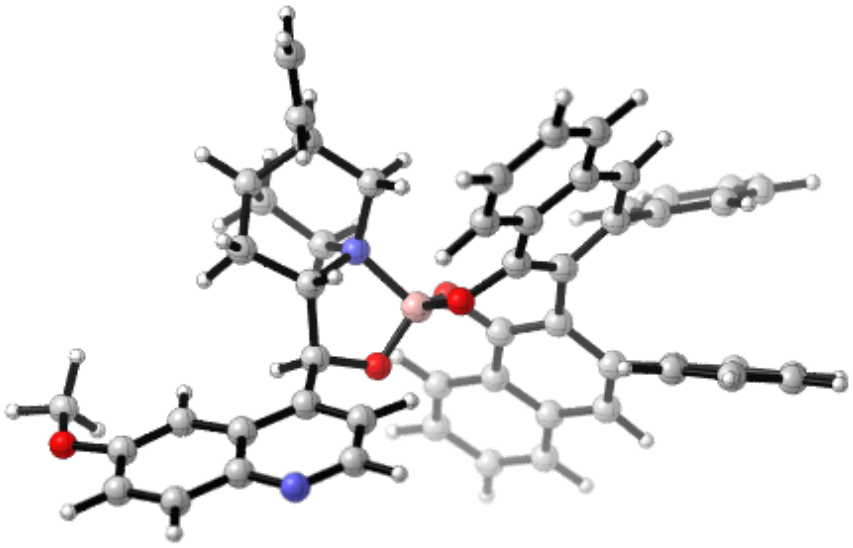
C	1.004315	-1.510893	2.238017
C	2.105384	-2.193362	3.116532
H	2.192930	2.601912	-0.364896
H	3.652497	4.618183	-0.378007
H	5.343982	-0.998778	-1.284500
H	9.067485	1.097836	-1.615758
H	7.896922	3.266707	-1.140855
H	8.116924	-3.148923	-2.138759
H	6.879611	-2.716364	-0.926278
H	6.578762	-2.406953	-2.663832
H	0.766747	-3.163846	0.166321
H	2.075018	-2.515042	-0.797241
H	2.271584	-4.359328	1.505891
H	3.572895	-3.830470	0.443772
H	4.059129	-3.091370	2.773922
H	4.442316	-0.695688	2.243204
H	4.641790	-1.632747	0.775447
H	0.723754	-0.529548	2.618293
H	0.093769	-2.112957	2.186983
H	1.701990	-3.133788	3.511884
C	2.502002	-1.337276	4.292310
H	2.830989	-0.321479	4.067317
C	2.468868	-1.735979	5.564264
H	2.768980	-1.080616	6.377097
H	2.136218	-2.734139	5.842818
O	1.579703	0.311663	-0.971394
H	3.303276	-0.780120	-1.218878
H	2.520698	0.362068	1.493416

C	-1.870770	-2.874935	-0.963719	H	-2.812635	-6.606510	-1.636156
C	-3.129660	-3.386912	-0.523934	C	-2.558884	-5.566474	-1.448689
C	-2.519827	-0.626002	-0.200225	C	-4.361417	1.293745	-1.691603
C	-4.016758	-2.521661	0.160684	C	-5.639509	1.860221	-1.554405
C	-1.561034	-1.500361	-0.706027	H	-5.820045	2.570232	-0.752588
C	-3.745858	-1.176346	0.324010	H	-7.662488	1.947597	-2.279425
C	-1.127481	1.367482	0.327003	C	-6.680223	1.500295	-2.409674
C	-2.282573	0.847021	-0.241914	C	-4.158873	0.352994	-2.715433
C	-1.954272	3.657025	0.031811	H	-3.174368	-0.082615	-2.852425
C	-3.232188	1.755371	-0.834446	C	-5.199545	-0.008480	-3.569928
C	-0.954764	2.769576	0.535738	H	-5.017578	-0.733247	-4.359341
C	-3.051183	3.117199	-0.683212	H	-7.275264	0.280685	-4.088798
H	-3.749707	3.801807	-1.156198	C	-6.464999	0.563014	-3.421491
H	-4.924312	-2.938244	0.588460	C	-4.704696	-0.369851	1.133111
C	-1.794767	5.053476	0.237164	C	-6.089252	-0.491820	0.929636
H	-2.550236	5.727231	-0.160328	H	-6.451173	-1.104073	0.108905
C	0.145123	3.305311	1.254406	C	-4.258433	0.456886	2.177798
H	0.882258	2.621815	1.660082	H	-3.193485	0.555095	2.362047
H	1.104439	5.061873	2.012613	C	-6.996970	0.186843	1.741888
C	0.261853	4.664800	1.452413	H	-8.063619	0.082857	1.559636
H	-0.608175	6.619357	1.085970	H	-4.796522	1.766739	3.794981
C	-0.713327	5.548761	0.931403	C	-5.165263	1.136645	2.989621
C	-0.993584	-3.730390	-1.682653	H	-7.245131	1.535911	3.408918
H	-0.070090	-3.316205	-2.070953	C	-6.538877	1.004796	2.776016
C	-3.436481	-4.752546	-0.767253	O	-0.146036	0.528969	0.773054
H	-4.389016	-5.141694	-0.415009	O	-0.316942	-1.076874	-1.065816
H	-0.658223	-5.683978	-2.489123	B	0.538865	-0.314155	-0.194482
C	-1.331744	-5.045242	-1.923540				

(*S*)-VANOL-quinidine-cyclicborate complex at the B3LYP/6-31G(d) level



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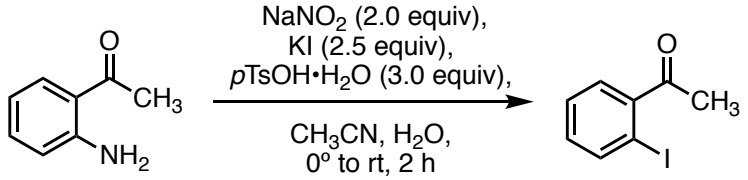
C	3.377640	-3.099518	0.512043
C	1.412880	-1.611895	-0.782931
C	3.340054	-1.729917	0.696929
C	1.197847	1.225040	0.363185
C	2.362168	0.544862	0.009186
C	2.440592	3.340959	0.540123
C	3.550578	1.314973	-0.265841
C	1.224633	2.612962	0.715326
C	3.564648	2.671166	-0.001015
H	4.450428	3.252244	-0.241626
H	4.093629	-3.690452	1.076511
C	2.468222	4.719482	0.881722
H	3.392566	5.273091	0.733668
C	0.095877	3.278876	1.263416
H	-0.808440	2.707475	1.443965
C	0.161361	4.613684	1.603261
H	1.395807	6.397890	1.665579
C	1.356037	5.344583	1.400897
C	0.494181	-3.697161	-1.797764
H	-0.286732	-3.115341	-2.273410
C	2.517475	-5.180126	-0.542201
H	3.299708	-5.751576	-0.047890
C	0.573716	-5.060302	-1.981195
H	1.644976	-6.884926	-1.496665
C	1.594556	-5.809453	-1.347612
C	4.747878	0.723815	-0.929426
C	6.043122	1.057083	-0.499692
H	6.164889	1.671184	0.387678
H	8.159717	0.848123	-0.817165
C	7.167670	0.582960	-1.173934
C	4.616246	-0.102702	-2.058106
H	3.625003	-0.361108	-2.416401
C	5.740217	-0.578456	-2.731802
H	5.613324	-1.212622	-3.605529
H	7.897203	-0.609663	-2.819065
C	7.021435	-0.237693	-2.293594
C	4.255063	-1.143570	1.718045
C	5.607427	-1.521064	1.764962
H	6.002091	-2.171453	0.989755
C	3.774394	-0.275918	2.713066
H	2.728789	0.014551	2.708029
C	6.451082	-1.048305	2.769439
H	7.495668	-1.349322	2.780123
H	4.221361	0.863487	4.479989
C	4.617657	0.198313	3.717030
H	6.616260	0.185137	4.533684
C	5.959942	-0.185044	3.750273
O	-0.005950	0.594724	0.472855
O	0.426320	-0.895920	-1.408415
C	-2.871791	-0.683543	-0.057031
C	-3.514921	-0.580848	1.321644
N	-4.584187	-0.246828	3.932150

C	-4.914658	-0.770243	1.546412
C	-2.717453	-0.267756	2.404864
C	-3.296150	-0.110665	3.682651
C	-5.390060	-0.579485	2.886701
C	-5.849038	-1.146752	0.536994
C	-7.185839	-1.313416	0.843309
C	-7.655740	-1.102091	2.167930
C	-6.777741	-0.748095	3.156664
O	-8.153108	-1.684001	-0.044836
C	-7.770280	-1.957287	-1.381528
C	-2.793170	0.703548	-0.758983
N	-1.546647	0.607894	-1.604438
C	-1.815943	-0.182072	-2.859197
C	-2.867187	0.538087	-3.739077
C	-3.435634	1.730836	-2.951826
C	-3.981262	1.196225	-1.609727
C	-1.117133	1.985915	-1.995143
C	-2.275412	2.741368	-2.727701
H	-1.647886	-0.149080	2.268686
H	-2.661962	0.141629	4.531910
H	-5.501228	-1.322479	-0.472136
H	-8.714413	-1.240461	2.363594
H	-7.107280	-0.591872	4.178891
H	-8.683216	-2.252673	-1.901710
H	-7.347347	-1.068064	-1.869205
H	-7.040915	-2.776748	-1.431563
H	-0.853819	-0.303112	-3.356483
H	-2.142523	-1.175233	-2.549421
H	-2.414808	0.885059	-4.675155
H	-3.671056	-0.155419	-4.011092
H	-4.236409	2.218525	-3.516656
H	-4.538743	1.966238	-1.068594
H	-4.687417	0.382457	-1.811426
H	-0.814428	2.507517	-1.087591
H	-0.232194	1.879360	-2.627401
H	-1.920180	3.047714	-3.719150
C	-2.702408	3.985099	-1.990230
H	-2.966382	3.861628	-0.939025
C	-2.771935	5.200006	-2.534770
H	-3.091877	6.065846	-1.962008
H	-2.505274	5.377388	-3.575000
B	-0.552445	-0.279437	-0.555375
O	-1.546362	-1.157204	0.010044
H	-3.457758	-1.375736	-0.679727
H	-2.545503	1.443163	0.006773
H	-0.152584	-5.567651	-2.610969
H	-0.705179	5.106781	2.035962

4.4 Experimental for Chapter Three

4.4.1 Synthesis of 2'-iodoacetophenone **III-28** (*Scheme 3.7*)



III-62
20 mmol
2.70 g

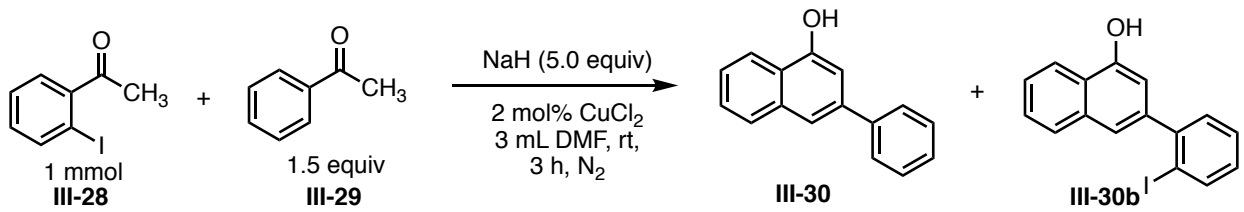
III-28
100%
4.92 g

*1-(tert-butyl)-2-iodobenzene **III-28**:* Acetophenone **III-28** was was prepared by the General Procedure **J** with 2-aminoacetophenone (2.43 mL, 20.0 mmol). The crude iodide was purified by flash chromatography (hexanes) to afford **II-28** as a as a yellow liquid (4.920 g, 20.00 mmol, 100%).

Spectral data for **III-28**: R_f = 0.53 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.10 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.39 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.44 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.71, 91.18, 128.23, 128.51, 131.98, 141.13, 144.20, 201.93. These spectral data match those previously reported for this compound.[16]

4.4.2 $CuCl_2$-catalyzed arylation/cycloaromatization reaction

entry 19 in *Table 3.4*



III-30/III-30b = 3.6:1

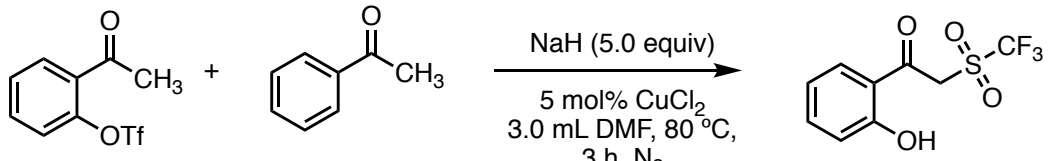
General Procedure **O** for $CuCl_2$-catalyzed arylation/cycloaromatization reaction with NaH -- illustrated for synthesis of 3-phenyl-1-naphthol **III-30** from o-iodoacetophenone **III-28** and acetophenone **III-29**:

*3-phenyl-1-naphthol **III-30***: To an oven-dried 25 mL round bottom flask was added NaH (200 mg, 60% in mineral oil, 5.00 mmol, 5.00 equiv), $CuCl_2$ (2.2 mg, 0.020 mmol, 2.0 mol%), DMF (3 mL) and acetophenone **III-29** (0.175 mL, 1.50 mmol, 1.50 equiv) was added in one portion at room temperature under N_2 atmosphere. After 1 min, to the reaction mixture was added iodoacetophenone **III-28** (0.143 mL, 1.00 mmol) portionwise in 5 min and then was kept stirring at rt for 3 h. After completion, the mixture was acidified with 2 M HCl (3 mL) at 0 ºC and then extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 5:1 to 3:1) to obtain a mixture of **III-30** and **III-30b** (202.9 mg) as a brown semi solid. Ratio of the **III-30** and **III-30b** was determined to be 3.6 :1 by ^{1}H NMR analysis of the proton signal of 8-position (8.27 ppm for **III-30** and 8.31 ppm for **III-30b**). Yield of the desired naphthol product the **III-30** was determined to be 65% by ^{1}H NMR analysis of

the crude reaction mixture by integration of the methylene protons (δ 3.94) relative to the internal standard (Ph_3CH).

Spectral data for **III-30**: R_f = 0.31 (hexanes/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 7.05 (td, *J* = 7.6, 2.0 Hz, 1H), 7.37 (ddd, *J* = 15.7, 7.5, 1.7 Hz, 3H), 7.52 (qd, *J* = 6.9, 3.3 Hz, 2H), 7.80 – 7.91 (m, 1H), 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.22 – 8.32 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.60, 110.59, 120.88, 121.81, 123.88, 125.60, 126.89, 128.02, 128.17, 128.93, 130.36, 134.38, 139.53, 141.90, 146.44, 151.07. These spectral data match those previously reported for this compound[17].

Scheme 3. 10

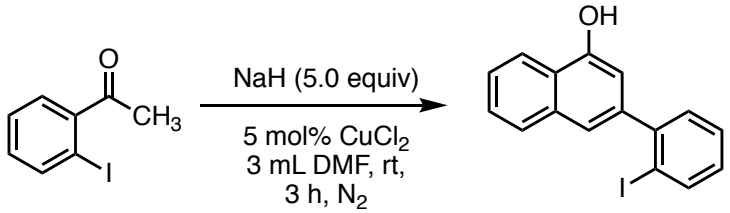


1 mmol **III-66** + 1.5 equiv **III-29** → 89% **III-67**

1-(2-hydroxyphenyl)-2-((trifluoromethyl)sulfonyl)ethan-1-one ***III-67***: Phenol **III-67** was obtained as a white solid (239 mg, 0.890 mmol) in 89% yield by following General Procedure **O** with 2-acetylphenyl trifluoromethanesulfonate **III-66** (268 mg, 1.00 mmol).

Spectral data for **III-30**: R_f = 0.38 (hexanes/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (s, 2H), 6.90 – 7.13 (m, 2H), 7.47 – 7.70 (m, 2H), 11.35 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.74, 118.78, 119.10, 119.94, δ 128.45 (d, *J* = 33.5 Hz), 130.72, 138.80, 163.37, 189.51. ^{19}F NMR (470 MHz, $CDCl_3$) δ -77.00. HRMS (ESI^-) *m/z* 266.9962 [calcd. for $C_9H_6O_4F_3S$ (M–H): 266.9939].

Scheme 3. 11



1 mmol
III-28

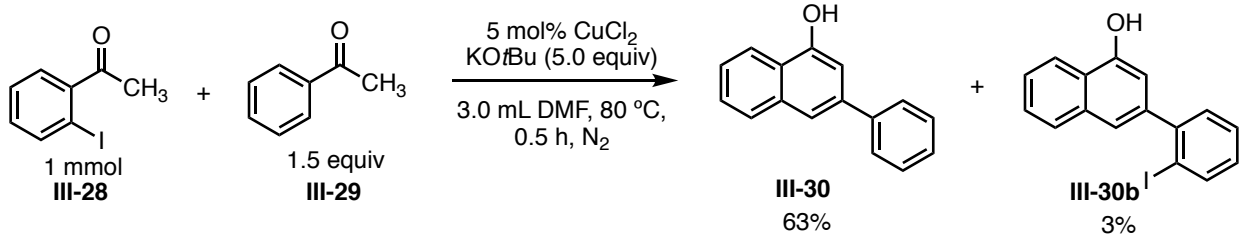
85% isolated yield
III-30b

3-(2-iodophenyl)-1-naphthol ***III-30b***: Naphthol **III-30b** was obtained as a yellow liquid (155 mg, 0.449 mmol) in 89% yield. by following General Procedure **O** without acetophenone with 5 mol% $CuCl_2$.

Spectral data for **III-30b**: R_f = 0.29 (hexanes/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 7.05 (td, *J* = 7.6, 2.0 Hz, 1H), 7.37 (ddd, *J* = 15.7, 7.5, 1.7 Hz, 3H), 7.52 (qd, *J* = 6.9, 3.3 Hz, 2H), 7.80 – 7.91 (m, 1H), 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.22 – 8.32 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.60, 110.59, 120.88, 121.81, 123.88, 125.60, 126.89, 128.02, 128.17, 128.93, 130.36, 134.38, 139.53, 141.90, 146.44, 151.07. These spectral data match those previously reported for this compound[18].

General procedure **P** for $CuCl_2$-catalyzed arylation/cycloaromatization reaction with K*t*OBu -- illustrated for o-iodoacetophenone **III-28** and acetophenone **III-29**:

entry 14 in *Table 3.6*



1 mmol
III-28

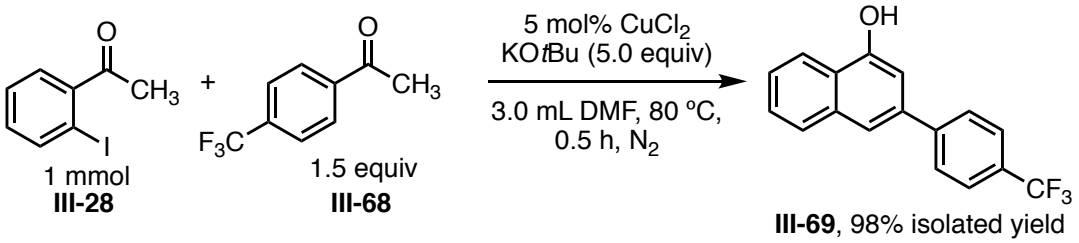
1.5 equiv
III-29

III-30
63%

III-30b
3%

3-phenyl-1-naphthol ***III-30***: To an oven-dried 25 mL round bottom flask was added KO*t*Bu (561 mg, 5.00 mmol, 5.00 equiv), $CuCl_2$ (5.4 mg, 0.050 mmol, 5.0 mol%), DMF (3

mL) and acetophenone **III-29** (0.175 mL, 1.50 mmol, 1.50 equiv) was added in one portion at room temperature under N_2 atmosphere and was heated in an 80 ºC oil bath. After 1 min, to the reaction mixture was added iodoacetophenone **III-28** (0.143 mL, 1.00 mmol) portionwise in 5 min and then was kept stirring at 80 ºC for 30 min. After completion, the mixture was acidified with 2 M HCl (3 mL) at 0 ºC and then extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 5:1 to 3:1) to obtain a mixture of **III-30** and **III-30b** (162.9 mg) as a brown semi solid. Ratio of the **III-30** and **III-30b** was determined to be 22.6 : 1 by ^{1}H NMR analysis of the proton signal of 8-position (8.27 ppm for **III-30** and 8.31 ppm for **III-30b**). Yield of the desired naphthol product the **III-30** was determined to be 63% by ^{1}H NMR analysis of the crude reaction mixture by integration of the methylene protons (δ 3.94) relative to the internal standard (Ph_3CH).

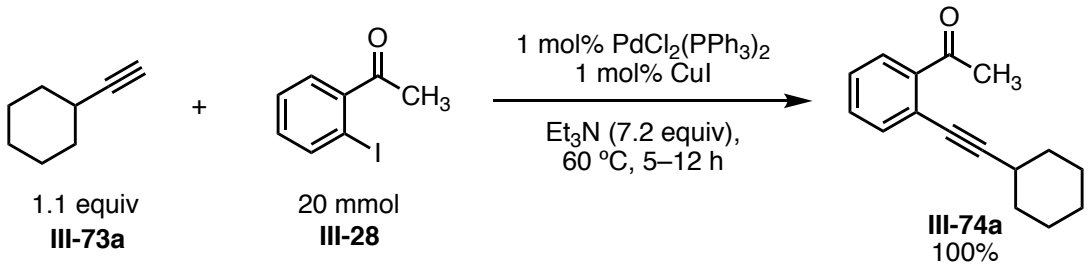


*3-(4-(trifluoromethyl)phenyl)-1-naphthol **III-69***: Naphthol **III-69** was obtained as a yellow solid (155 mg, 0.449 mmol) in 89% yield. by following General Procedure **P** without acetophenone with 5 mol% $CuCl_2$.

Spectral data for **III-30b**: R_f = 0.29 (hexanes/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (s, 1H), 7.03 (d, J = 1.6 Hz, 1H), 7.43 – 7.59 (m, 2H), 7.59 – 7.76 (m, 6H), 7.86 (dd, J = 7.5, 1.7 Hz, 1H), 8.16 – 8.29 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 108.05,

119.13, 121.66, 123.26, 124.09, 125.70 (q, J = 3.8 Hz), 125.89, 127.21, 127.47, 128.18, 128.77, 129.36 (q, J = 32.4 Hz), 134.87, 137.30, 144.33, 144.34, 152.15. ^{19}F NMR (470 MHz, $CDCl_3$) δ –62.29. These spectral data match those previously reported for this compound[16].

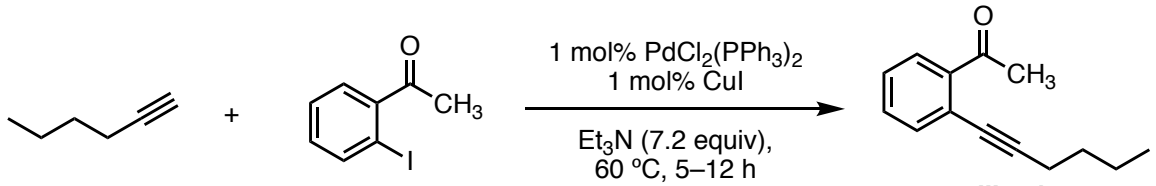
4.4.3 Syntheses of o-alkynylacetophenone **III-74** (*Scheme 3.14*)



*General Procedure **Q** for the Sonagashira reaction -- illustrated for o-iodoacetophenone **III-28** and ethynylcyclohexane **III-73a**:*

*o-(cyclohexylethynyl)acetophenone **III-74a***: To a flame-dried 500 mL round bottom flask was added $PdCl_2(PPh_3)_2$ (140 mg, 0.200 mmol), CuI (38.2 mg, freshly purified, 0.200 mmol), ethynylcyclohexane **III-73a** (3.17 mL, 22.0 mmol, 1.10 equiv), 2′-iodoacetophenone **III-28** (2.86 mL, 20.0 mmol) and triethylamine (40 mL, 7.2 equiv) at room temperature and the reaction mixture was heated to 60 °C under N_2 atmosphere. After 12 h, triethylamine was removed under reduced pressure. The residue was then diluted with DCM and water. The organic layer was separated and the aqueous layer was extracted DCM (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 40:1 to 20:1) to obtain **III-74a** (4.530 g, 20.00 mmol) as a yellow liquid in 100% isolated yield.

Spectral data for **II-74a**: R_f = 0.63 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (m, 3H), 1.55 (m, 3H), 1.74 (m, 2H), 1.78 – 1.95 (m, 2H), 2.63 (m, 1H), 2.68 – 2.77 (s, 3H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.94, 25.84, 29.98, 30.27, 32.36, 79.67, 100.83, 122.50, 127.51, 128.29, 131.04, 133.93, 141.04, 201.26. These spectral data match those previously reported for this compound[19].



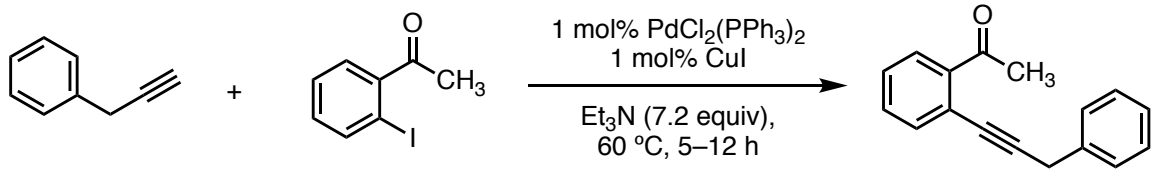
1.1 equiv
III-73b

20 mmol
III-28

III-74b
97%

*o-(butylethynyl)acetophenone **III-74a***: Acetophenone **III-74b** was prepared from 1-hexyne **III-73b** (2.60 mL, 22.0 mmol, 1.10 equiv) by the general procedure with a reaction time of 12 hours. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 40:1 to 20:1) to give **III-74b** as a yellow liquid in 97% isolated yield (3.884 g, 19.40 mmol).

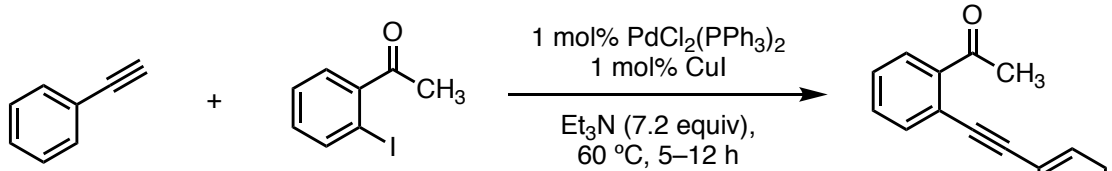
Spectral data for **II-74b**: R_f = 0.65 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.34 – 1.52 (m, 2H), 1.52 – 1.62 (m, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 7.30 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38 (td, *J* = 7.5, 1.5 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.64 (ddd, *J* = 7.7, 1.5, 0.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.62, 19.40, 22.09, 30.10, 30.51, 79.62, 96.87, 122.45, 127.51, 128.28, 131.05, 133.95, 141.01, 201.14. These spectral data match those previously reported for this compound[20].



1.1 equiv **III-73c** + 20 mmol **III-28** → **III-74c** 67%

*o-(benzylethynyl)acetophenone **III-74c***: Acetophenone **III-74c** was prepared from 3-phenyl-1-propyne (2.86 mL, 22.0 mmol, 1.20 equiv, prepared by a reported two step procedure[21] from benzylbromide and ethynyltrimethylsilane in 51% overall yield) by the general procedure with a reaction time of 12 hours. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 40:1 to 20:1) to give **III-74c** as a yellow liquid in 67% isolated yield (3.142 g, 13.40 mmol).

Spectral data for **II-74c**: R_f = 0.60 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63 (d, *J* = 27.6 Hz, 3H), 3.87 (s, 2H), 7.21 – 7.27 (m, 1H), 7.31 – 7.36 (m, 3H), 7.37 – 7.43 (m, 3H), 7.53 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.66 (ddd, *J* = 7.7, 1.4, 0.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.09, 30.01, 81.59, 93.73, 121.99, 126.77, 127.86, 127.99, 128.40, 128.63, 131.13, 134.12, 136.17, 140.99, 200.83. HRMS (ESI$^-$) *m/z* 233.0969 [calcd. for $C_{17}H_{13}O$ (M–H): 233.0966].

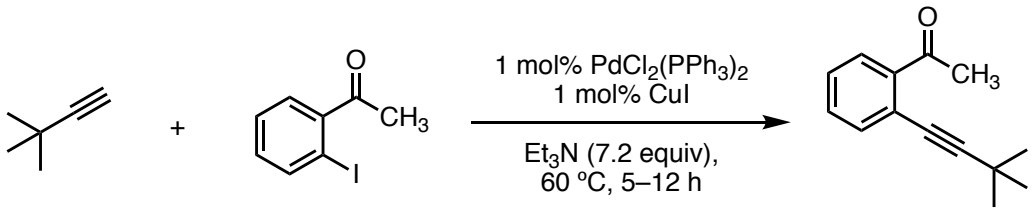


1.1 equiv **III-73d** + 20 mmol **III-28** → **III-74d** 92%

*o-(pheylethynyl)acetophenone **III-74d***: Acetophenone **III-74d** was prepared from phenylacetylene **III-73d** (2.42 mL, 22.0 mmol, 1.20 equiv) by the General Procedure **Q** with a reaction time of 12 hours. The crude product was purified by column

chromatography (silica gel, hexanes/EtOAc 19:1 to 9:1) to give **III-74d** as a yellow liquid in 92% isolated yield (4.053 mg, 18.40 mmol).

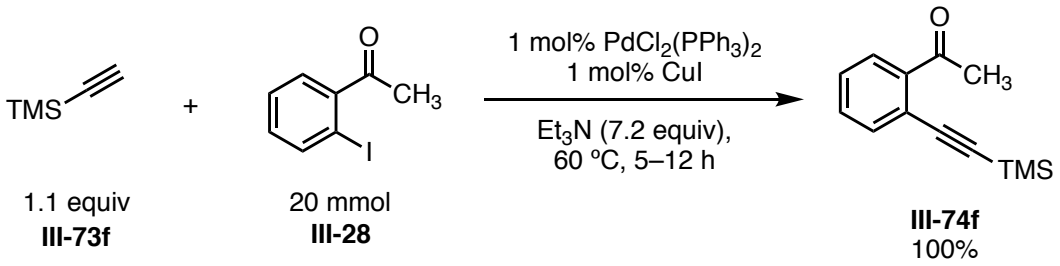
Spectral data for **II-74d**: R_f = 0.45 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.78 (s, 3H), 7.32 – 7.41 (m, 4H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.48 – 7.57 (m, 2H), 7.62 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.74 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.03, 88.46, 95.02, 121.69, 122.86, 128.28, 128.45, 128.70, 128.77, 131.31, 131.51, 133.88, 140.74, 200.40. These spectral data match those previously reported for this compound[20].



1.1 equiv **III-73e** + 20 mmol **III-28** → **III-74e** 97%

*o-(tButylethynyl)acetophenone **III-74e***: Acetophenone **III-74e** was prepared from 3,3-Dimethyl-1-butyne **III-73e** (2.71 mL, 22.0 mmol, 1.20 equiv) by the General Procedure **Q** with a reaction time of 12 hours. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 40:1 to 20:1) to give **III-74e** as a colorless liquid in 97% isolated yield (3.885 g, 18.40 mmol).

Spectral data for **II-74e**: R_f = 0.67 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.72 (s, 3H), 7.25 – 7.33 (m, 1H), 7.37 (td, *J* = 7.6, 1.5 Hz, 1H), 7.45 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.64 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.28, 30.30, 30.63, 78.46, 104.66, 122.41, 127.56, 128.30, 131.04, 133.81, 141.04, 201.30. These spectral data match those previously reported for this compound[22].



1.1 equiv
III-73f

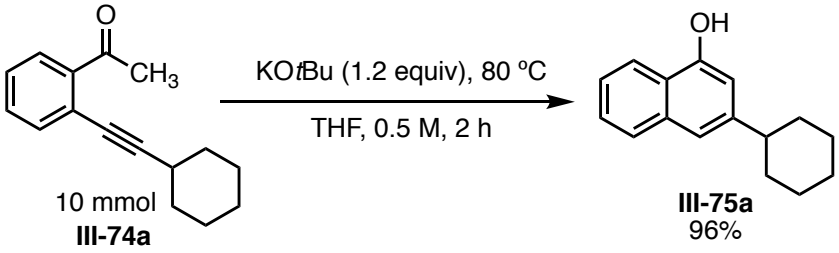
20 mmol
III-28

III-74f
100%

*o-(trimethylsilylethynyl)acetophenone **III-74f***: Acetophenone **III-74f** was prepared from ethynyltrimethylsilane **III-73f** (3.41 mL, 22.0 mmol, 1.20 equiv) by the General Procedure **Q** with a reaction time of 12 hours. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 40:1 to 20:1) to give **III-74f** as a colorless liquid in 100% isolated yield (4.330 g, 20.00 mmol);

Spectral data for **II-74f**: R_f = 0.70 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.24 (d, *J* = 1.0 Hz, 9H), 2.73 (d, *J* = 1.3 Hz, 3H), 7.33 – 7.44 (m, 2H), 7.50 – 7.56 (m, 1H), 7.62 – 7.70 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ -0.33, 30.18, 101.12, 103.83, 121.40, 128.41, 128.57, 131.10, 134.21, 141.51, 200.80. These spectral data match those previously reported for this compound[23].

4.4.4 Base-promoted cycloaromatization (*Scheme 3.15*)



10 mmol
III-74a

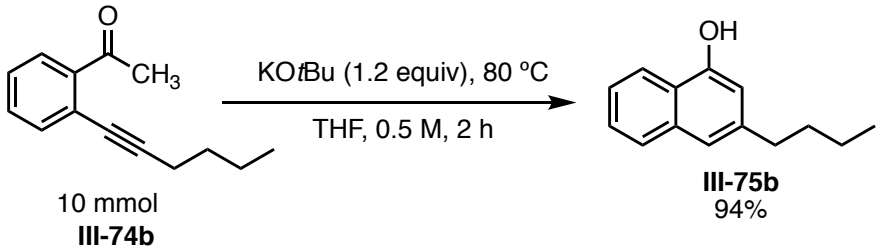
III-75a
96%

*General Procedure **R** for the KtOBu promoted cycloaromatization -- illustrated for the synthesis of 3-cyclohexyl-1-naphthol **III-75a**:*

*3-cyclohexyl-1-naphthol **III-75a***: To an oven-dried 100 mL round bottom flask was added K*t*OBu (1.347 g, 12.00 mmol, 1.200 equiv) and THF (20 mL). *o*-

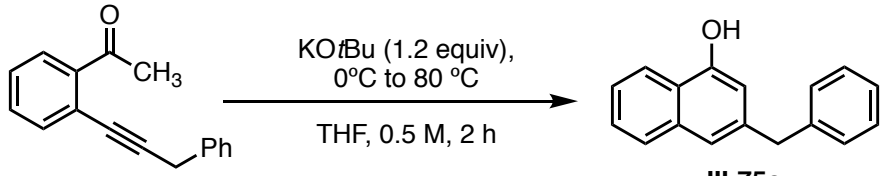
(cyclohexylethynyl)acetophenone **III-74a** (2.264 g, 10.00 mmol) was added in one portion at room temperature and the reaction mixture was heated to 80 °C under N_2 atmosphere. After 2 h, the reaction mixture was acidified with 1 M H_2SO_4 (50 mL) at 0 ºC and then extracted with EtOAc (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 20:1 to 10:1) to obtain **III-75a** (2.124 g, mp 100-101 ºC, 9.380 mmol) as a white solid in 94% isolated yield.

Spectral data for **III-75a**: R_f = 0.41 (hexanes/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 – 1.55 (m, 6H), 1.76 – 2.00 (m, 5H), 2.57 (tt, *J* = 11.5, 3.2 Hz, 1H), 6.31 (s, 1H), 6.69 (d, *J* = 1.4 Hz, 1H), 7.28 – 7.38 (m, 1H), 7.51 (dddd, *J* = 25.4, 8.1, 6.8, 1.3 Hz, 2H), 7.78 – 7.93 (m, 1H), 8.27 (dd, *J* = 8.4, 1.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.28, 27.01, 34.32, 44.74, 109.29, 117.62, 121.54, 123.29, 124.65, 126.52, 127.58, 135.03, 146.32, 151.14. HRMS (ESI^-) *m/z* 225.1296 [calcd. for $C_{16}H_{17}O$ (M–H): 225.1279].



3-butyl-1-naphthol ***III-75b***: Naphthol **III-75b** was prepared from *o*-(butylethynyl)acetophenone **III-74a** (2.003 g, 10.00 mmol) by the General Procedure **R**. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 40:1 to 9:1) to give **III-75b** as a yellow liquid in 94% isolated yield (1.889 g, 9.430 mmol).

Spectral data for **III-75b**: R_f = 0.45 (hexanes/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (td, *J* = 7.3, 1.1 Hz, 3H), 1.37 (qd, *J* = 7.5, 1.9 Hz, 2H), 1.65 (tt, *J* = 9.0, 6.8 Hz, 2H), 2.55 – 2.76 (m, 2H), 5.14 (s, 1H), 6.67 (d, *J* = 1.3 Hz, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 7.35 – 7.50 (m, 2H), 7.72 (dt, *J* = 7.6, 1.4 Hz, 1H), 8.02 – 8.13 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 13.99, 22.37, 33.33, 35.81, 110.08, 119.23, 121.28,122.77, 124.38, 126.42, 127.19, 134.82, 140.85, 151.10. HRMS (ESI$^-$) *m/z* 199.1129 [calcd. for $C_{14}H_{15}O$ (M–H): 199.1123].

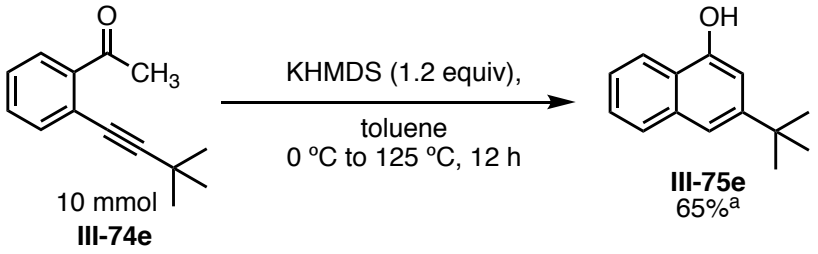


10 mmol
III-74c

III-75c
93%

3-benzyl-1-naphthol ***III-75c***: Naphthol **III-75c** was prepared from *o*-(benzylethynyl)acetophenone **III-74c** (2.003 g, 10.00 mmol) by the General Procedure **R**. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc 40:1 to 9:1) to give **III-75c** as a colorless liquid in 59% isolated yield (1.370 g, 5.850 mmol). The reaction with modification that the KO*t*Bu was added at 0 ºC and then slowly heated to 80 ºC gave **III-75b** (2.182 g, 9.310 mmol) in 93% yield.

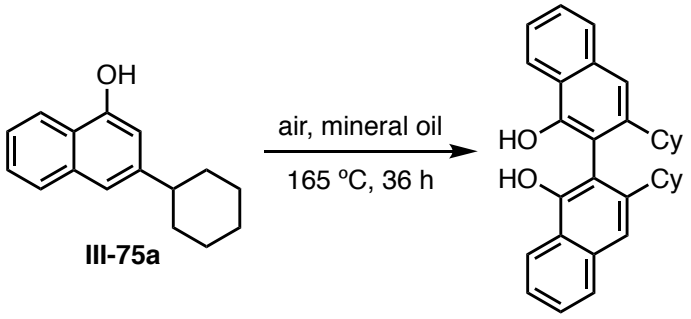
Spectral data for **III-75b**: R_f = 0.44 (hexanes/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (s, 2H), 5.29 (s, 1H), 6.59 (d, *J* = 1.4 Hz, 1H), 7.21 – 7.31 (m, 3H), 7.31 – 7.39 (m, 3H), 7.50 (dddd, *J* = 21.9, 8.2, 6.8, 1.4 Hz, 2H), 7.80 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 42.15, 110.30, 120.07, 121.56, 123.17, 124.86, 126.30, 126.72, 127.44, 128.57, 129.14, 134.87, 139.06, 140.90, 151.45. HRMS (ESI$^-$) *m/z* 233.0972 [calcd. for $C_{17}H_{13}O$ (M–H): 233.0966].



3-tert-butyl-1-naphthol ***III-75e***: To an oven-dried 100 mL round bottom flask equipped with a condenser was added *o*-(*tert*-butylethynyl)acetophenone **III-74e** (4.002 g, 20.00 mmol) and toluene (20 mL). The mixture was cooled to 0 ºC for 10 min. KHMDS (48 mL, 0.5 M in toluene, 1.2 equiv) was added in one portion. The resulting mixture was warmed to rt and then was heated in an oil bath at 125 ºC for 12 h. The reaction mixture was acidified with 1 M H_2SO_4 (100 mL) at 0 ºC and then extracted with EtOAc (100 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc 20:1 to 10:1) to obtain **III-75e** (2.599 g, 9.380 mmol) as a yellow semisolid in 94% isolated yield.

Spectral data for **III-75e**: R_f = 0.52 (hexanes/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 9H), 6.91 (d, *J* = 1.7 Hz, 1H), 7.36 (s, 1H), 7.36 – 7.49 (m, 2H), 7.71 – 7.80 (m, 1H), 8.08 (ddd, *J* = 8.1, 1.6, 0.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.20, 34.84, 107.75, 115.87, 121.08, 122.64, 124.65, 126.40, 127.75, 134.58, 149.14, 150.97. HRMS (ESI^-) *m/z* 199.1136 [calcd. for $C_{14}H_{15}O$ (M–H): 199.1123].

4.4.5 Syntheses of 3,3'-dialkylVANOL (*Scheme 3.15*)

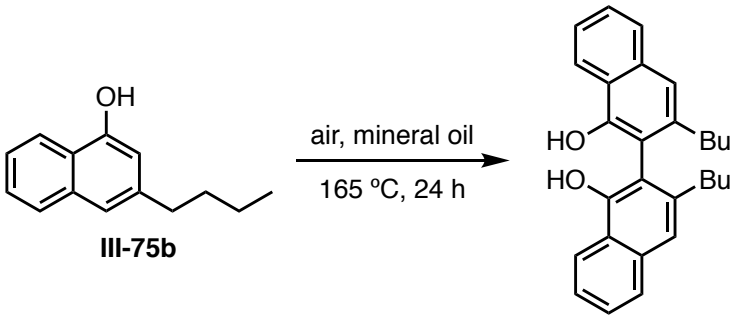


III-75a

III-76a
51%

*3,3'-Cy$_2$VANOL **II-76a***: VANOL derivative **III-76a** was prepared from 3-cyclohexyl-1-naphthol **III-75a** (6.64 mL, 29.3 mmol) by the General Procedure **I** with heating at 165 °C for 36 h. The crude product was purified by column chromatography (silica gel, DCM/hexanes: 1:3 to 1:1) to give **II-76a** as an off-white solid in 51% combined isolated yield (3.360 g, mp 196-198 °C, 7.460 mmol).

Spectral data for **III-76a**: R_f = 0.41 (hexanes/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 – 1.38 (m, 8H), 1.52 – 1.81 (m, 12H), 2.20 (tt, *J* = 11.8, 3.3 Hz, 2H), 5.19 (s, 2H), 7.42 – 7.58 (m, 6H), 7.83 (dt, *J* = 8.3, 0.8 Hz, 2H), 8.22 (ddd, *J* = 8.3, 1.3, 0.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.01, 26.78, 26.81, 33.71, 36.09, 41.42, 112.75, 117.92, 122.44, 122.70, 124.78, 127.11, 127.23, 134.96, 146.15, 149.80. HRMS (ESI$^-$) *m/z* 449.2519 [calcd. for $C_{32}H_{33}O_2$ (M–H): 449.2481].

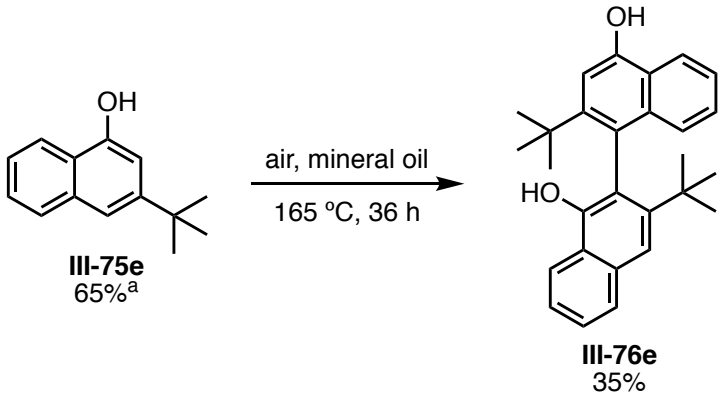


III-75b

III-76b
44%

3,3'-Bu$_2$VANOL ***II-76b***: VANOL derivative **III-76b** was prepared from 3-butyl-1-naphthol **III-75b** (6.822 g, 34.10 mmol) by the General Procedure **I** with heating at 165 ºC for 24 h. The crude product was purified by column chromatography (silica gel, DCM/hexanes: 1:3 to 1:2) to give **II-76b** as a yellow semi solid in 44% combined isolated yield (3.360 g, 7.550 mmol).

Spectral data for **III-76b**: R_f = 0.39 (hexanes/EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.4 Hz, 6H), 1.30 (qd, *J* = 7.3, 2.0 Hz, 4H), 1.60 (p, *J* = 7.6 Hz, 4H), 2.52 (qt, *J* = 14.8, 7.8 Hz, 4H), 5.41 (s, 2H), 7.52 – 7.59 (m, 4H), 7.64 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 8.36 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.97, 22.62, 32.22, 33.32, 113.42, 120.00, 122.73, 122.80, 124.95, 127.21, 127.29, 134.95, 140.41, 150.20. HRMS (ESI$^-$) *m/z* 397.2189 [calcd. for $C_{28}H_{29}O_2$ (M–H): 397.2168].



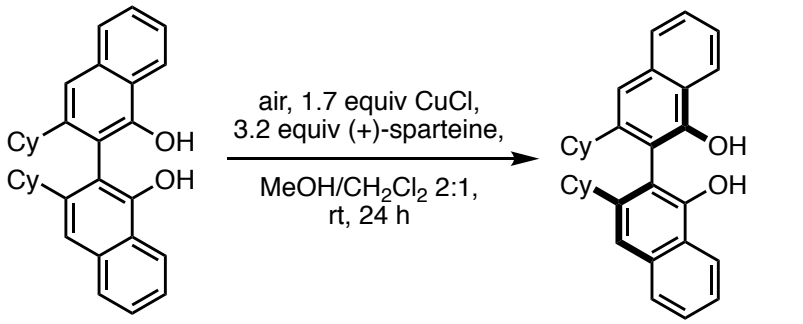
III-75e
65%[a]

III-76e
35%

2,3'-di-tert-butyl-[1,2'-binaphthalene]-1',4-diol ***II-76e***: VANOL isomer **III-76e** was obtained from 3-tert-butyl-1-naphthol **III-75e** (1.856 g, 9.270 mmol) by the General Procedure **I** with heating at 165 ºC for 24 h. The crude product was purified by column chromatography (silica gel, DCM/hexanes 1:3 to 1:2) to give **II-76e** as an off-white semisolid in 35% combined isolated yield (649.1 g, 1.629 mmol).

Spectral data for **III-76e**: R_f = 0.29 (hexanes/DCM 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.4 Hz, 6H), 1.30 (qd, *J* = 7.3, 2.0 Hz, 4H), 1.60 (p, *J* = 7.6 Hz, 4H), 2.52 (qt, *J* = 14.8, 7.8 Hz, 4H), 5.41 (s, 2H), 7.52 – 7.59 (m, 4H), 7.64 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 8.36 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.97, 22.62, 32.22, 33.32, 113.42, 120.00, 122.73, 122.80, 124.95, 127.21, 127.29, 134.95, 140.41, 150.20. HRMS (ESI^-) *m/z* 397.2173 [calcd. for $C_{28}H_{29}O_2$ (M–H): 397.2168].

4.4.6 General Procedure **S** for deracemization of 3,3'-dialkylVANOL (*Scheme 3.16*) -- illustrated for 3,3'-Cy_2VANOL **III-76a**

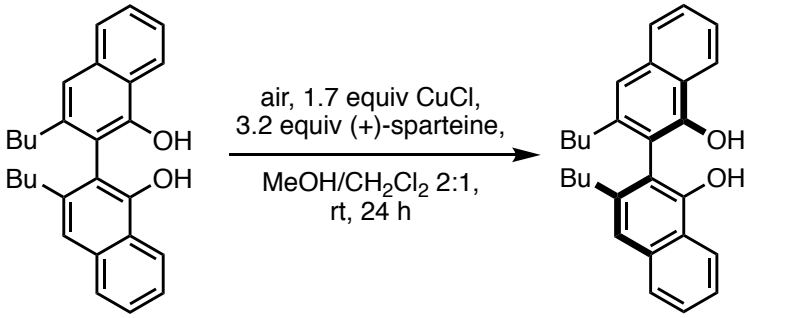


III-76a

(*R*)-3,3'-Cy_2VANOL
(*R*)-**III-76a**
70%, >99% ee

*(R)-3,3'-Cy_2VANOL (R)-**III-76a***: To a 100 mL round bottom flask was added (+)-sparteine (0.81 mL, 3.5 mmol, 3.5 equiv), CuCl (168 g, 1.70 mmol) and MeOH (27 mL) under an atmosphere of air. The reaction mixture was sonicated in a water bath for 60 minutes with exposure to air. The flask was then sealed with a septum and purged with argon, which was introduced by a needle under the surface for 60 minutes. At the same time, to a 250 mL flame-dried round bottom flask was added racemic **III-76a** (451 mg, 1.00 mmol) and DCM (54 mL). The resulting solution was purged with argon for 60 minutes under the surface. The green Cu(II)-sparteine solution was then transferred via cannula to the solution of racemic **III-76a** under argon and then the combined mixture was sonicated for 15 minutes and then allowed to stir at room temperature overnight with an argon balloon attached to the flask which was covered with aluminum foil. The reaction was quenched by slow addition of $NaHCO_3$ (sat. aq. 15 mL), H_2O (40 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with DCM (30 mL × 3). The combined organic layer was dried over anhydrous

Na_2SO_4, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (DCM/hexanes 1:2) gave the product (*R*)-**III-76a** as an off-white foamy solid (315 mg, mp 196-198 ºC, 0.699 mmol, 70%). The optical purity was determined to be >99% ee by HPLC analysis (Pirkle DPhenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 8.69 min for (*R*)-**III-76a** (major) and R_t = 10.36 min for (*S*)-**III-76a** (minor).

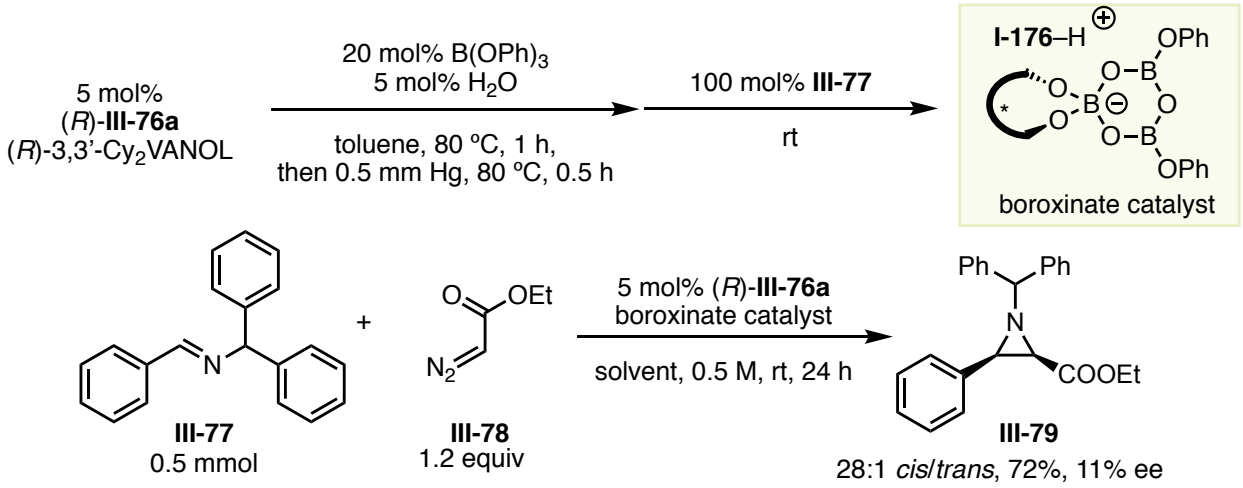


III-76b

(*R*)-3,3'-Bu_2VANOL
(*R*)-**III-76b**
19%, 95% ee

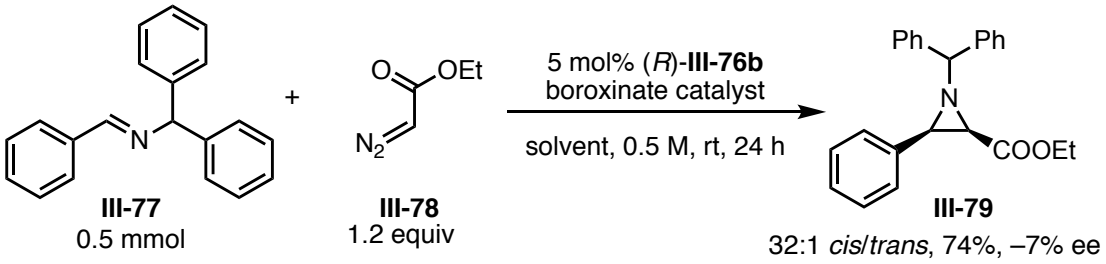
*(R)-3,3'-Bu_2VANOL (R)-**III-76b***: The General Procedure **S** was followed with (±)-3,3'-*n*Bu_2VANOL (1.568 g, 3.930 mmol). Purification of the crude product by column chromatography on silica gel (DCM:hexanes 1:2) gave the product (*R*)-**III-76b** as an off-yellow foamy semisolid (293 mg, 0.735 mmol, 19%). The optical purity was determined to be 95% ee by HPLC analysis (Pirkle DPhenylglycine column, 98:2 hexane/iPrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 8.73 min for (*R*)-**III-76b** (major) and R_t = 10.37 min for (*S*)-**III-76b** (minor).

4.4.7 Aziridination catalyzed by boroxinate of 3,3'-dialkylVANOL (*Scheme 3.17*)



Preparation of the boroxinate catalyst stock solution: To a 50 mL flame-dried home-made Schlenk flask, prepared from a single-necked 50 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and flushed with nitrogen was added (*R*)-3,3'-Cy_2VANOL (11.3 mg, 0.0250 mmol), $B(OPh)_3$ (29.0 mg, 0.100 mmol) and H_2O (0.45 µL, 0.025 mmol). Under a nitrogen flow through the side-arm of the Schlenk flask, dry toluene (1 mL) was added through the top of the Teflon valve to effect dissolution. The flask was sealed by closing the Teflon valve, and then placed in an 80 °C oil bath for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 °C (oil bath). The flask was then allowed to cool to room temperature and opened to nitrogen through the side-arm of the Schlenk flask. This residue was then completely dissolved in dry toluene (1 mL) under a nitrogen flow through side-arm of the Schlenk flask to afford the solution of the catalyst.

(2R,3R)-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate ***III-79*****:** The General Procedure **G** was followed using (*R*)-3,3'-Cy_2VANOL boroxinate catalyst prepared by the procedure mentioned above (4.4.7). Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 19:1 hexanes/EtOAc as eluent, under gravity) afforded pure *cis*-aziridine **III-79** as a white solid in 72% isolated yield (129 mg, 0.360 mmol); *cis/trans*: 28:1. The optical purity of **III-79** was determined to be 11% *ee* by HPLC analysis ((CHIRALCEL OD-H column, 90:10 hexanes/iPrOH at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.01 min (major enantiomer, **III-79**) and R_t = 4.67 min (minor enantiomer, *ent*-**III-79**).



III-77
0.5 mmol

III-78
1.2 equiv

III-79
32:1 *cis*/*trans*, 74%, –7% ee

(2R,3R)-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate ***III-79*****:** The General Procedure **G** was followed using boroxinate catalyst prepared by the procedure mentioned above (4.4.7) with (*R*)-3,3'-*n*Bu_2VANOL (10.0 mg, 0.0250 mmol, 95% ee). Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 19:1 hexanes/EtOAc as eluent, under gravity) afforded pure *cis*-aziridine **III-79** as a white solid in 74% isolated yield (133 mg, 0.371 mmol); *cis/trans*: 32:1. The optical purity of **III-79** was determined to be 7% *ee* by HPLC analysis ((CHIRALCEL OD-H column, 90:10 hexanes/iPrOH at 222 nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.01 min (minor enantiomer, *ent*-**III-79**) and R_t = 4.67 min (major enantiomer, **III-79**).

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