

CONSTRUCTION OF A VAULTED BIARYL LIGAND LIBRARY
FOR THE AZIRIDINATION REACTION

By

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ABSTRACT

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A highly enantioselective asymmetric catalytic synthesis of alkynyl aziridines can be achieved from alkynyl imines with diazo compounds mediated by a chiral boroxinate (BOROX) catalyst generated from VANOL or VAPOL ligand. In contrast to the aziridination reaction (AZ reaction) with aryl and alkyl substituted imines, alkynyl imines react to give *cis*-substituted aziridines with both diazo esters and diazo acetamides. Unexpectedly, the two diazo compounds afford different enantiomers of the *cis*-aziridine from the same enantiomer of the catalyst. The (*S*)-BOROX catalyst promotes the reaction of ethyl diazoacetate such that reaction occurs with the Si-face of the imine and the Si-face of the diazo compound. However, in the case of a diazo acetamide, the (*S*)-BOROX catalyst switches the facial selectivity for reaction of both substrates from Si-face to Re-face.

A diverse family of chiral boroxinate Brønsted acids is generated from a library of thirty-one VANOL derivatives that are substituted in the 7,7'-positions. A direct and convergent synthetic access to the ligand library is made viable by a cycloaddition/electrocyclization cascade from various *p*-substituted phenyl acetic acids. The family of ligands is used to screen the catalytic asymmetric AZ reaction of two different benzhydryl imines, one from an aryl aldehyde and the other from an aliphatic aldehyde. Remarkably, the highest asymmetric induction for each substrate was recorded with the same ligand, 7,7'-di-*t*-butylVANOL. This ligand was in turn

screened with a set of 10 different benzhydryl imines to find that this ligand gives an average of 97% ee over all ten imines whereas the corresponding unsubstituted ligand VANOL gives an average of 87% ee and the VAPOL ligand gives an average of 86% ee.

Three sets of VANOL ligands: 1) naphthalene skeleton modified; 2) C3-aryl group modified; 3) *CI*-symmetric VANOL derivatives were synthesized and evaluated in the AZ reaction. Those modifications lead to complicated outcomes. Generally, 7,7'-substituents are beneficial to the AZ reaction, whereas 4,4'- or 8,8'-substituents are detrimental to the AZ reaction. Modification of the C3-aryl effects the enantioselectivity to some extent.

Four VAPOL derivatives were prepared and evaluated in the AZ reaction. In addition to the AZ reaction, those VANOL and VAPOL derivatives were evaluated in the reduction of 2-quinolines and VAPOL was found to be the optimal ligand.

A novel DMAP-squaramide catalyst was prepared from BINAM and evaluated in the Michael addition of a nitroalkane to a nitroalkene.

To my dearest parents

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ABBREVIATIONS

AZ : aziridination

Bh : benzhydryl

BINAP : 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BINOL : 1,1'-binaphthol

Boc : *tert*-butyloxycarbonyl

BUDAM : bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl

DCM : dichloromethane

DIBAL : diisopropyl aluminum hydride

DME : 1,2-dimethoxy ethane

DMAP : 4-*N,N'*-dimethylaminopyridine

DMF : *N,N*-dimethylformamide

EDA : ethyl diazoacetate

ee : enantiomeric excess

EI : electron ionization

ESI : electrospray ionization

HRMS : high resolution mass spectrometry

MALDI : matrix-assisted laser desorption Ionization

MS : mass spectrometry

MEDAM : bis(3,5-di-methyl-4-methoxyphenyl)methyl

NBS : *N*-bromosuccinimide

TBAF : tetrabutylammonium fluoride

TBDPS : *tert*-butyldiphenylsilyl

TfOH : trifluoromethanesulfonic acid

THF : tetrahydrofuran

TIPS : triisopropylsilyl

TLC : thin layer chromatography

TMS : trimethylsilyl

VANOL : vaulted 2,2'-binaphthol

VAPOL : vaulted 2,2'-biphenanthrol

CHAPTER ONE

VANOL/VAPOL: A NEW CLASS OF PRIVILEGED LIGAND

1.1 Background

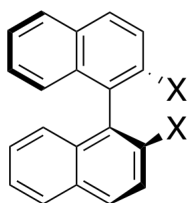
The demand to develop synthetic methods for optically active compounds in an efficient way is increasing dramatically due to the inherent relationship between biological activity and absolute configuration of stereogenic centers.¹ Compared to nature, which makes utility of enzymes, the most efficient and elaborate devices to generate optically enriched molecules, organic chemists with limited tools were struggling until the 1980s with the advances in the asymmetric epoxidation of alkenes and asymmetric hydrogenation reactions.^{2,3} On one hand, enzymes normally have a limited substrate scope, while synthetic asymmetric catalysts possess a broader substrate scope. On the other hand, enzymes can sense subtle differences, whereas synthetic asymmetric catalysts can hardly achieve that high level of distinction. One of the ultimate goals for today's organic chemist is to unveil or generate a catalyst that is suitable for all substrate and at the same time demonstrates excellent enantioselectivity for a given type of transformation.

Diversity in catalysis is crucial and essential: 1) a flexible collection of catalysts (i.e. Buchwald ligand kit) enhances the possibility that reactivity and selectivity can be optimized for an individual substrate;⁴ 2) the evolutionary development of ligands enables the realization of new transformations (i.e. nitration of aryl chlorides with *t*-BuBrettPhos);⁵ 3) The performance of a ligand library could shed an insightful light on the transition states. Consequently, continuous development of ligands is one the main themes in organic chemistry.

Traditionally, asymmetric catalysts have been metal complexes bearing chiral ligands. While the metal dominates the reactivity, the chiral ligand modifies the reactivity and selectivity of the metal center in such a way that one enantiomer is formed preferentially over the other. As a result, the key to obtaining efficient asymmetric catalysis lies in the generation of robust chiral catalysts by properly pairing chiral ligands with a metal core. Rigid and stable ligands with tunable steric and electronic properties are the ideal choices.

Since the pioneering development of DIOP by Kagan,⁶ many C_2 symmetric ligands have been synthesized and investigated. A few classes, which are designated as “privileged” ligands by Jacobsen and coworkers, have been found to be truly general in scope.⁷ The important members are shown in Scheme 1.1. The majority of the successes in asymmetric catalysis have been accomplished with these ligands.

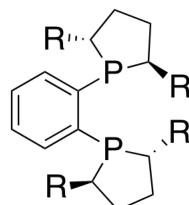
Scheme 1.1 Privileged ligand



Diels-Alder
Mukaiyama aldol
aldehyde allylation
hydrogenation
alkene isomerization
Heck reaction

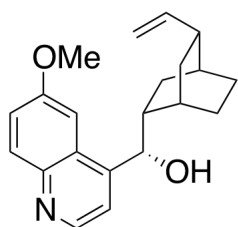
X = OH: BINOL

X = PPh₂: BINAP



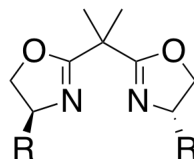
hydrogenation
hydrophosphination
hydroacylation
hydrosilylation
Bayer-Villager oxidation

DuPhos



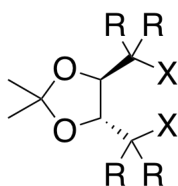
Cinchona alkaloid
derivatives

dihydroxylation
acylation
heterogenous hydrogenation
phase transfer catalysis



Diels-Alder
Mukaiyama aldol
conjugate addition
cyclopropylation
aziridination

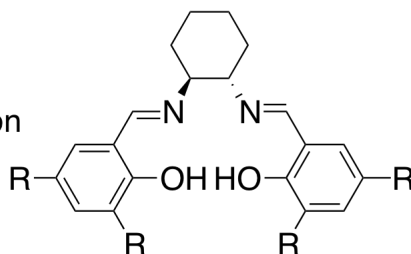
Bis(oxazoline)



Diels-Alder
ester alcoholysis
aldehyde alkylation
iodolactonization
hydrogenation

X = OH: TADDOL

X = PPh₂: DIOP



Diels-Alder
epoxidation
epoxide ring opening
imine cyclization
conjugate addition

Salen

1.2 BINOL vs VANOL/VAPOL

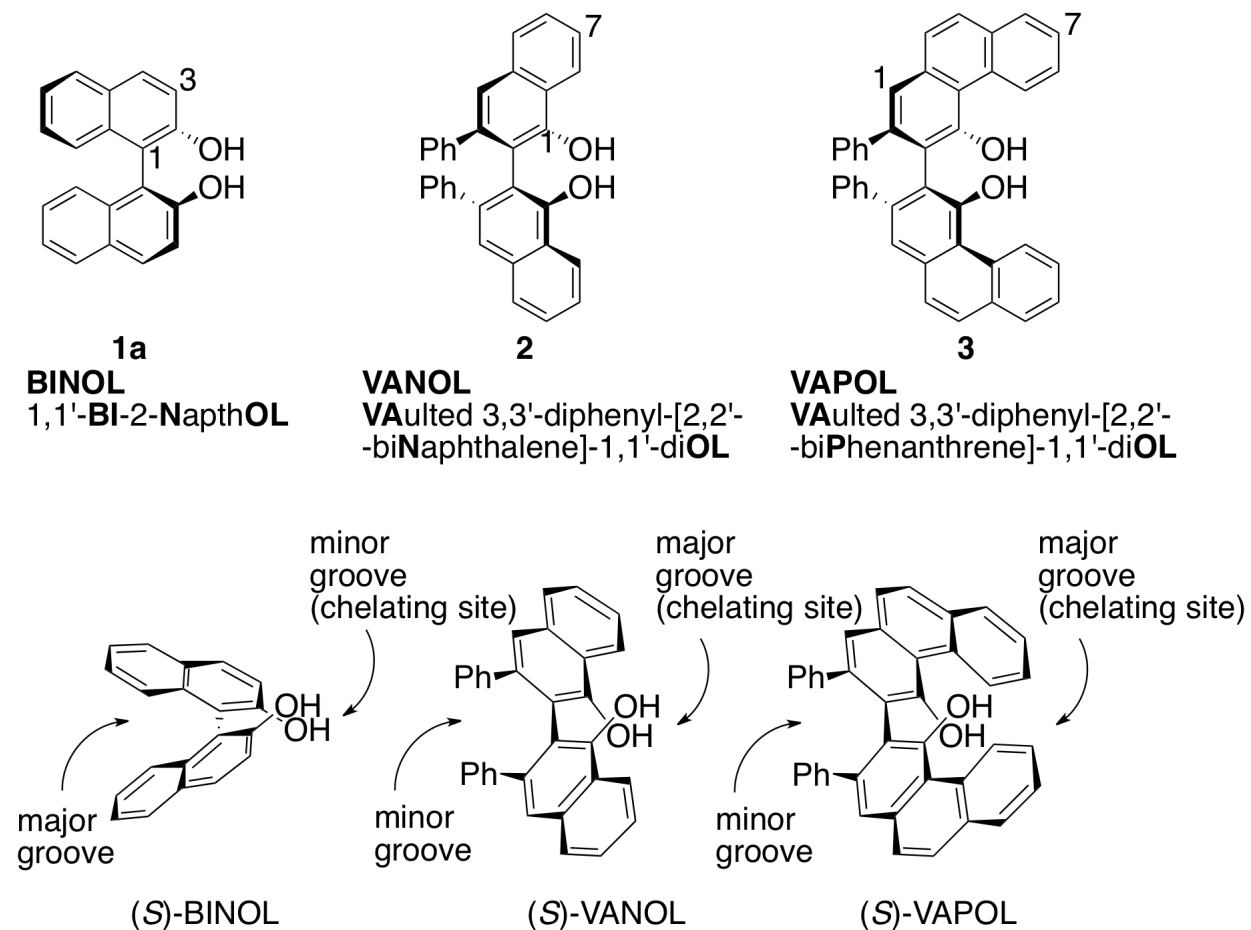
Listed as one of the “privileged” ligands, BINOL (short for 1,2'-bi-2-naphthol) was first prepared as a racemate by von Richter in 1873 and the enantiopure version was made by Pummerer in 1926.^{8,9} It was not until 1979 that Noyori discovered the potential of BINOL as a useful chiral ligand in his report on the asymmetric reduction of aromatic ketones and aldehydes.¹⁰ Since then, tremendous work has been put into developing the catalytic potential of BINOL and its derivatives.¹¹

In spite of its efficacy in asymmetric catalysis, a major limitation of BINOL is that the chiral pocket (major groove) formed by the two naphthyl rings is far away from the diols, the bidentate chelating site (minor groove) (Scheme 1.2). One of the solutions to gain increased enantioselection is to introduce substituents at the 3,3'-positions. However, the rotation of the C-C or C-X single bonds between the 3,3'-groups and the binaphthyl motif increases the flexibility of the skeletal backbone, leading to more conformational isomers in transition states and decreased enantioselectivity.

Inspired by the structural topology of gossypol,¹² a naturally occurring compound found in cotton seeds, our group designed and synthesized vaulted 2,2'-binaphthol (VANOL) and vaulted 3,3'-biphenanthrol (VAPOL) a new class of biaryl ligands (Scheme 1.2).¹³ The major feature of VANOL and VAPOL is that annulated benzene ring is extended in the direction of the nascent active site of the phenol units. Therefore, a much deeper chiral pocket is formed and the chelating site is in the major groove. Another feature is that the bulkiness of the adjacent phenyl groups constrains the rotation of the C-C single bond connecting the two naphthyl rings. The

choice of phenyls on the 3,3'-positions of VANOL and the 2,2'-positions of VAPOL was made out of concern for synthetic convenience.

Scheme 1.2 BINOL vs VANOL/VAPOL



1.3 VANOL/VAPOL in asymmetric catalysis

Since the debut of VANOL and VAPOL, our group as well as other research groups initiated extensive investigations on the applications of these new ligands and this will be reviewed below.

Scheme 1.3 Diels-Alder reaction of methyl acrylate and cyclopentadiene

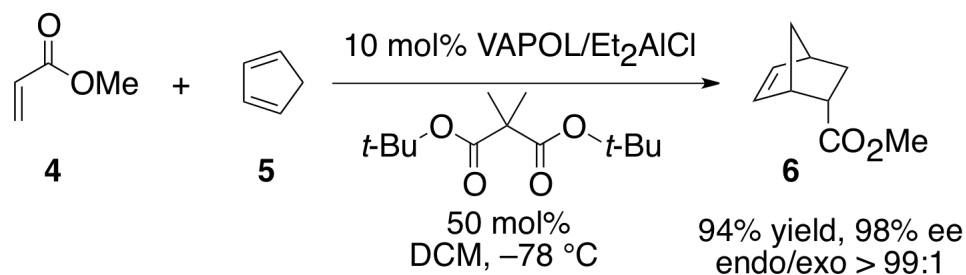


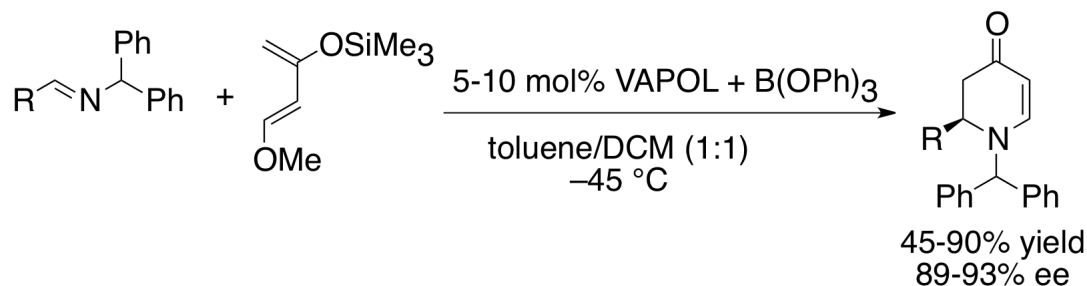
Table 1.1 Diels-Alder reaction of methacrolein and cyclopentadiene

Reaction scheme showing the Diels-Alder reaction of methacrolein (**7**) and cyclopentadiene (**5**) catalyzed by 10 mol% Ligand/ Et_2AlCl in DCM at $-78\text{ }^\circ\text{C}$ to form product **8**.

entry	ligand	% yield	exo/endo	% ee
1	(<i>S</i>)-BINOL	99	32.3	23
2	(<i>S</i>)-3,3'-(SiPh_3) ₂ -BINOL	69	11.5	20
3	(<i>S</i>)-VANOL	84	13.3	5
4	(<i>S</i>)-VAPOL	100	49.0	91
5	(<i>S</i>)-6,6'-Br ₂ -VAPOL	>95	8.3	18
6	(<i>S</i>)-6,6'-Me ₂ -VAPOL	>95	14.4	30
7	(<i>S</i>)-6,6'-Ph ₂ -VAPOL	76	11.7	-41
8	(<i>S</i>)-6,6'-(3,5-(<i>t</i> -Bu) ₂ -C ₆ H ₃) ₂ -VAPOL	>95	8.4	62

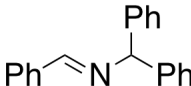
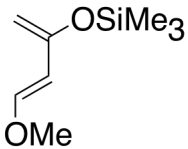
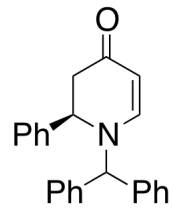
The Diels-Alder reaction of methyl acrylate and cyclopentadiene was investigated in our group. Catalysts generated from various biaryl ligands and Et_2AlCl were examined, and significant asymmetric induction was achieved with VAPOL as the ligand along with the addition of a carbonyl mimic (Scheme 1.3).¹⁴ A dramatic phenomenon from this study is the occurrence of an autoinduction resulting from a coordination complex between the product and the catalyst. A similar study on the Diels-Alder reaction of methacrolein and cyclopentadiene was also carried out (Table 1.1).^{14,15} Among the ligands BINOL, 3,3'-disubstituted BINOL and VANOL, VAPOL stands out as the optimal ligand, giving 91% ee. A number of 6,6'-disubstituted VAPOL derivatives were also prepared and evaluated. However, none of these were found to exceed VAPOL in terms of asymmetric induction.

Scheme 1.4 Aza Diels-Alder reaction of Bh imines



Dr. Newman from our group developed a protocol for the aza-Diels-Alder reactions of *N*-benzhydryl imines and Danishefsky's diene with a catalyst derived from VAPOL and B(OPh)₃ (Scheme 1.4).¹⁶ A similar catalyst derived from BINOL and B(OPh)₃ does not provide any turnover while the catalyst generated from VAPOL and B(OPh)₃ furnishes good turnover, giving excellent enantioselectivity and yield (Table 1.2).

Table 1.2 Aza Diels-Alder reaction with Danishesky's diene

	+		$\xrightarrow[\text{toluene/DCM (1:1)}]{\begin{array}{l} 10 \text{ mol\% Ligand} \\ 100 \text{ mol\% B(OPh)}_3 \\ -45^\circ\text{C} \end{array}}$	
9a		10		11a
entry	ligand	% yield	% ee	
1	BINOL	0	-	
2	VAPOL	94	94	

An asymmetric imine aldol reaction of silyl ketene acetals and aryl imines provides an important method for access to chiral β -amino esters. Kobayashi and coworkers reported the first useful catalytic asymmetric version of this transformation with a zirconium complex derived from 6,6'-Br₂-BINOL.¹⁷ Our group also became interested in the same reaction and published a temperature independent and highly catalytic asymmetric version (Scheme 1.5).¹⁸ The VAPOL derived catalyst gives a much higher asymmetric induction than does either BINOL or 3,3'-Br₂-BINOL derived catalysts. Later on, 7,7'-Me₂-VAPOL prepared by Dr. Rampalakos from our group was demonstrated to give an even more efficient catalyst and this confirmed the model proposed for the intermediates in this reaction (Table 1.3).¹⁹

Scheme 1.5 Imino Aldol reaction

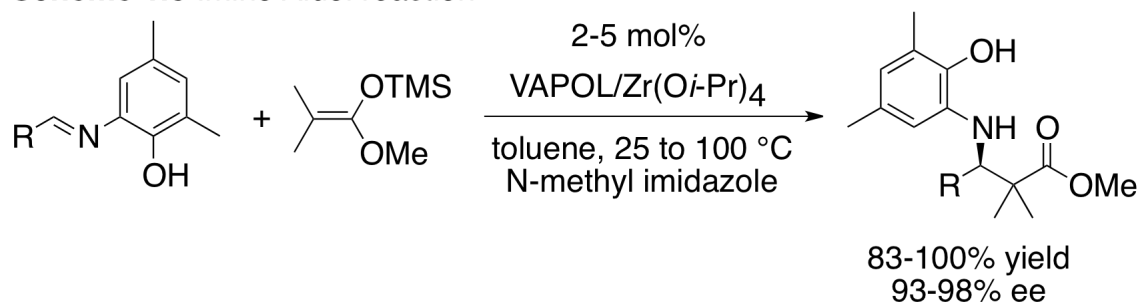


Table 1.3 Imino aldol reaction with silyl ketene acetal **13**

20 mol%			
Ligand/Zr(Oi-Pr) ₄			
N-methyl imidazole			
toluene, 25 °C			
12	13	14	
entry	ligand	% yield	% ee
1	VAPOL	94	89
2	BINOL	100	28
3	3,3'-Br ₂ -BINOL	87	48
4	7,7'-Me ₂ -VAPOL	97	86

The utility of VANOL and VAPOL has been extended to the Baeyer-Villiger reaction producing γ -butyrolactones (Scheme 1.6).²⁰ Bolm and coworkers reported that VANOL is superior to VAPOL and BINOL with respect to asymmetric induction for a catalyst generated from VANOL and Me₂AlCl (Table 1.4). The enantioselectivities are claimed to be among the best for those simple substrates.

Scheme 1.6 Baeyer-Villiger reaction

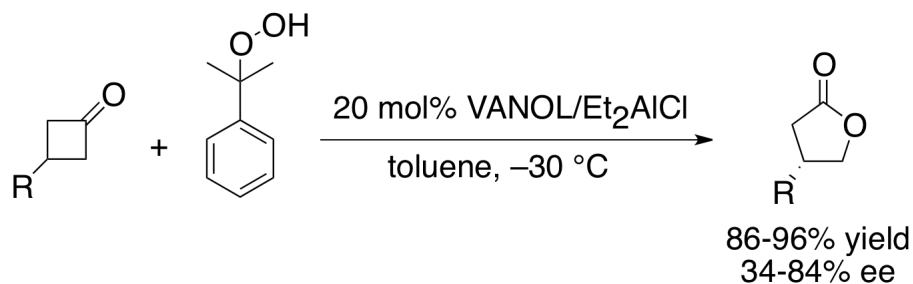


Table 1.4 Baeyer-Villiger reaction of 3-phenylcyclobutanone

entry	ligand	% ee
1	BINOL	68
2	VAPOL	14
3	VANOL	80

A collaboration project on catalytic asymmetric ring opening reactions of rac-epoxides with alcohols was initiated by Prof. Nyugen and coworkers at Northwestern University.²¹ Their study suggested that VAPOL was the best ligand for the transformation (Table 1.5).

Table 1.5 Desymmetrization of *meso*-epoxide

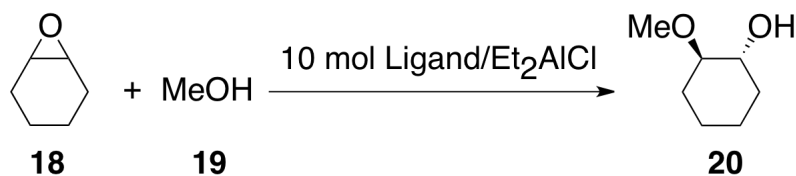


Table 1.5 (cont'd)

entry	ligand	% yield	% ee
1	BINOL	51	59
2	3,3'-Ph ₂ -BINOL	19	63
3	VAPOL	69	81
4	VANOL	-	20

Schaus and coworkers developed the asymmetric Petasis reaction between alkenyl boronates, secondary amines and glyoxylates to generate α -amino esters (Scheme 1.7).²² BINOL and 3,3'-disubstituted BINOL derivatives provide low to modest asymmetric inductions, while VANOL and VAPOL produce products in good yields with excellent enantioselectivities (Table 1.6).

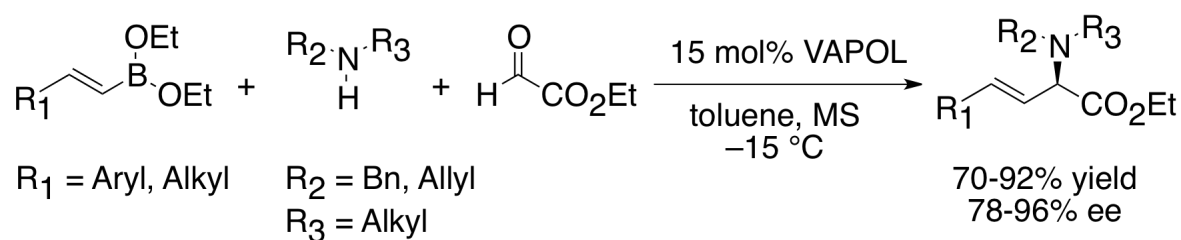
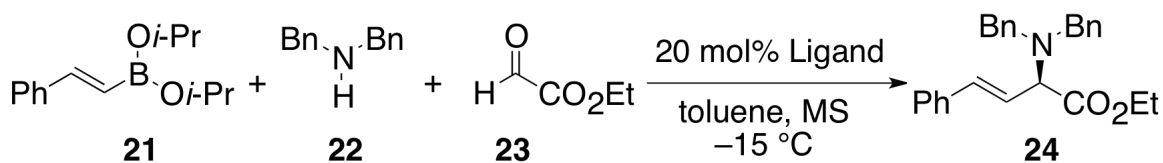
Scheme 1.7 Petasis reaction**Table 1.6** Petasis reaction catalyzed by chiral diols

Table 1.6 (cont'd)

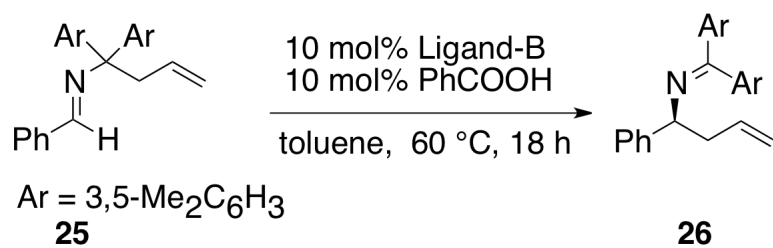
entry	ligand	% yield	% ee
1	BINOL	45	20
2	3,3'-Br ₂ -BINOL	65	50
3	3,3'-Ph ₂ -BINOL	51	40
4	3,3'-(3,5-Me ₂ -C ₆ H ₃) ₂ -BINOL	25	18
5	3,3'-(SO ₂ CF ₃) ₂ -BINOL	70	10
6	VANOL	77	70
7	VAPOL	80	74

Asymmetric aminoallylation of aldehydes is a good way to synthesize chiral homoallylic amines. Rueping and coworkers demonstrated the first asymmetric version of this transformation catalyzed by a Brønsted acid.²³ Hong Ren from our group developed a highly enantioselective aminoallylation of aldehyde which is synergistically catalyzed by a chiral Brønsted acid derived from VANOL and a non-chiral Brønsted acid (Scheme 1.8).²⁴ Good to excellent inductions and yields for both aryl and alkyl aldehydes were obtained. During the optimization of aza-Cope rearrangement, catalysts derived from BINOL derivatives or VAPOL could not compete with VANOL (Table 1.7).

$$\text{R}-\text{CHO} + \text{1,1'-(2,2'-bis(4-methylphenyl))-2,2'-bis(methylene)-5,5'-bibenzylamine} \xrightarrow[\text{2) 2N HCl, THF/H}_2\text{O}]{\text{1) 5 mol\% VANOL BOROX, 5 mol\% benzoic acid, MS, m-xylene, 60 }^\circ\text{C}}$$

$$\text{R}-\text{CH}(\text{NH}_2\cdot\text{HCl})-\text{CH}_2\text{CH}=\text{CH}_2$$

R = aryl, alkyl
 57-99% yield
 72-96% ee



entry	ligand	% yield	% ee
1	(<i>R</i>)-BINOL	78	36
2	(<i>R</i>)-3,3'-Ph ₂ -BINOL	62	−7
3	(<i>R</i>)-VAPOL	84	9
4	(<i>R</i>)-VANOL	89	78

The applications of the VANOL/VAPOL ligands have been extended to the Ugi reactions, for which no successful catalytic asymmetric version has yet been realized. Dr. Huang from our group has made great efforts on the Ugi-type reactions of an aldehyde, secondary amine and *t*-Bu isocyanide. Various biaryl ligands have been evaluated and a boroxinate catalyst prepared from VAPOL turned out to be the optimal at this early stage (Table 1.8).²⁵

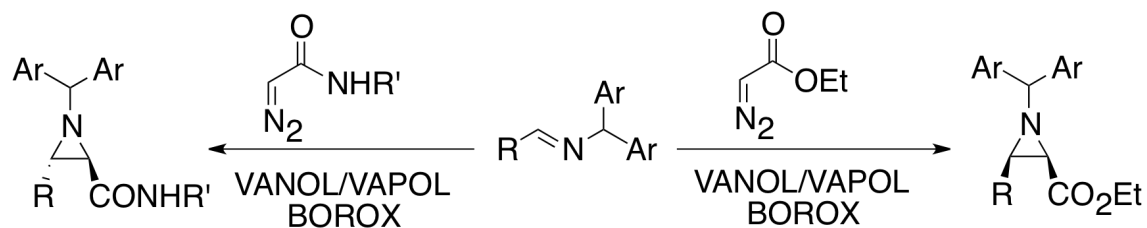
Table 1.8 Ugi-type reaction

27	22	28	29
entry	ligand	% yield	% ee
1	(<i>R</i>)-VAPOL	76	−18
2	(<i>S</i>)-VANOL	60	6
3	(<i>R</i>)-3,3'-Ph ₂ -BINOL	37	−11
4	(<i>R</i>)-3,3'-Br ₂ -BINOL	30	−11
5	(<i>R</i>)-3,3'-(SiPh ₃) ₂ -BINOL	trace	-

Aziridination is one of the most important applications of the VANOL/VAPOL ligands. Our group first developed a protocol for the highly enantioselective *cis*-selective aziridination reactions of imines and ethyl diazoacetate (Scheme 1.9).²⁶ This transformation is catalyzed by a self-assembled boroxinate derived from VANOL/VAPOL and B(OPh)₃. Later on, Dr. Desai from our group realized the highly enantioselective *trans*-selective aziridination reactions of

imines and diazoacetamides catalyzed by the same boroxinate catalyst.²⁷

Scheme 1.9 Wulff universal aziridination reactions



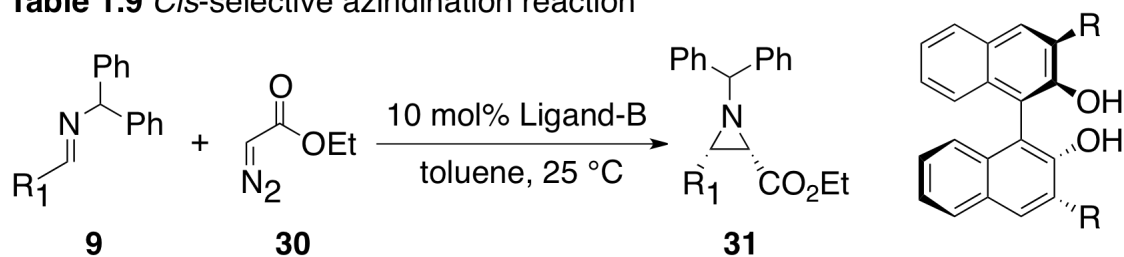
trans-AZ

R = aryl, 1°, 2°, 3° alkyl
up to 90% yield, 99% ee
up to >50:1 *trans*:*cis*

cis-AZ

R = aryl, 1°, 2°, 3° alkyl
up to 99% yield, 99% ee
up to >50:1 *cis*:*trans*

Table 1.9 *Cis*-selective aziridination reaction



entry	R ₁	R	% yield	% ee
1	Ph	H	40	17
2	Ph	Ph	88	76
3	Ph	Br	89	55
4	Ph	SiPh ₃	80	1
5	Ph	9-anthracenyl	65	3
6	4-Br-C ₆ H ₄		68	69
7	4-Br-C ₆ H ₄		76	78
8	4-Br-C ₆ H ₄	2-naphthyl	63	58

In case of the *cis*-selective aziridination reactions, a number of BINOL derivatives were evaluated by our group and Wipf's group, and low to moderate asymmetric inductions were observed (1-78% ee) (Table 1.9).^{25,28} Installation of proper steric can improve the induction from 17% ee (BINOL, Table 1.9, entry 1) to 76% ee (3,3'-Ph₂-BINOL, Table 1.9, entry 2). If the substituent in the 3,3'-positions of BINOL is too big (Table 1.9, entry 4 and 5), racemic product was obtained.

With the success of universal catalytic asymmetric aziridination protocol established, Dr. Huang from our group developed the first procedure for the catalytic asymmetric synthesis of trisubstituted aziridines from Boc-imines and diazo compounds with excellent diastereoselectivities and enantioselectivities (Scheme 1.10).²⁹ Catalysts prepared from BINOL derivatives could not compete with those generated from VANOL.

Scheme 1.10 Asymmetric synthesis of trisubstituted aziridines

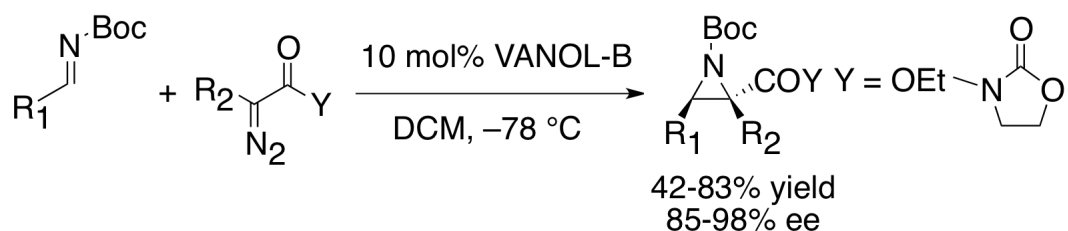


Table 1.10 Asymmetric synthesis of trisubstituted aziridine from Boc imine

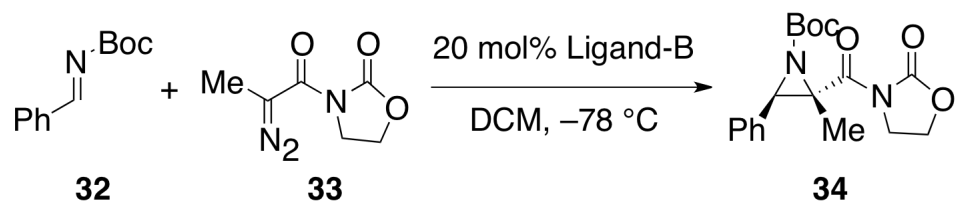
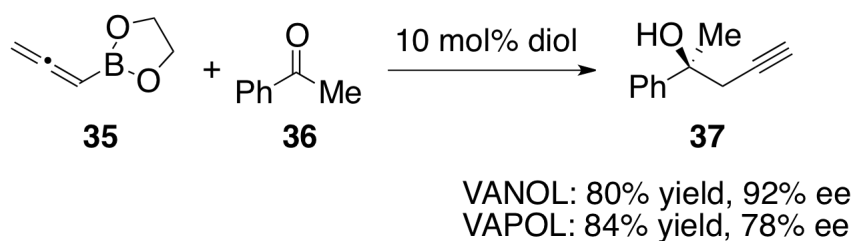


Table 1.10 (cont'd)

entry	ligand	% conv.	% yield	% ee
1	(S)-VANOL	100	80	94
2	(S)-VAPOL	66	21	-8
3	(S)-BINOL	92	56	40
4	(S)-3,3'-Br ₂ -BINOL	100	79	53
5	(S)-3,3'-Ph ₂ -BINOL	65	14	0

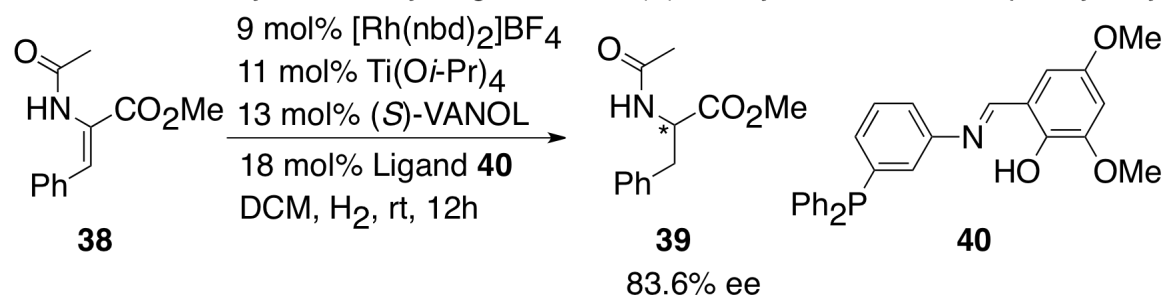
Schaus and coworkers demonstrated that VANOL and VAPOL could catalyze the asymmetric propargylation of acetophenone with allenylboronate, giving medium to good enantioselectivities (Scheme 1.11).³⁰

Scheme 1.11 Propargylation of acetophenone



Van Leeuwen and coworkers reported that supermolecular complex assembled from Ti(Oi-Pr)₄, [Rh(nbd)₂]BF₄, achiral ditopic ligand **40** and VAPOL could catalyzed the asymmetric hydrogenation of (*Z*)-methyl-2-acetamido-3-phenylacrylate **38**, giving 83.6% ee (Scheme 1.12).³¹

Scheme 1.12 Asymmetric hydrogenation of (*Z*)-methyl-2-acetamido-3-phenylacrylate



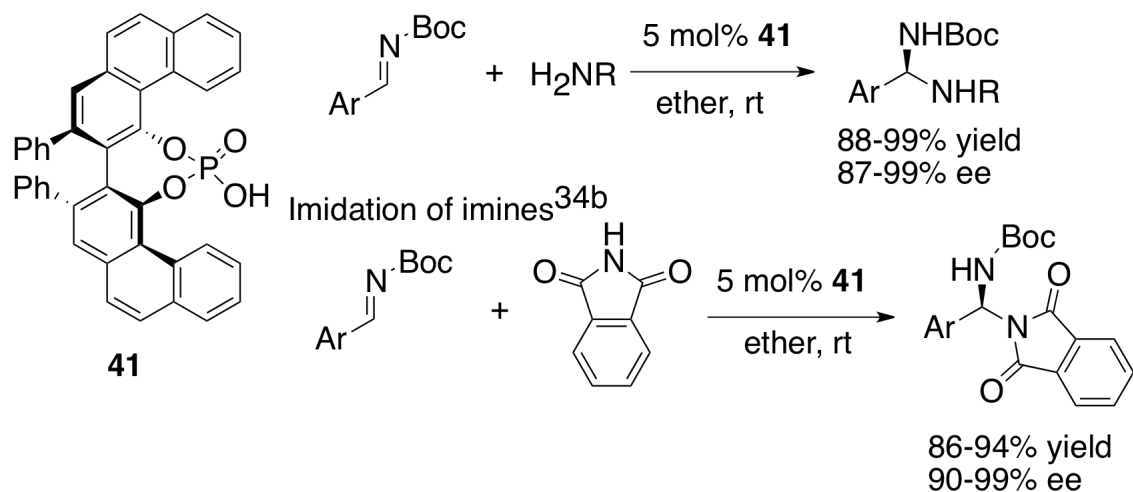
1.4 VANOL/VAPOL derivatives in asymmetric catalysis

The last decade has witnessed the flourishing of organocatalysis in synthesis, the third pillar of asymmetric catalysis after biocatalysis and metal catalysis. In this new trend, Akiyama and Terada pioneered the BINOL based chiral phosphoric acid catalyzed reactions.³² The phosphoric acid center activates substrates by either protonation or H-binding.³³

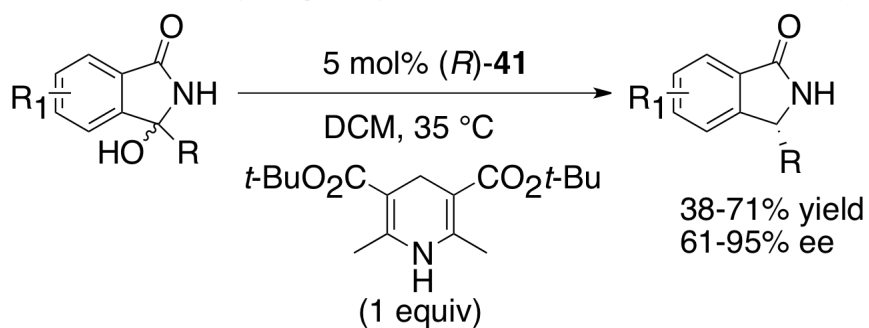
Antilla and coworkers have successfully employed VANOL/VAPOL phosphoric acids in a number of reactions, such as imine amidation^{34a} and imidation^{34b} reduction of α -imino esters to α -amino esters,^{34c} as well as the desymmetrization of *meso*-aziridines with azide^{34d} or thiols^{34e} (Scheme 1.13). Almost At the same time, Della Sala and coworkers reported a similar desymmetrization of *meso*-aziridines with Me₃SiSPh.^{35a} Later on, they extended the nucleophile in this transformation to selenium nucleophiles.^{35b}

Zhou and coworkers developed an asymmetric synthesis of 3-substituted isoindolin-1-ones via the VAPOL phosphoric acid catalyzed transfer hydrogenolysis of racemic 3-substituted 3-hydroxyisoindolin-1-ones with a Hantzsch ester (Scheme 1.14).³⁶

Scheme 1.13 Various reactions catalyzed by VAPOL phosphoric acid
Amidation of imines^{34a}

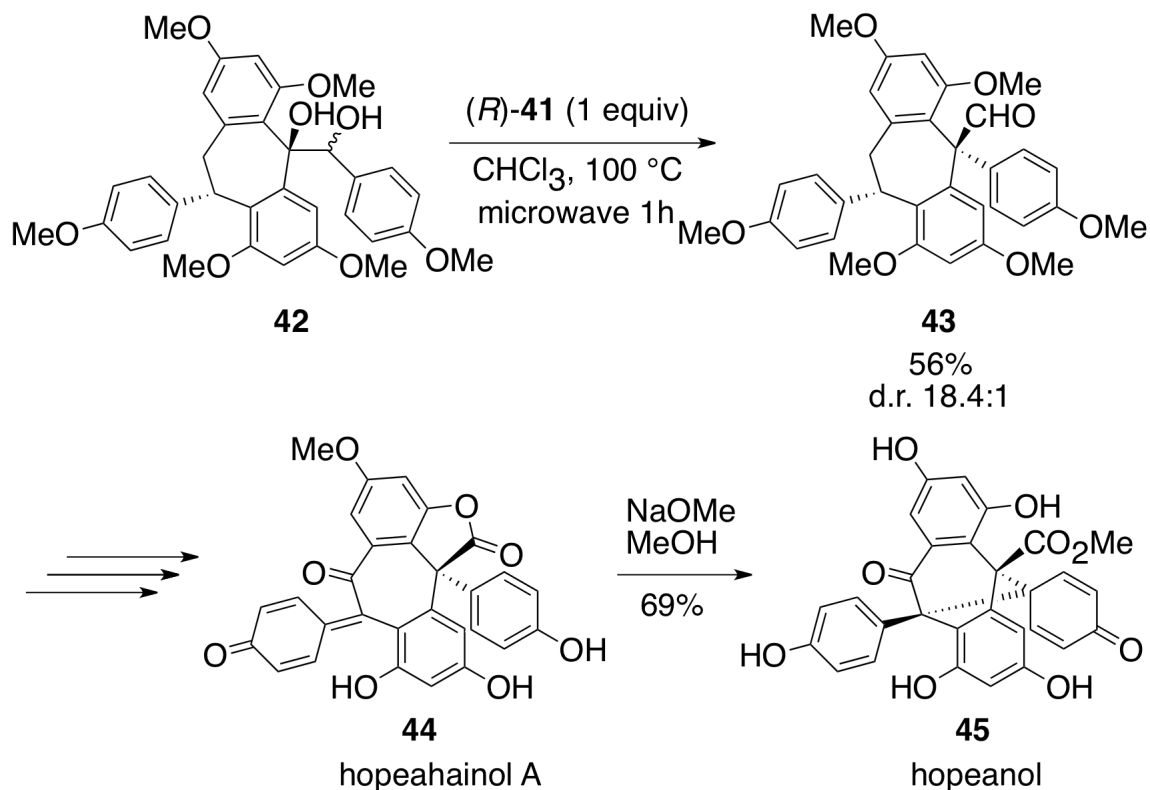


Scheme 1.14 Hydrogenolysis of racemic 3-substituted 3-hydroxyisoindolin-1-ones

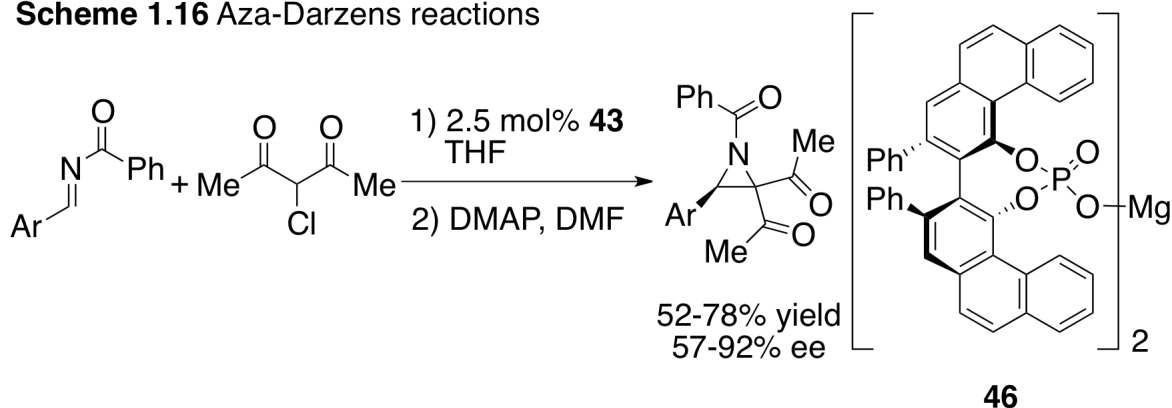


Snyder and coworkers applied VAPOL phosphoric acid in the total synthesis of hopeahainol and hopeanol (Scheme 1.15).³⁷ One critical step is the VAPOL phosphoric acid mediated pinacol rearrangement of intermediate **42** to **43** with high diastereoselectivity.

Scheme 1.15 Utility of VAPOL phosphoric acid in the total synthesis of hopeahainol A and hopeanol



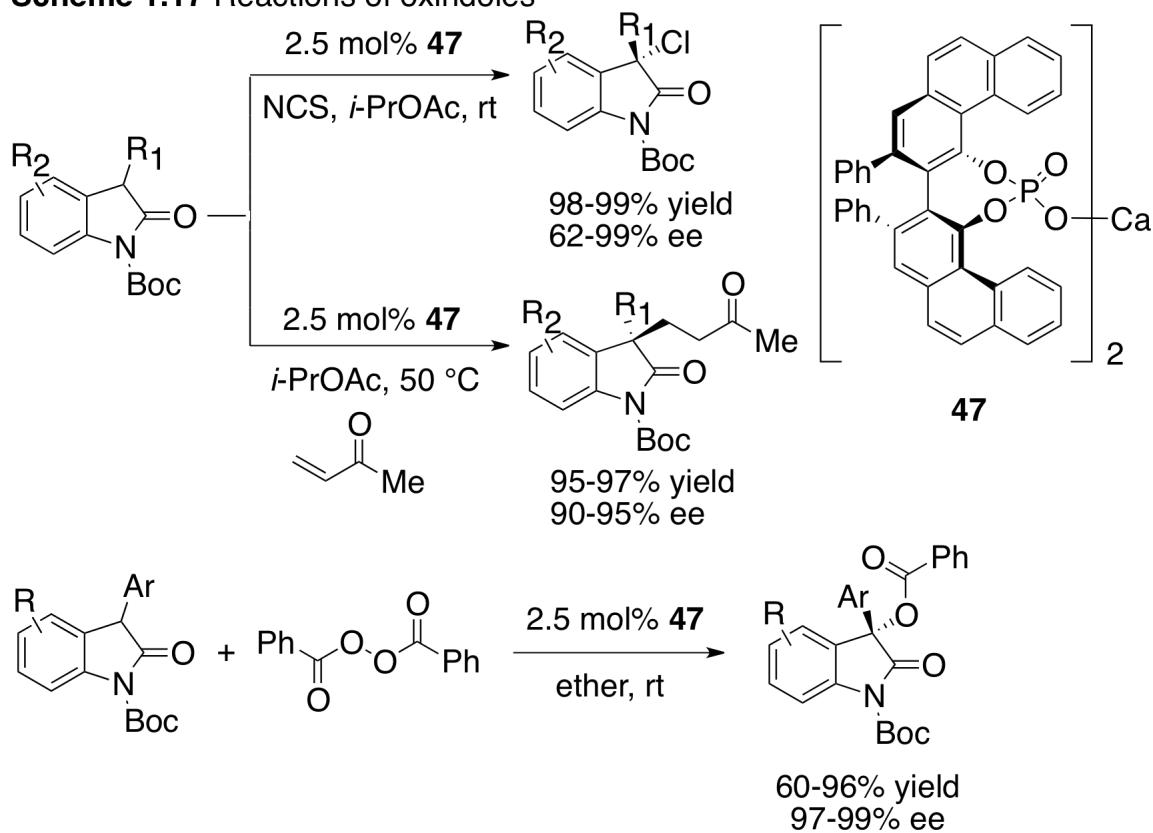
Scheme 1.16 Aza-Darzens reactions



In addition to VAPOL phosphoric acid, Antilla and coworkers also utilized the corresponding metal salts in several asymmetric transformations. They developed an asymmetric aza-Darzens reaction in which trisubstituted aziridines was obtained via the nucleophilic addition of α -chloro-1,3-diketones to *N*-benzoyl imines (Scheme 1.16).³⁸ This was claimed to be the first example of an enantioselective Mannich-type reaction catalyzed by a magnesium salt of a chiral phosphoric acid.

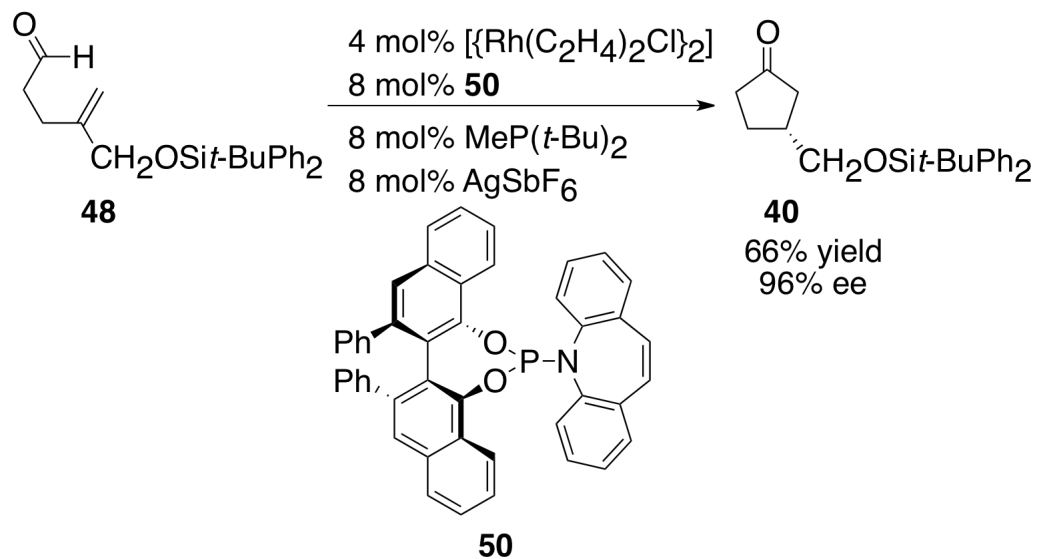
Chiral 3,3'-disubstituted oxindoles are important structural units in alkaloids and pharmaceuticals. Antilla and coworkers realized a highly enantioselective chlorination of 3-substituted oxindoles catalyzed by a chiral calcium VAPOL phosphate salt (Scheme 1.17).³⁹ The same calcium phosphate salt was also found to be an efficient catalyst in the asymmetric Michael addition of 3-aryloxindoles to methyl vinyl ketone,³⁹ as well as the asymmetric benzoyloxylation of 3-aryloxindoles.⁴⁰

Scheme 1.17 Reactions of oxindoles



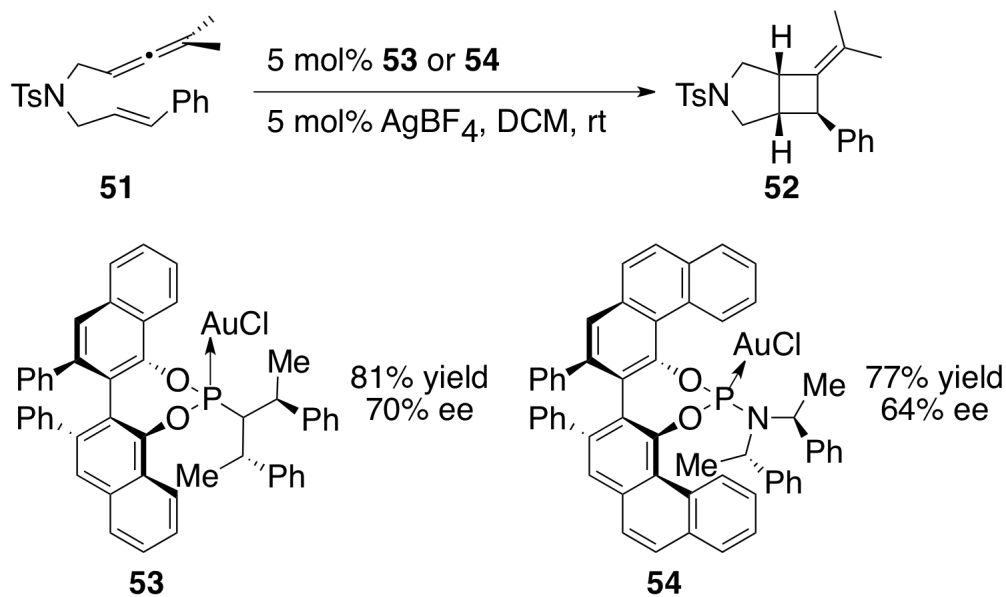
Phosphoramidites derived from VANOL/VAPOL also demonstrated potential in some asymmetric catalytic reactions. Carreira and coworkers showed that intramolecular hydroacylation of pent-4-enals affording β -substituted cyclopentanones could be catalyzed by cationic rhodium complexes prepared from VANOL phosphoramidite-alkene ligand and an achiral phosphine ligand (Scheme 1.18).⁴¹

Scheme 1.18 Hydroacylation of pent-4-enal

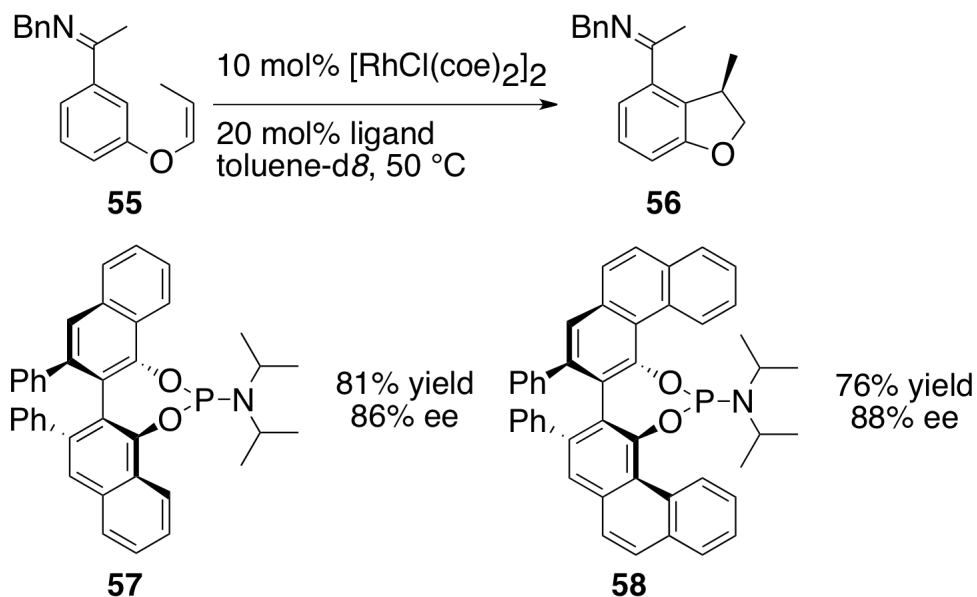


Toste and coworkers explored the potential of VANOL/VAPOL phosphoramidite ligands in the Au(I)-catalyzed asymmetric intramolecular [2+2] cycloaddition of allenenes (Scheme 1.19).⁴²

Scheme 1.19 Cycloaddition of alkene



Scheme 1.20 Hydroarylation of alkene



Ellman and coworkers found that the enantioselective catalytic intramolecular hydroarylation of alkenes via imine directed C-H activation could be promoted by rhodium complexes which are prepared from VANOL/VAPOL phosphoramidite ligands **57** and **58** (Scheme 1.20).⁴³

1.5 Conclusion

The advent of VANOL and VAPOL, a new ligand class, opens a new door to a number of catalytic asymmetric reactions. More and more attention on VANOL/VAPOL has been drawn by the chemical community, as we have seen a rapid increasing demand for VANOL and VAPOL from other research groups and commercial suppliers (i.e. Sigma-Aldrich).

Inspired by the big library of existing BINOL derivatives currently in service, we initiated the project on constructing a library of VANOL/VAPOL derivatives. With the library in hand, a number of reactions could be further optimized. The first highly enantioselective catalytic synthesis of *cis*-alkynyl aziridine-2-carboxylate esters or amides was developed (Chapter 2). This protocol features an unprecedented reagent-dependent catalytic enantiodivergent synthesis of alkynyl aziridines. A large diverse library of 7,7'-disubstituted VANOL derivatives were designed, synthesized and evaluated in the Wulff aziridination reactions of imines and ethyl diazoacetate (Chapter 3). 7,7'-*t*Bu₂-VANOL turned out to be the best and is superior to VANOL/VAPOL for 14 different substrates. Ligands with various substitution patterns on different positions of the VANOL backbone were successfully prepared and evaluated in the Wulff aziridination reactions of imines and ethyl diazoacetate (Chapter 4). This study could shed some light on the critical non-covalent binding interactions between the substrate and the catalyst in the transition states. The synthesis and evaluation of several VAPOL derivatives, the examination of VANOL derivatives in reduction of 2-quinoline, and the synthesis and application of a novel bifunctional squaramide catalyst based on BINAM as a chiral scaffold will also be discussed (Chapter 5).

CHAPTER TWO

REAGENT-DEPENDENT CATALYTIC ENANTIOTHERVEGENT

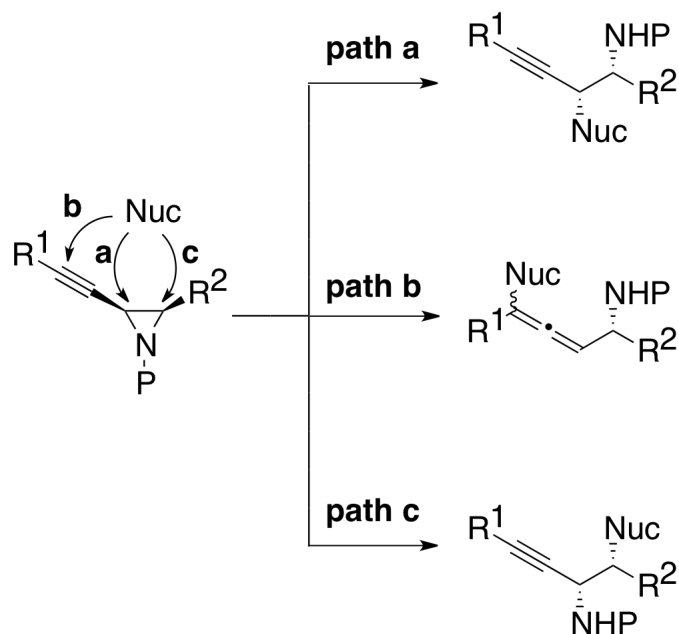
SYNTHESIS OF ALKYNYL AZIRIDINES

2.1 Introduction

The last decade has seen the development of plethora of development of application of the chemistry of alkynyl aziridine. Like other aziridines, alkynyl aziridines with 3-membered cores are of importance for ring opening reactions, and are used in natural products synthesis.

2.1.1 Utility of alkynyl aziridines in organic transformations

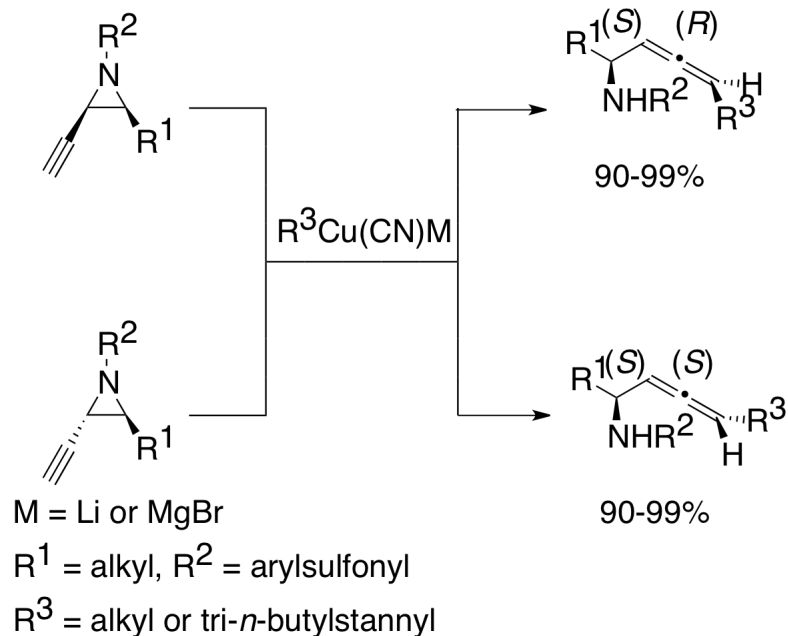
Scheme 2.1 Nucleophilic addition of alkynyl aziridines



Ring opening of alkynyl aziridines could occur in three ways (Scheme 2.1).⁴⁴ The most common attack occurs at the propargylic position (path a) due to activation from the alkyne. A mixture of regioisomers could be obtained with nucleophilic attack on the alkyne carbon to afford an allene (path b) or attack occurring at the homopropargylic carbon (path c). Many variations of the

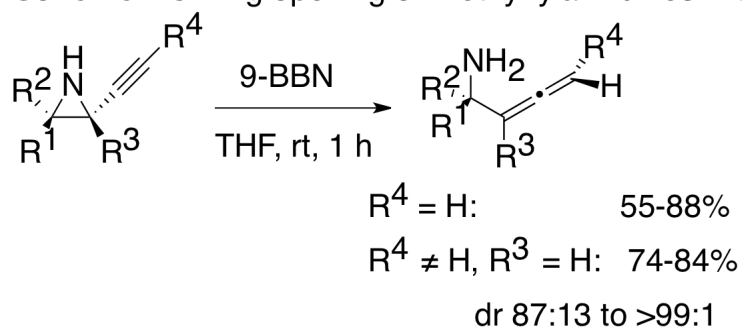
conjugate S_N2' ring opening reactions of alkynyl aziridines with various nucleophiles provide diverse motifs and useful building blocks.

Scheme 2.2 Organocopper-mediated ring opening of 2-ethynylaziridines



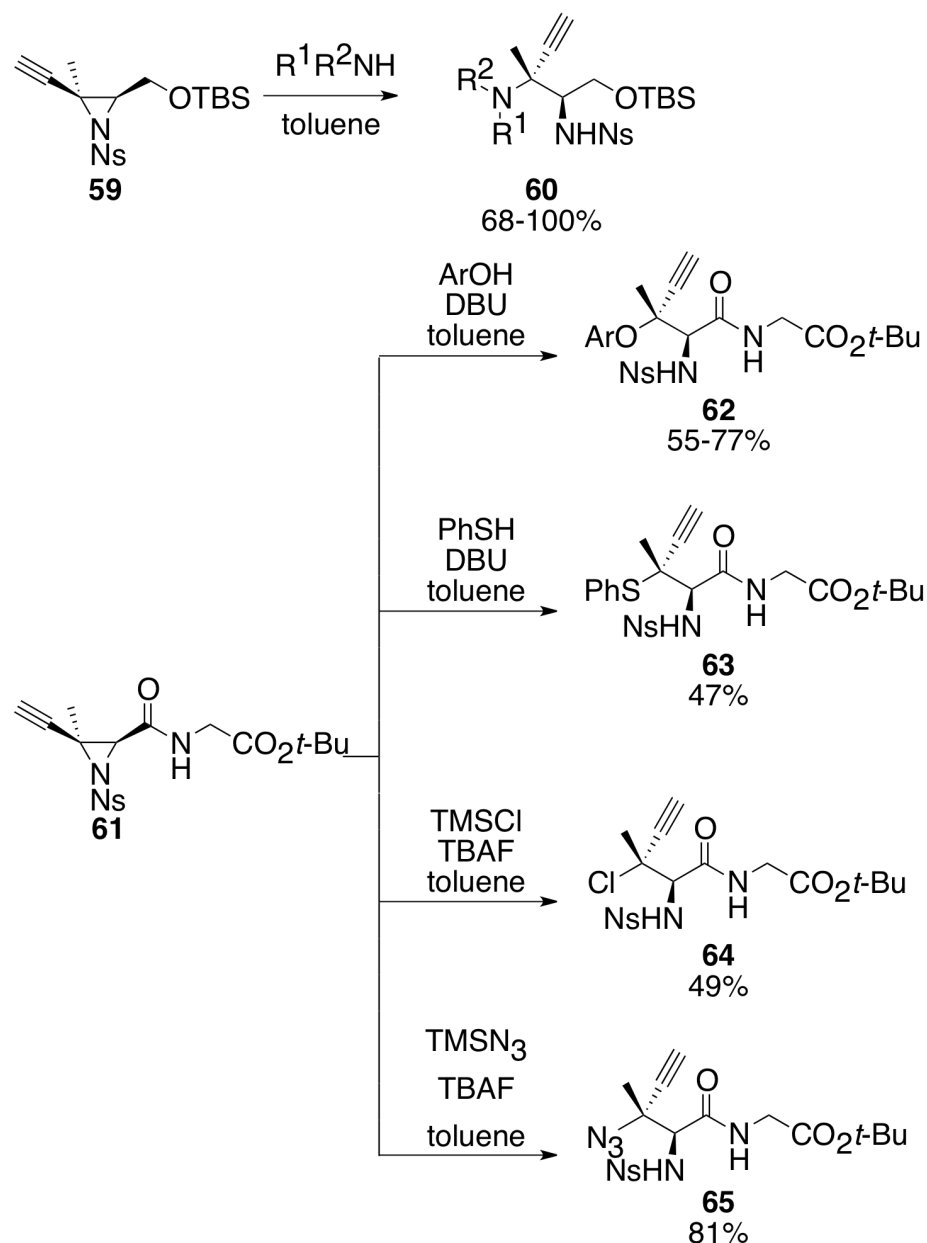
Ohno and coworkers reported that the 3-alkyl-2-ethynylaziridines could be converted to *N*-protected amino allenes stereospecifically via an anti- S_N2' ring opening with organocopper species (Scheme 2.2).⁴⁵ While treatment of (2*S*,2*S*)-2,3-*cis*-3-alkyl-2-ethynylaziridines gives (*S*,*R*)-amino allenes, reaction of (2*R*,2*S*)-2,3-*trans*-3-alkyl-2-ethynylaziridines generates (*S*,*S*)-isomers.

Scheme 2.3 Ring opening of 2-ethynylaziridines with hydride



Yudin and coworkers showed that unprotected α -amino allenes could be accessed via a S_N2' scission of *N*-H alkynyl aziridines with a boron hydride (Scheme 2.3).⁴⁶ A *syn* hydride transfer was suggested following the pre-coordination of boron to the aziridine nitrogen atom.

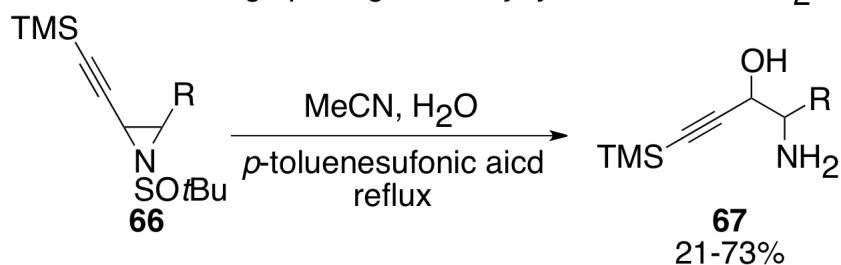
Scheme 2.4 Ring opening of trisubstituted ethynylaziridines with various nucleophiles



In general, ring opening occurs at the more substituted carbon when a trisubstituted ethynylaziridines is employed. Joullié and coworkers demonstrated that ring opening of a

trisubstituted alkynyl aziridines could provide 1,2-diamines in a complete regio- and stereoselective way. They found that the nucleophile could be extended to phenols, thiols, azide and chloride, affording diverse building blocks (Scheme 2.4).⁴⁷

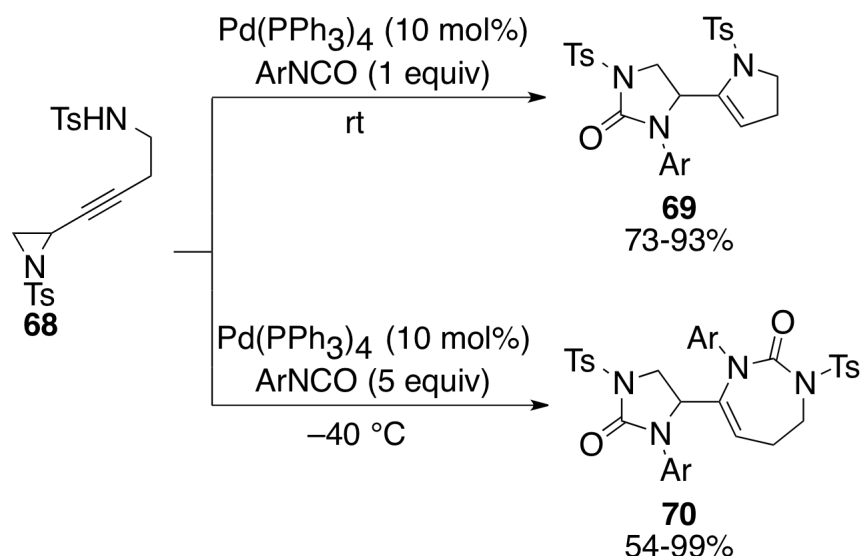
Scheme 2.5 Ring opening of 2-ethynylaziridines with H₂O



Ferreira and coworkers developed a protocol for the synthesis of acetylenic α -amino alcohols via ring opening of 2,3-disubstituted ethynyl *N*-*tert*-butanesulfinylaziridines with *p*-toluenesulfonic acid (Scheme 2.5).⁴⁸ *Cis* and *trans* aziridines furnish *syn* and *anti* α -amino alcohols, respectively. High regio- (>20:1) and diastereoselectivities (>20:1) were achieved.

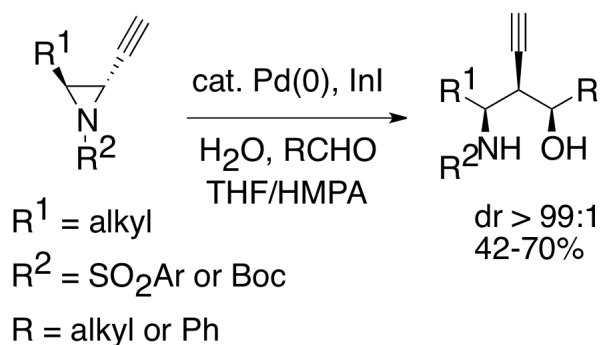
Ohno and coworkers developed a Pd(0) catalyzed domino cyclization/ring expansion of 2-ethynylaziridines bearing a *N*-protected 2-aminoethyl group (Scheme 2.6).⁴⁹ The reaction of *N*-protected 2-(4-aminobut-1-ynyl)aziridine derivatives and aryl isocyanates (1 equiv) at room temperature generates 4-(4,5-dihydropyrrol-2-yl)imidazolidin-2-one derivatives **69**. Interestingly, the reaction of the same substrates with excess isocyanates (5 equiv) at -40 °C affords bis-adducts **70** as the major products.

Scheme 2.6 Cyclization/ring expansion of ethynylaziridines with isocyanates



Ohno and coworkers found that allenylindium reagents with a protected amino group could be synthesized via a Pd(0) catalyzed ring opening of optically pure N-protected 3-alkyl-2-ethynylaziridines by treatment with InI in the presence of H_2O (Scheme 2.7).⁵⁰ The subsequent stereoselective addition of allenylindium reagent to aldehydes yields chiral 1,3-amino alcohols. While 2,3-*trans*-aziridines give *syn,syn*-1,3-amino alcohols, 2,3-*cis*-aziridines give *anti,syn*-1,3-amino alcohols.

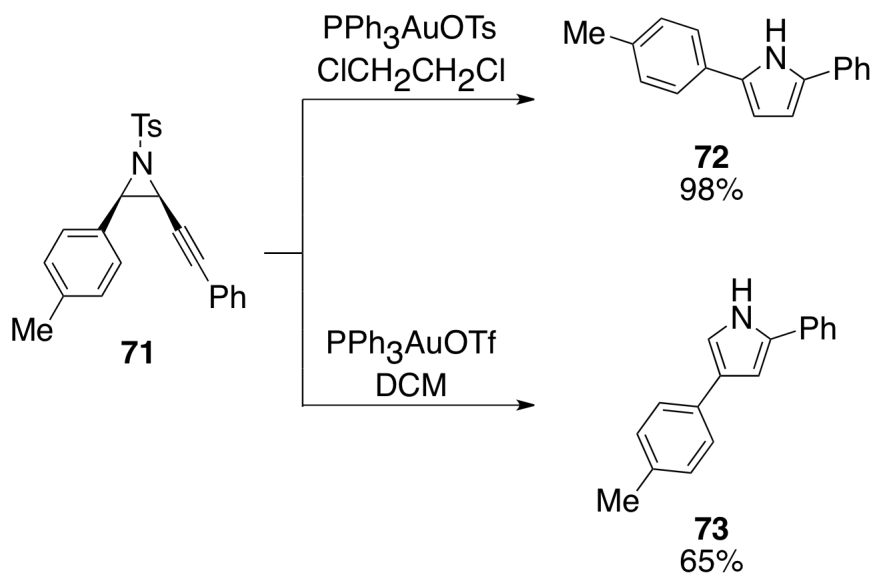
Scheme 2.7 Synthesis of 1,3-amino alcohols



That pyrroles can be prepared from alkynyl aziridines has drawn substantial interest.⁵¹ Davies and coworkers showed that 2,5-substituted pyrroles are formed when OTs is present as the

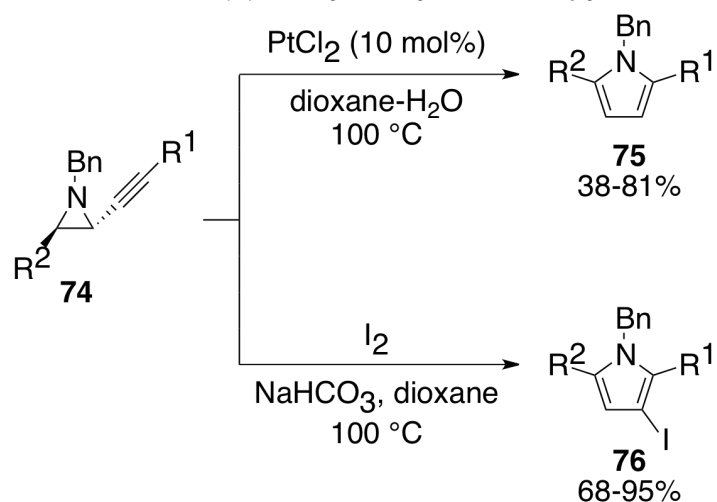
counterion of Au(I) catalyst (Scheme 2.8).^{51a} While with OTf as the counterion, 2,4-substituted pyrroles are obtained via a ring expansion and rearrangement. At the same time, Hou and coworkers reported similar results.^{51c}

Scheme 2.8 Counterion effects in the Au(I) catalyzed synthesis of pyrroles



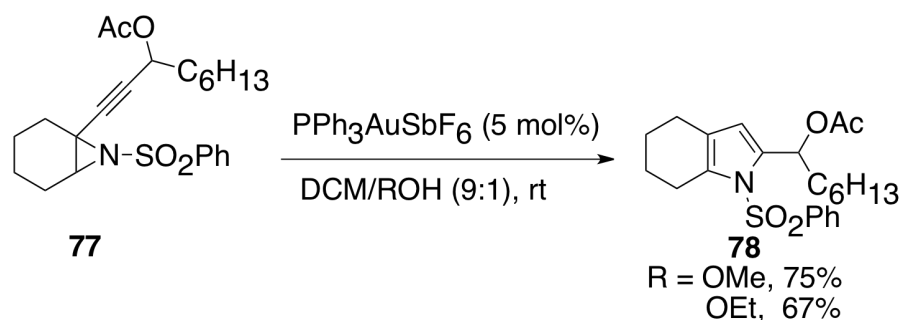
Yoshida and coworkers demonstrated that 2,5-substituted pyrroles could be obtained via a Pt(II) catalyzed cyclization of alkynyl aziridines in aqueous media (Scheme 2.9).^{51b} Treatment of the same substrates with I_2 and NaHCO_3 leads to 3-iodo-2,5-substituted pyrroles.^{51j}

Scheme 2.9 Pt(II) catalyzed synthesis of pyrroles from disubstituted ethynylaziridines



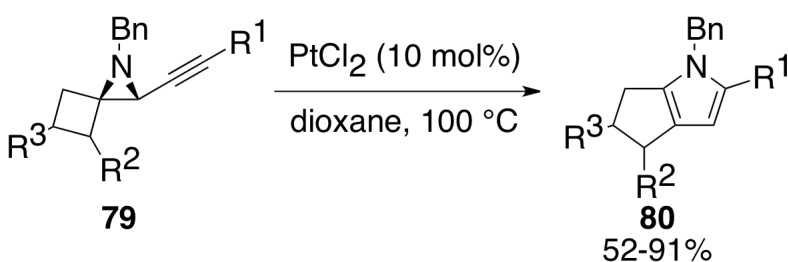
Pale and coworkers found that acyloxylated ethynylaziridines could be efficiently converted into pyrroles catalyzed by Au(I) in the presence of MeOH or EtOH (Scheme 2.10).^{51e}

Scheme 2.10 Au(I) catalyzed synthesis of pyrroles from trisubstituted ethynylaziridines



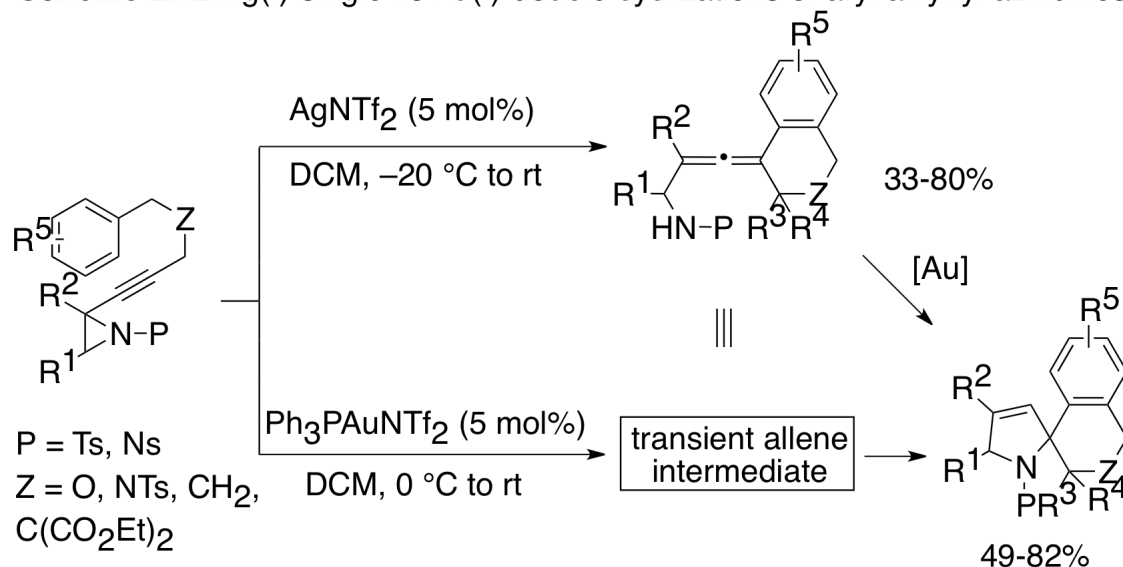
Yoshida and coworkers revealed that 1,4,5,6-tetrahydropenta[b]pyrroles could be accessed from 2-alkyl-1-azaspiro[2.3]hexanes with the aid of the Au(I) catalyst (Scheme 2.11).⁵¹ⁱ

Scheme 2.11 Pt(II) catalyzed synthesis of 1,4,5,6-tetrahydropenta[b]pyrroles



Pale and coworkers showed that alkynyl aziridines with an aryl group could be transformed into aminoallenylidene isochromans, isoquinolines or tetrahydronaphthalenes by Ag(I) and into 1-azaspiro[4.5]decane derivatives by Au(I) (Scheme 2.12).⁵² Both reactions went through a Friedel-Crafts type intramolecular reaction leading to an allene intermediate. This first cyclization was suggested to be an anti-S_N2' reaction. Au(I) also catalyzed a second intramolecular cyclization of the allene intermediate to the spiro species.

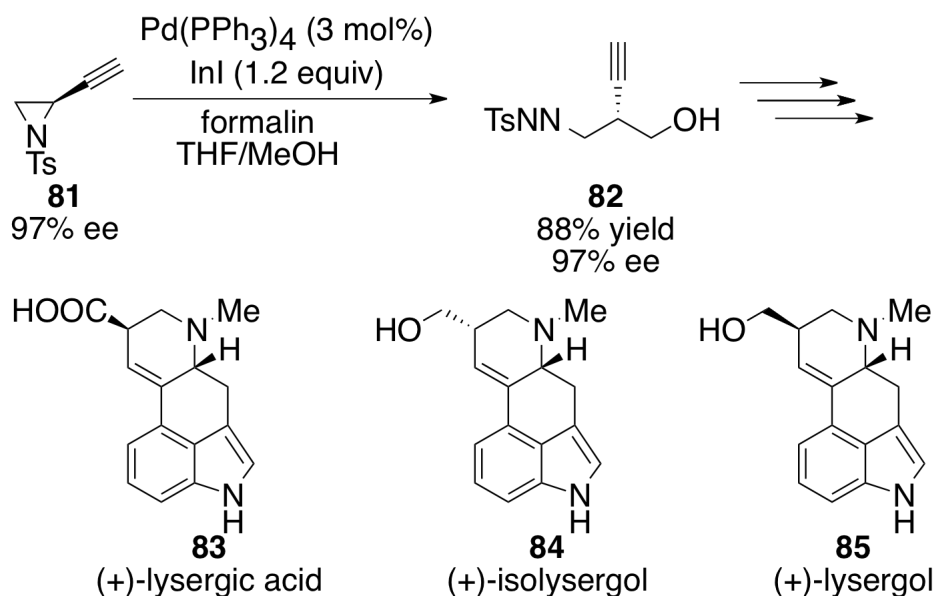
Scheme 2.12 Ag(I)-single vs Au(I)-double cyclizations of aryl alkynyl aziridines



2.1.2 Utility of alkynyl aziridines in natural products synthesis

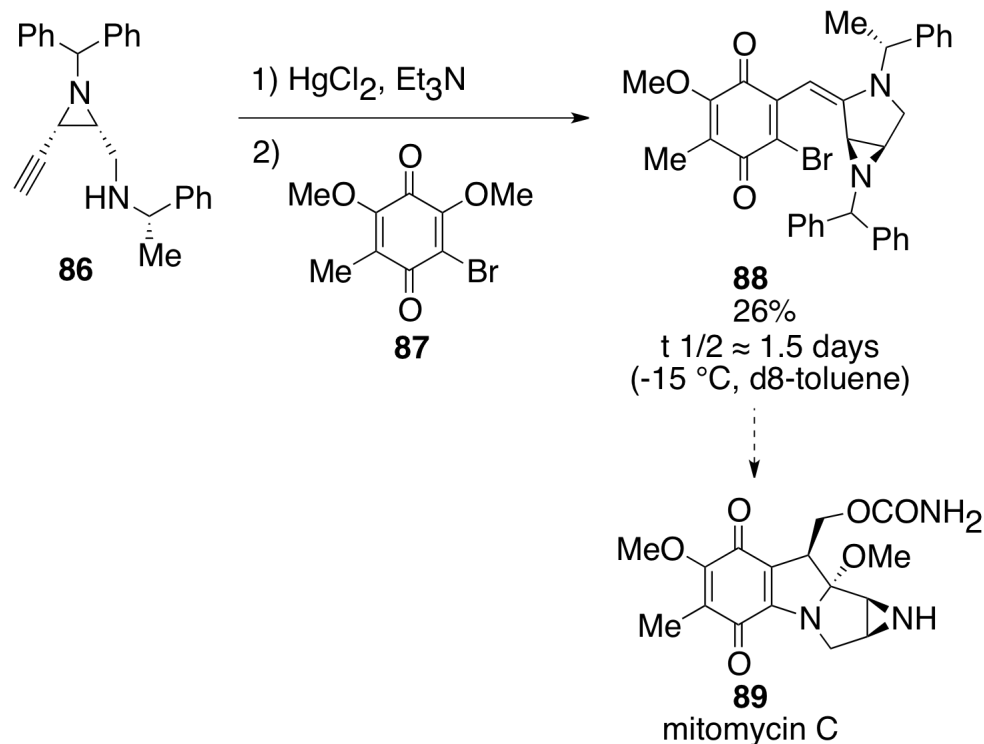
A number of research groups have taken advantages of the established useful transformations of alkynyl aziridines in the total synthesis of natural products.

Scheme 2.13 Total synthesis of (+)-lysergic acid, (+)-isolysergol and (+)-lysergol



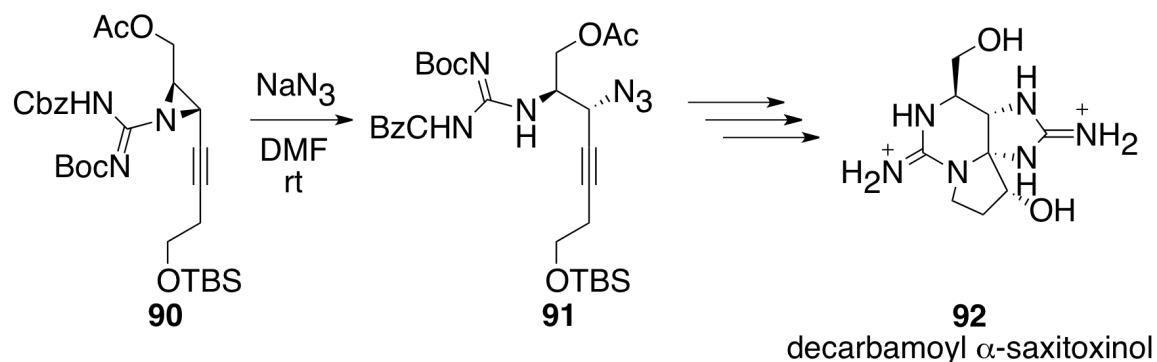
Ohno and coworkers synthesized chiral 1,3-amino alcohol **82** from the Pd(0)- and InI(I)-mediated reductive coupling of the L-serine derived 2-ethynylaziridine **81** and formaldehyde (Scheme 2.13).^{50c} From this intermediate, indole alkaloids (+)-lysergic acid, (+)-isolysergol and (+)-lysergol were synthesized enantioselectively.

Scheme 2.14 Towards total synthesis of mitomycin C



Johnston and coworkers are working on the synthesis of mitomycin natural products. An aminomercuration/coupling sequence on alkynyl amine **86** with quinone **87** gave an advanced intermediate **88** towards the total synthesis of the antitumor agent mitomycin C (Scheme 2.14).⁵³

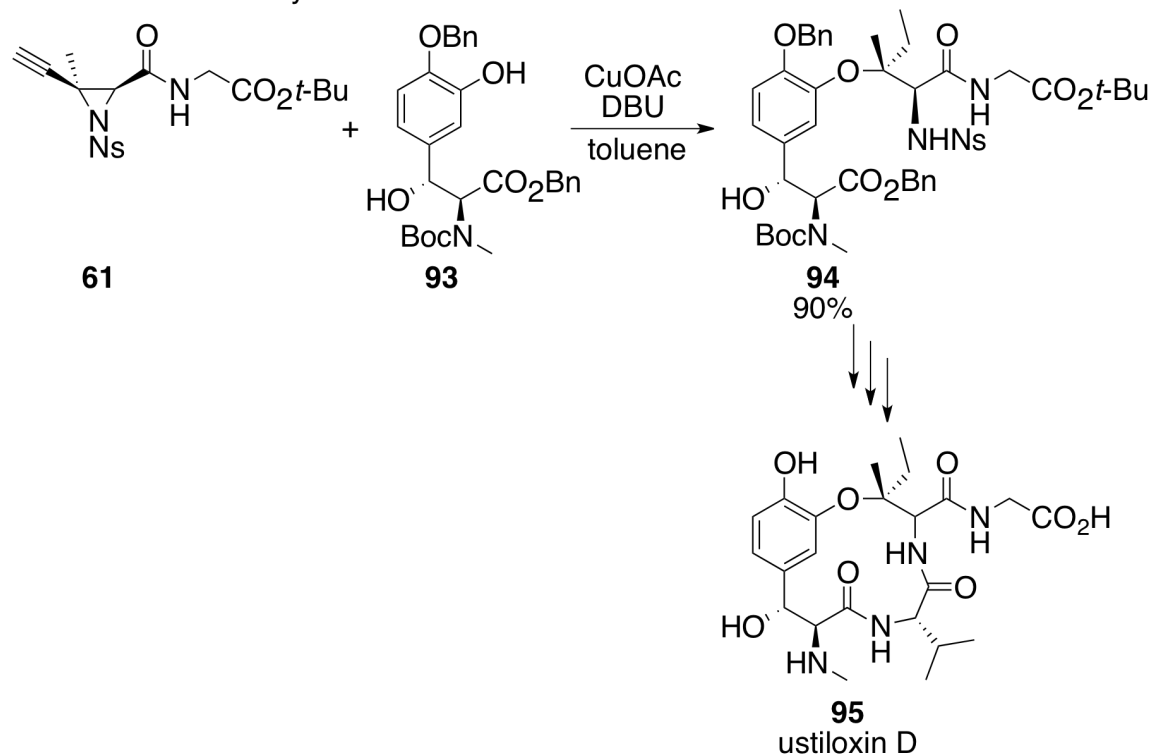
Scheme 2.15 Total synthesis of decarbamoyl α -saxitoxinol



Saxitoxin is a potent and specific blocker of voltage-gated sodium channels. Nishikawa and coworkers completed the total synthesis of decarbamoyl α -saxitoxinol (Scheme 2.15).⁵⁴ One of

the key reactions is the ring opening of guanidino ethynylaziridine **90** with NaN_3 to afford intermediate **91**.

Scheme 2.16 Total synthesis of ustiloxin D

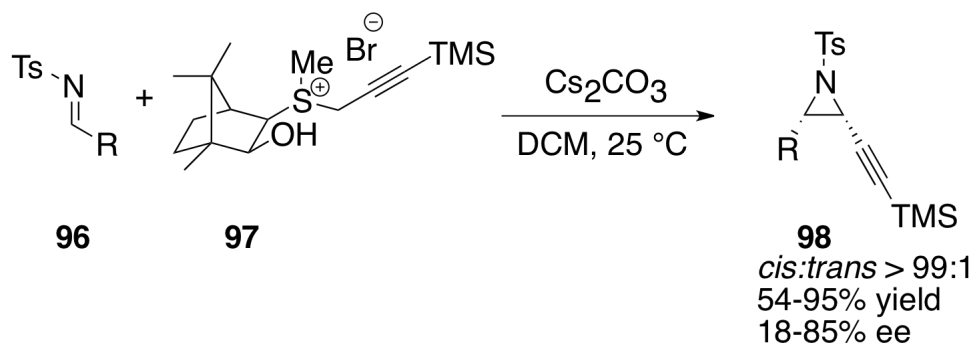


With their previous studies on the chemistry of ethynylaziridines, Joullié and coworkers accomplished the total synthesis of ustiloxin D (Scheme 2.16).^{47c} One of the featured steps is that of a Cu(I) promoted ring opening of an ethynylaziridine with a phenol to yield an alkyl aryl ether in 90% yield. In addition to ustiloxin D, they were able to synthesize ustiloxin F and eight analogues of this family.^{47e} By employing the same chemistry, Wandless and coworkers finished the total synthesis of antimitotic phomposin B.^{47b}

2.1.3 Previous study on the synthesis of alkynyl aziridines

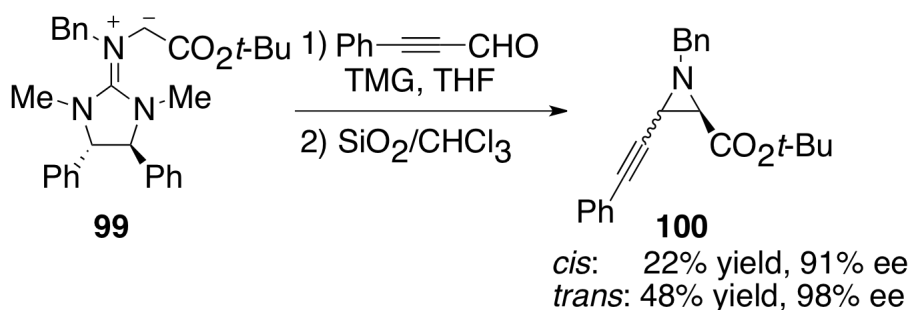
In 1997, Dai and coworkers reported the first asymmetric synthesis of an ethynylaziridine which involves the reaction of *N*-tosylimines with D-(+)-camphor derived chiral sulfonium ylide (Scheme 2.17).⁵⁵ Moderate to good enantioselectivities and excellent *cis/trans* selectivities were obtained.

Scheme 2.17 Reaction of sulfonium ylide with imines



Ishikawa and coworkers showed that reaction of a chiral guanidinium ylide with 3-phenylprop-2-ynal gave an ethynylaziridine with excellent asymmetric induction, though the *trans/cis* ratio was low (Scheme 2.18).⁵⁶

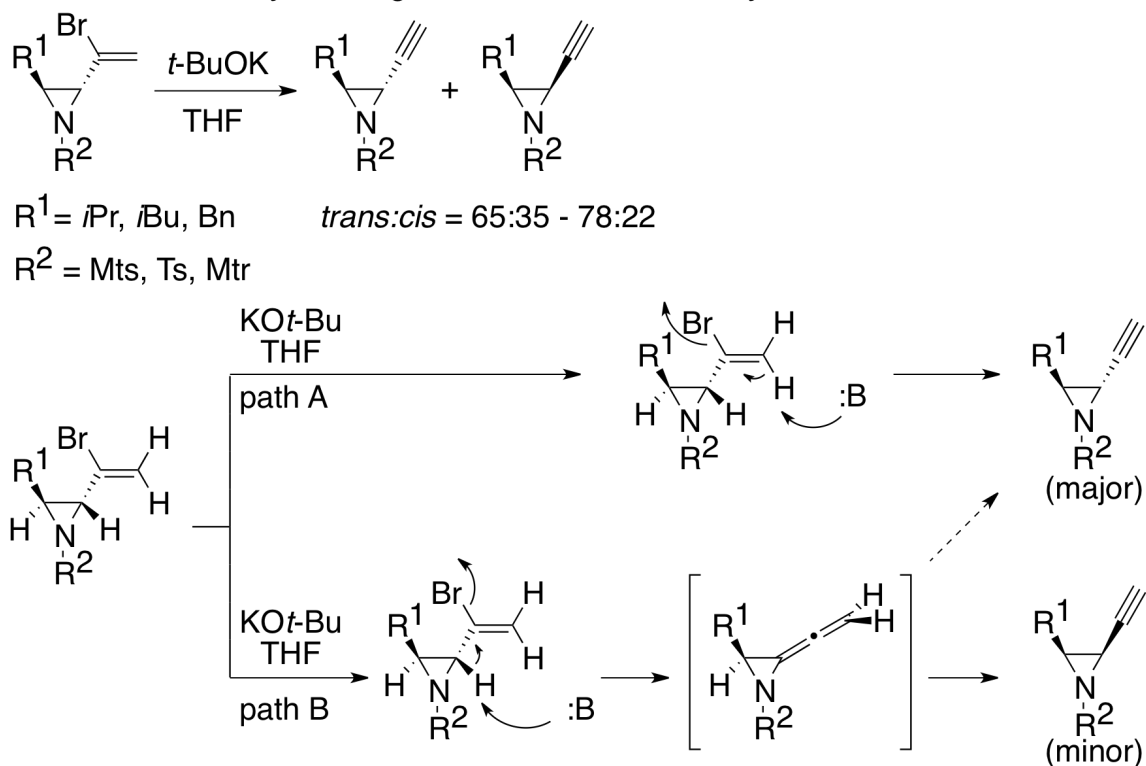
Scheme 2.18 Reaction of guanidinium ylide with aldehydes



Ibuka and coworkers demonstrated that dehydrohalogenation of α -bromoalkenyl aziridines yielded 2,3-*cis*- and 2,3-*trans*-*N*-arylsulfonyl-2-ethynylaziridine with high enantiomeric purity (>99% ee) (Scheme 2.19).⁵⁷ Though the details of the dehydrobromination reactions are not clear, they proposed two pathways which were depicted in Scheme 2.19. If the

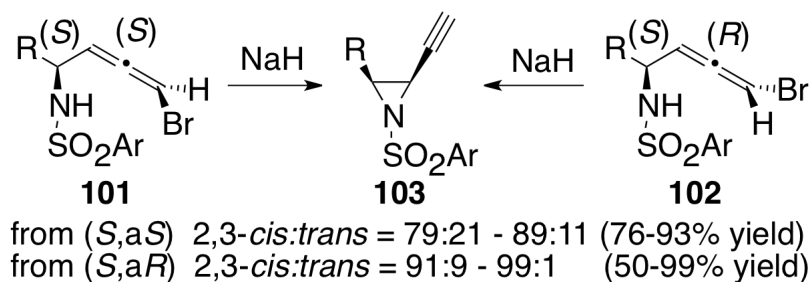
dehydrobromination goes by path A, it will generate the 2,3-*trans*-ethynylaziridine and if it proceeds by path B, it will provide either only 2,3-*trans*-ethynylaziridine or 2,3-*cis*-ethynylaziridine or a mixture of both.

Scheme 2.19 Dehydrohalogenation of α -bromoalkenyl aziridines



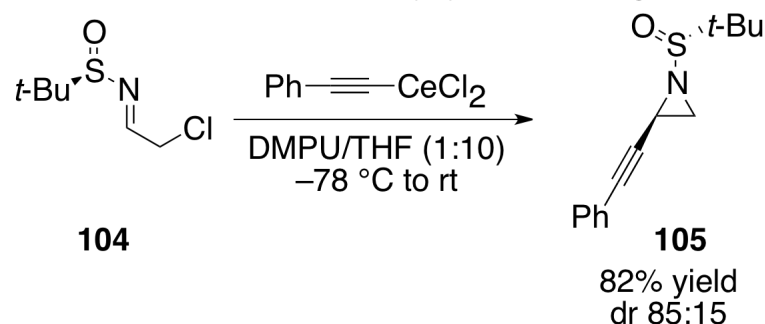
Ohno and coworkers reported that stereoselective synthesis of 2,3-*cis*-2-ethynylaziridines can be achieved from chiral amino allenes mediated by NaH (Scheme 2.20).⁵⁸ Both (4*S*,*aS*)-4-alkyl-[*N*-(arylsulfonyl)amino]-1-bromobuta-1,2-dienes and their (4*S*,*aR*)-isomers give a mixture of 2,3-*cis*- and 2,3-*trans*-2-ethynylaziridines with the former product predominating. The amination of (4*S*,*aR*)-bromoallenes affords better selectivities.

Scheme 2.20 Amination of chiral bromoallenes



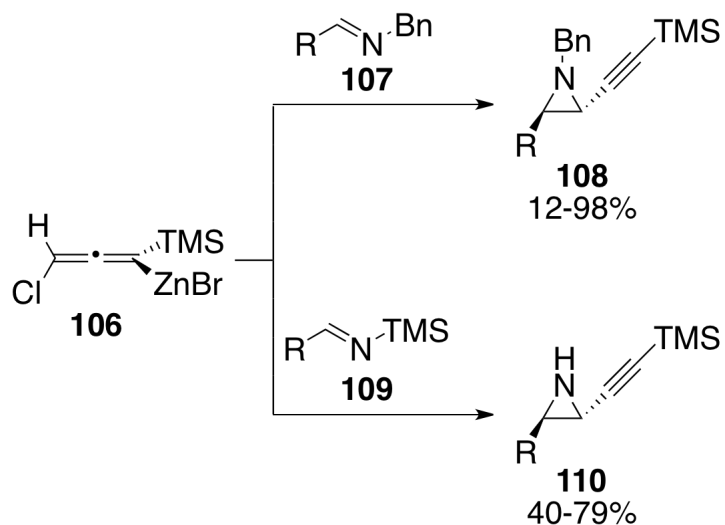
Hodgson and coworkers showed that addition of alkynyl cerium reagent to *N*-(2-chloroethylidene)-*tert*-butylsulfonamide provided alkynyl aziridine **105** in 82% yield with good diastereoselectivity (85:15) (Scheme 2.21).⁵⁹ This was the only example of an ethynylaziridine generated by their protocol.

Scheme 2.21 Addition of alkynyl cerium reagent to α -chloroiminine



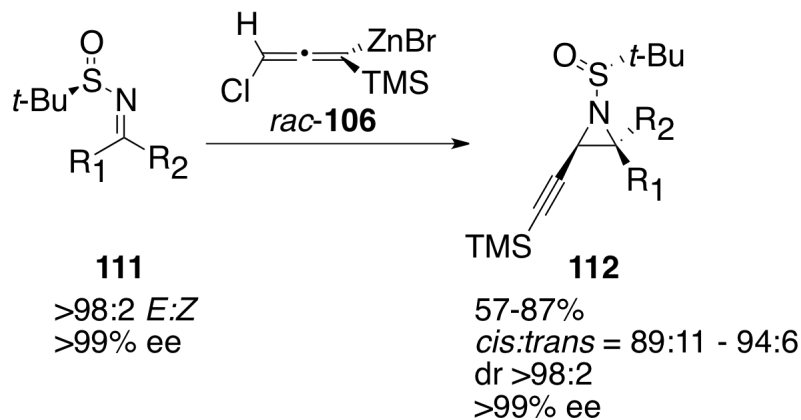
Chemla and coworkers demonstrated that reactions of allenylzinc carbenoid **106** with various imines afforded 2,3-*trans*-ethynylaziridines with excellent stereoselectivities (Scheme 2.22).^{60a,60b} While the reactions of *N*-benzylaldimines **107** gave *N*-benzyl aziridines, the reactions of *N*-(trimethylsilyl)imines **109** gave *N*-H aziridines.

Scheme 2.22 Addition of alkynylzinc reagent to imines



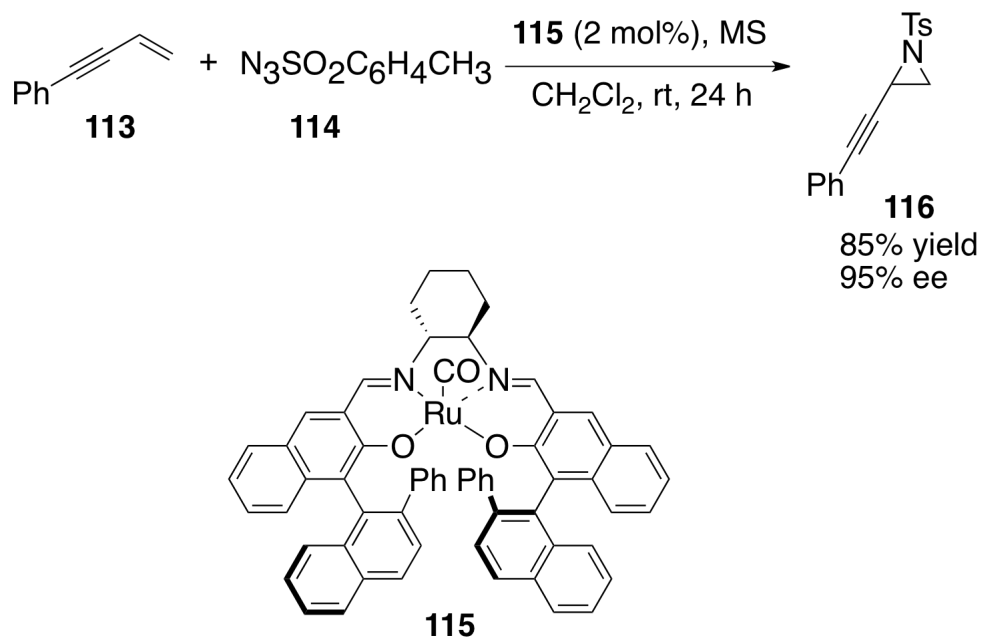
Ferreira and coworkers showed that enantiopure ethynyl *N-tert*-butanesulfinylaziridines could be prepared from the condensation of the *rac* allenylzinc carbenoid **106** onto enantiopure *N-tert*-butanesulfinylaldimines and ketimines **111** in good to excellent yields (Scheme 2.23).^{60c,d,e}

Scheme 2.23 Synthesis of chiral alkynyl aziridines from *rac* allenylzinc reagent



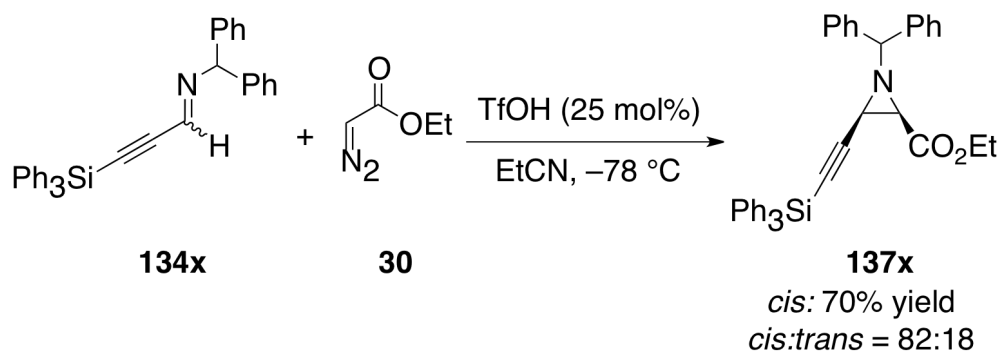
Katsuki and coworkers reported that the (*R,R*)-Ru(salen)(CO) complex **115** can catalyze the asymmetric aziridination of 1-phenyl-3-buten-1-yne, yielding ethynylaziridine **116** in 85% yield and 95% ee (Scheme 2.24).⁶¹ This was the only example of an ethynylaziridine produced by this catalyst.

Scheme 2.24 Catalytic asymmetric aziridination of 1-phenyl-3-buten-1-yne



In their effort towards the total synthesis of mitomycin C, Johnston and coworkers found that the Brønsted acid TfOH will catalyze the aziridination of the imine **134x** and ethyl diazoacetate, providing 2,3-*cis*-2-ethynylaziridine **137x** in 70% yield (Scheme 2.25).^{53b}

Scheme 2.25 Brønsted acid catalyzed aziridination of imine and ethyl diazoacetate

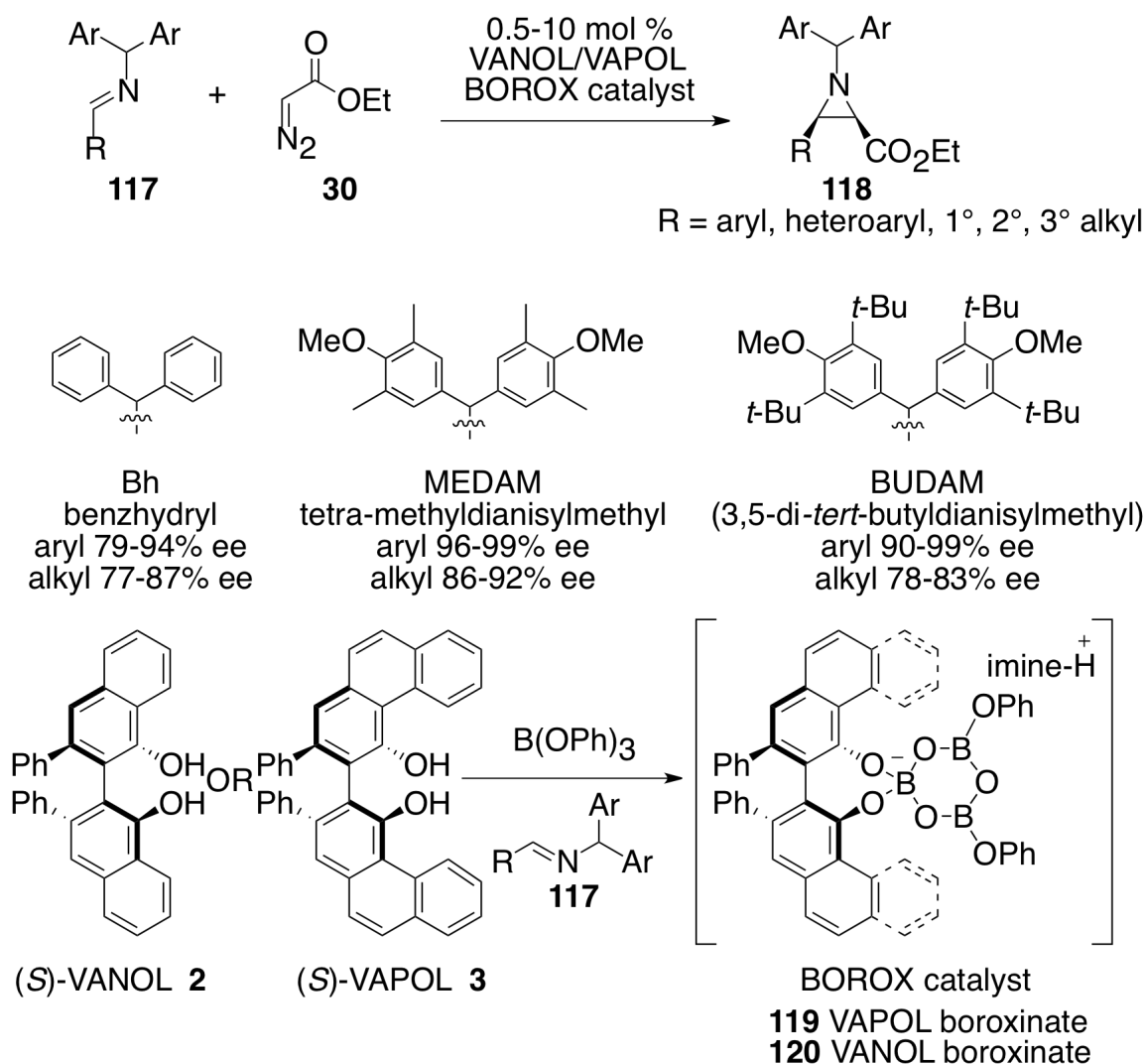


Although great effort has been put into the synthesis of ethynylaziridines, there is no reported procedure that features an asymmetric catalyst that gives high enantioselectivity, high diastereoselectivity and a broad substrate scope.

2.2 Background

Our group has developed an enantioselective catalytic *cis*-aziridination reaction (Wulff *cis*-aziridination) involves imines and diazo compounds.²⁶ Since the first report from our group in 1999, we have put a lot of effort into the continuous study of this transformation (Scheme 2.26). The catalyst in the Wulff *cis*-aziridination was originally believed to be a Lewis acid. Later on we obtained the crystal structure of the complex of the catalyst and the imine which revealed that the actual catalyst is a Brønsted acid.^{26i,26l} The Brønsted acid is a boroxinate which is self-assembled from VANOL or VAPOL, B(OPh)₃ and imine. Imines with various substituents, such as aryl, heteroaryl, 1°, 2°, 3° alkyl, will proceed successfully under the reaction condition. Recently, we have developed a multi-component process from an aldehyde, an amine and a diazo compound.^{26p} As a result, the substrate scope was further broadened.

Scheme 2.26 Wulff *cis*-aziridination reaction

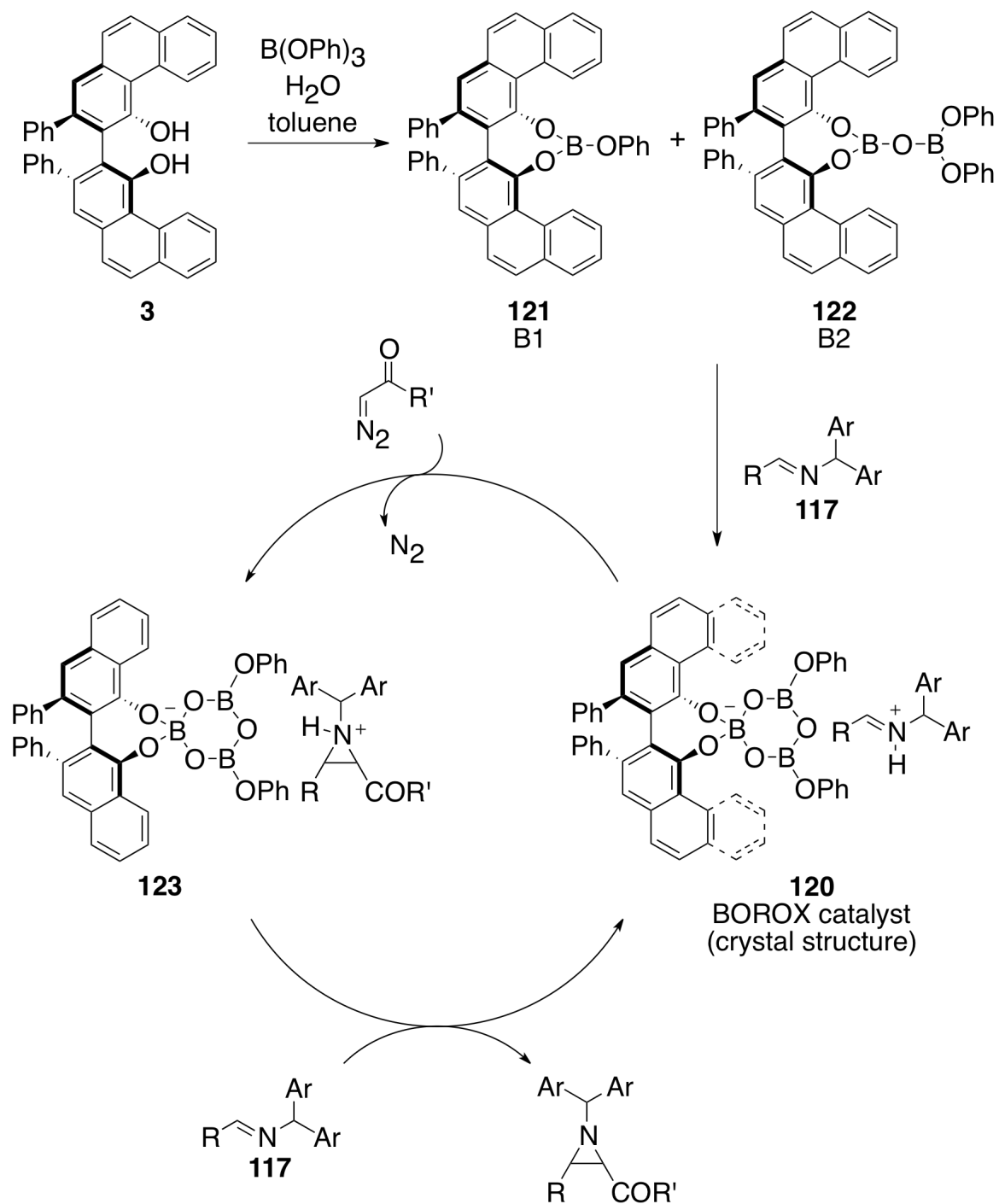


The initial reaction was developed with imines prepared from commercially available benzhydryl amine. Dr. Zhang and Dr. Lu undertook an investigation to extensively probe the effects of changes in the conformation, electronics, and sterics of the two phenyl groups in the *N*-benzhydryl substituent.^{26h,j} The study provided a clearer picture of important non-covalent interactions between the catalyst and the imine. In addition, two useful *N*-substituents, tetra-methyldianisylmethyl (MEDAM) and 3,5-di-*tert*-butyldianisylmethyl (BUDAM), were identified from their study. Subsequently, the reaction scope was defined for the MEDAM group

by Dr. Mukherjee. Clean and high yielding reactions with high enantioselectivities for both aryl and alkyl imines became possible with the Wulff *cis*-aziridination reaction.

The proposed catalytic cycle is shown in Scheme 2.27. VANOL/VAPOL, B(OPh)₃ and H₂O, upon heating generate meso-monoborate (B1) and pyroborate (B2). After addition of the imine substrate, a spiroboroxinate catalyst-imine complex, BOROX (B3) is formed. The diazo compound, upon coordinating with the BOROX catalyst, reacts with the imine to afford the aziridine. The imine will replace the aziridine and regenerate the loaded BOROX catalyst, thus releasing the aziridine product.

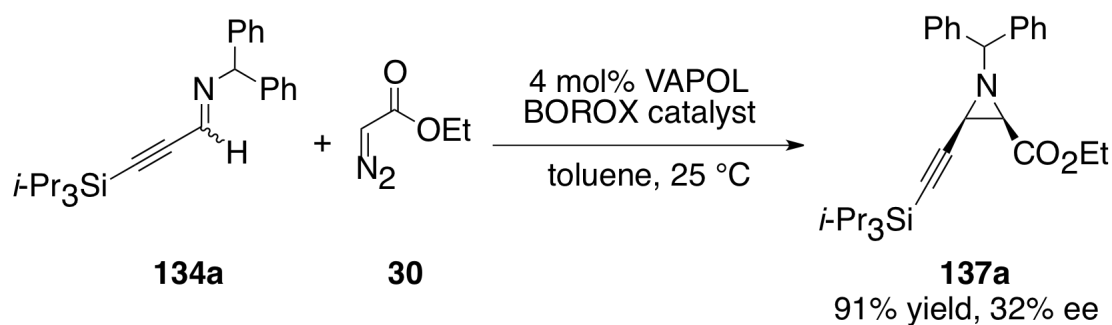
Scheme 2.27 Proposed catalytic cycle of Wulff *cis*-aziridination reaction



2.3 Results and discussion

2.3.1 Aziridinations with ethyl diazoacetate

Scheme 2.28 Wulff *cis*-aziridination reaction of imine

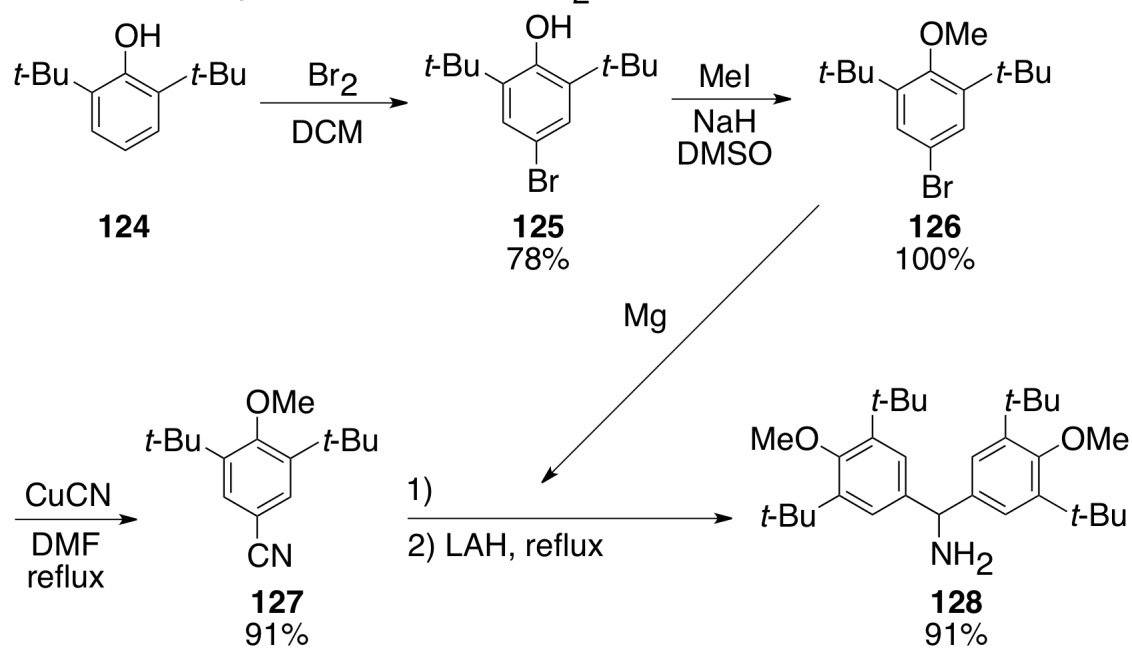


Dr. Patwardhan was the first to examine the Wulff *cis*-aziridination of alkynyl imine derived from 3-phenyl propynal and the result was not promising, giving only moderate yields and asymmetric induction. Dr. Lu found that the yield but not the asymmetric induction could be improved with tri-isopropyl silyl imine **134a** (91% yield and 32% ee) (Scheme 2.28). As had proven to be the case with aryl and alkyl imines it was thought that imines from BUDAM-NH₂ or MEDAM-NH₂ might increase the low induction.

BUDAM-NH₂ **128** was prepared according the published procedure (Scheme 2.29) in a large scale.^{26h} MEDAM-NH₂ **129** was prepared in a similar fashion.^{26j}

Since very few alkynyl aldehydes are commercially available, two practical routes were employed. Each route has its own advantages and shortcomings.

Scheme 2.29 Synthesis of BUDAM-NH₂



The first route involves the formylation of acetylides with DMF (Table 2.1).⁶²

Table 2.1 Synthesis of ynals: Route I

$\text{R}-\text{C}\equiv\text{C} \xrightarrow[2) \text{DMF}]{1) n\text{-BuLi}} \text{R}-\text{C}\equiv\text{C}-\text{CHO}$		
entry	R	% yield
1	C ₆ H ₅	85
2	3-MeC ₆ H ₄	75
3	2-MeC ₆ H ₄	69
4	cyclohexyl	74
5	<i>n</i> -butyl	56
6	<i>t</i> -Bu	50
7	<i>i</i> -Pr ₃ Si	78

The second route consists of a two-step sequence (Table 2.2).⁶³ Sonogashira coupling of aryl iodides with propargyl alcohols and subsequent oxidation with MnO₂ furnishes the preparation of ynals. Compared with the alkynes used in Route I, aryl iodides are cheaper and available in greater variety. However, Route I is more straightforward.

Table 2.2 Synthesis of ynals: Route II

$ \begin{array}{c} \text{HC}\equiv\text{CCH}_2\text{OH} \text{ (1.1 equiv)} \\ \text{Pd(PPh}_3)_2\text{Cl}_2 \text{ (1.5 mol\%)} \\ \text{Cul (1.5 mol\%)} \\ \text{Et}_3\text{N (4 equiv)} \\ \text{THF, N}_2 \end{array} \xrightarrow{\text{R-I}} \begin{array}{c} \text{R-C}\equiv\text{CCH}_2\text{OH} \\ \text{133} \end{array} \xrightarrow[\text{DCM}]{\text{MnO}_2} \begin{array}{c} \text{R-C}\equiv\text{CCHO} \\ \text{131} \end{array} $			
entry	R	% yield (coupling)	% yield (oxidation)
1	4-BrC ₆ H ₄	82	66
2	4-NO ₂ C ₆ H ₄	93	70
3	4-MeOC ₆ H ₄	59	67
4	4-MeO ₂ CC ₆ H ₄	87	67
5	1-naphthyl	55	72

With the ynals and amines in hand, the imines were prepared with a known procedure (Scheme 2.30). Most imines were obtained as a mixture of *trans* and *cis* isomers, which is different from aryl and alkyl imines where only the *trans* isomer is observed.

Scheme 2.30 Preparation of imines

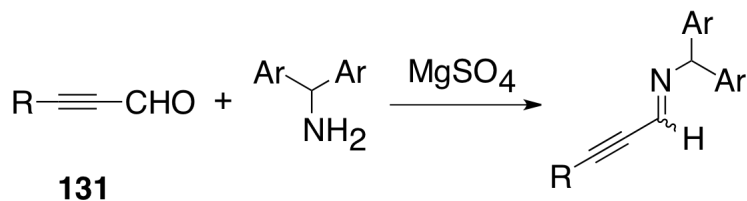


Table 2.3 Optimization of the catalytic asymmetric aziridination of silyl substituted alkynyl imines^a

$$\text{R}-\text{C}\equiv\text{C}-\text{N}=\text{P} + \text{N}_2\text{C}=\text{C}(\text{OEt}) \xrightarrow[\text{toluene, 25 } ^\circ\text{C}]{\text{VAPOL/VANOL BOROX catalyst}} \text{R}-\text{C}\equiv\text{C}-\text{N}(\text{P})-\text{C}(\text{OEt})_2$$

P = Bh **134**
 MEDAM **135**
 BUDAM **136**

P = Bh **137**
 MEDAM **138**
 BUDAM **139**

entry	R	P	ligand	imine	<i>cis/trans</i> imine	AZ	% yield AZ ^b	% ee AZ ^c
1	<i>i</i> -Pr ₃ Si	Bh	(<i>S</i>)-VAPOL	134a	1.3:1	137a	91	32
2	<i>i</i> -Pr ₃ Si	Bh	(<i>R</i>)-VANOL	134a	nd	137a	87	-21
3	Me ₃ Si	Bh	(<i>S</i>)-VAPOL	134b	nd	137b	78	32
4	<i>i</i> -Pr ₃ Si	MEDAM	(<i>S</i>)-VAPOL	135a	1.5:1	138a	87	44
5	<i>i</i> -Pr ₃ Si	MEDAM	(<i>R</i>)-VANOL	135a	nd	138a	89	-40
6	<i>i</i> -Pr ₃ Si	BUDAM	(<i>S</i>)-VAPOL	136a	nd	139a	97 ^d	83
7	<i>i</i> -Pr ₃ Si	BUDAM	(<i>S</i>)-VANOL	136a	nd	139a	97 ^d	78
8	Me ₃ Si	BUDAM	(<i>S</i>)-VAPOL	136b	19:1 ^e	139b	93	85
9	Me ₃ Si	BUDAM	(<i>S</i>)-VAPOL	136b	1.6:1	139b	86 ^f	84
10	Me ₃ Si	BUDAM	(<i>R</i>)-VANOL	136b	19:1 ^e	139b	91	-74
11	Me ₃ Si	BUDAM	(<i>S</i>)-VAPOL	136b	19:1 ^e	139b	87 ^{d,f}	80

^a Unless otherwise specified, all reactions were performed at 0.5 M in ether with 1.1 equiv of EDA for 24 h with 10 mol% catalyst. The catalyst was prepared from 1 equiv VAPOL or

Table 2.3 (cont'd)

VANOL, 4 equiv B(OPh)₃ and 1 equiv H₂O at 80 °C in toluene for 1 h, followed by removal of volatiles under vacuum (0.5 mm Hg) at 80 °C for 0.5 h. No *trans*-aziridine was detected in any reaction.^b Isolated yield of *cis*-aziridine **137**, **138**, **139** after chromatography on silica gel.^c Determined by HPLC on a Chiralcel OD-H column. The induction in all entries was determined after conversion of **139b** to the *N*-H aziridine **141**.^d 2 mol% catalyst.^e The isomer ratio was enhanced by crystallization from EtOAc/hexane.^f Overall yield of **141** from **136b**.

Dr. Zhang and Dr. Lu performed optimization experiments on the catalytic asymmetric aziridination of silyl substituted alkynyl imines (Table 2.3).⁶⁴ The focus was on the *N*-substituent and the difference between VANOL and VAPOL. VAPOL gives a better enantioselectivity than VANOL. For example, the reaction of Bh imine with VAPOL gave 32% ee, while with VANOL as ligand, the reaction yielded 21% ee (Table 2.3, entry 1 vs 2). With the same silyl substituent, same ligand, BUDAM was the optimal *N*-substituent (83% ee, entry 6), followed by MEDAM (44% ee, Table 2.3, entry 4) and benzhydryl (32% ee, Table 2.3, entry 1). TMS and TIPS substituted alkynyl imines gave similar results. Another interesting finding is that the enantioselectivities are independent of the geometry of the imine, since both 1.6:1 and 19:1 mixtures of imine **136b** gave the same asymmetric induction (Table 2.3, entries 8 & 9).

Dr. Lu and Dr. Lopez-Alberca undertook a further optimization of the temperature and solvent (Table 2.4).⁶⁴ The optimal temperature was found to be –20 °C in terms of both asymmetric induction and yield (Table 2.4, entries 1-4). Solvent screening revealed that ether was the best

(Table 2.4, entries 5-7). With the optimal conditions, the aziridine **139b** could be obtained in 86% yield and 95% ee (Table 2.4, entry 7).

Table 2.4 Optimization of the catalytic asymmetric aziridination of imine **136b**^a

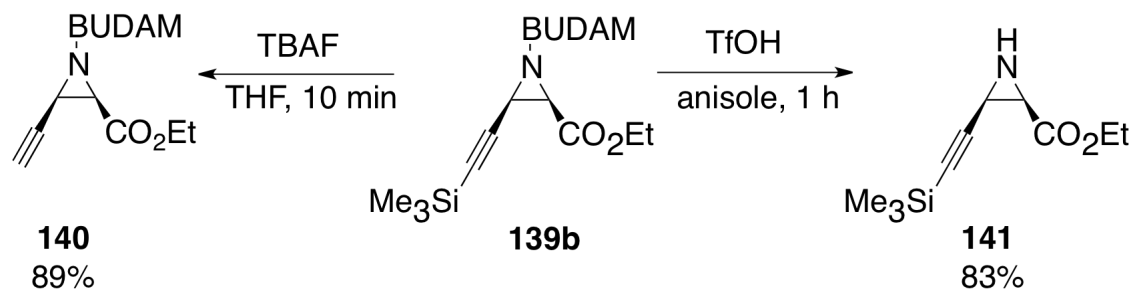
$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}=\text{N}-\text{BUDAM}$ 136b + $\text{CH}_2=\text{N}_2-\text{C}(=\text{O})\text{OEt}$ 30 $\xrightarrow[\text{solvent, temp}]{\text{VAPOL, BOROX catalyst}}$ 139b					
entry	mol% catalyst	temp (°C)	solvent	% yield AZ ^b	% ee AZ ^c
1	4	25	toluene	81	80
2	4	0	toluene	86	83
3	4	-20	toluene	90	87
4	4	-40	toluene	69	75
5	10	-20	toluene	90	90
6	10	-20	CCl ₄	86	74
7	10	-20	Et ₂ O	86	95

^a Unless otherwise specified, all reactions were performed at 0.5 M in ether with 1.1 equiv of EDA for 24 h with 10 mol% catalyst. The catalyst was prepared as described in Table 2.3. ^b Isolated yield after chromatography on silica gel. ^c Determined by HPLC on a Chiralcel OD-H column. The induction in all entries was determined after conversion of to the *N*-H aziridine **141**.

The ee of aziridine **139b** was measured by chiral HPLC after the removal of BUDAM (Scheme 2.31). Treatment of BUDAM aziridine **139b** with 5 equivalents of triflic acid in anisole for 1 h at

room temperature gave the *N*-H aziridine **141** in 83% yield. Orthogonal removal of TMS could be achieved with tetra-butylammonium fluoride, affording ethynyl aziridine **140** in 89% yield.

Scheme 2.31 Transformations of BUDAM alkynyl aziridine **139b**



The reaction of imines from phenylpropynal gave an unexpected side product in addition to the desired alkynyl aziridine (Table 2.5). Analysis of the purified side product revealed that it resulted from both a [3+2] and a [2+1] cycloaddition with two molecules of ethyl diazoacetate. Based on the structures of reported [3+2] adducts of ethyl diazoacetate with α,β -unsaturated alkynyl esters, ketones and aldehydes, the regiochemistry of this [3+2] adduct was assumed by analogy.⁶⁵ Again, BUDAM imine was superior to MEDAM or benzhydryl imines in terms of asymmetric induction and reaction conversion under the same conditions (Table 2.5, entries 1-6). Ether was a superior solvent to toluene (Table 2.5, entry 9 vs 6) and VAPOL was a better ligand than VANOL (Table 2.5, entry 9 vs 10).

Table 2.5 Optimization of the catalytic asymmetric aziridination of phenylpropynyl imines^a

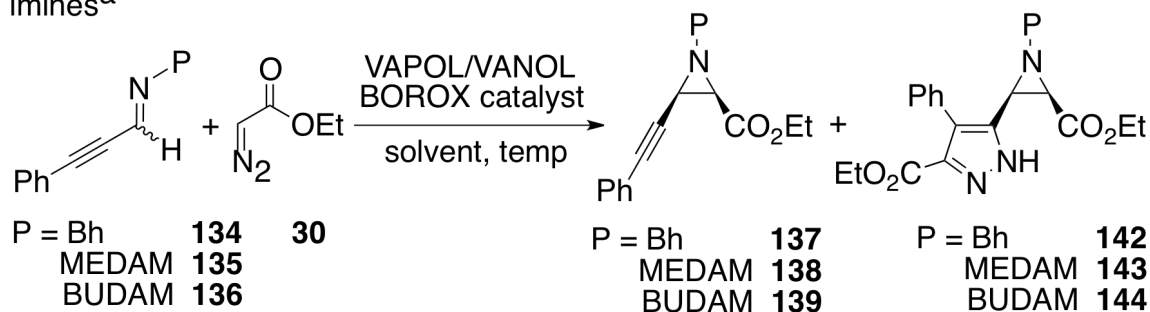


Table 2.5 (cont'd)

entry	P	ligand	solvent	temp (°C)	% conv ^b	% yield AZ ^c	% ee AZ ^d	% yield, 142-144 ^e
1	Bh	(<i>S</i>)-VAPOL	toluene	25	39	21	17	2
2	Bh	(<i>R</i>)-VANOL	toluene	25	47	30	0	1
3	MEDAM	(<i>S</i>)-VAPOL	toluene	25	22	14	49	<1
4	MEDAM	(<i>R</i>)-VANOL	toluene	25	21	14	-25	<1
5	BUDAM	(<i>S</i>)-VAPOL	toluene	25	100	61	87	4
6	BUDAM	(<i>S</i>)-VAPOL	toluene	-20	100	67	92	11
7	BUDAM	(<i>S</i>)-VAPOL	ether	25	100	52	93	15
8	BUDAM	(<i>S</i>)-VAPOL	ether	0	100	61	96	10
9	BUDAM	(<i>S</i>)-VAPOL	ether	-20	100	66	97	18
10	BUDAM	(<i>R</i>)-VANOL	ether	-20	100	49	-85	17
11 ^f	BUDAM	(<i>S</i>)-VAPOL	ether	-20	100	56	95	14
12 ^g	BUDAM	(<i>S</i>)-VAPOL	ether	-20	100	32 ^h	nd	6
13 ⁱ	BUDAM	(<i>S</i>)-VAPOL	ether	-20	100	58 ^h	nd	3
14	BUDAM	(<i>S</i>)-VAPOL	ether	-40	100	57	98	23

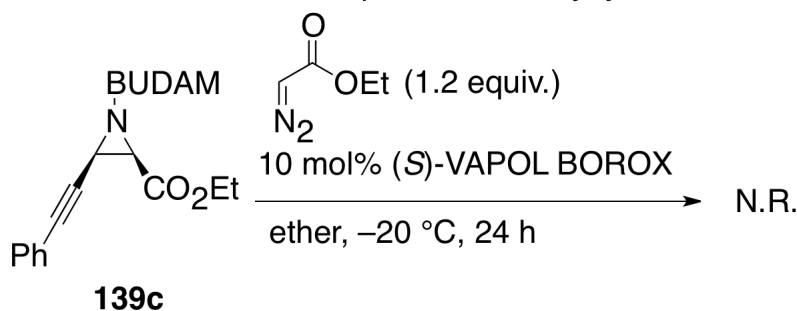
^a Unless otherwise specified, all reactions were performed at 0.5 M in ether with 1.2 equiv of EDA for 24 h with 10 mol% catalyst. The catalyst was prepared as described in Table 2.3. nd = not determined. No *trans*-aziridine was detected in any reaction. ^b Determined from ¹H NMR

Table 2.5 (cont'd)

spectrum of the crude reaction mixture. ^c Isolated yield after chromatography on silica gel. ^d Determined on purified *cis*-aziridine by HPLC. ^e Determined from ¹H NMR spectrum of the crude reaction mixture and based on isolated yield of *cis*-aziridine. ^f 5 mol% catalyst. ^g Reaction with 0.9 equiv of EDA. ^h Determined from ¹H NMR spectrum of the crude reaction mixture with Ph₃CH as internal standard. ⁱ Reaction with 4.0 equiv of EDA. ^j A third product is produced in 14% yield and is tentatively assigned as the regioisomer of **144**.

When 4.0 equivalents of ethyl diazoacetate was used, the yield of the alkynyl aziridine didn't increase (Table 2.5, entry 13). A control experiment was performed with alkynyl aziridine **139c**, ethyl diazoacetate and VAPOL-BOROX catalyst generated from VAPOL, B(OPh)₃, H₂O and benzhydryl imine **9d**, but no [3+2] pyrrazole side product was formed.

Scheme 2.32 Control experiment of alkynyl aziridine



Scheme 2.33 Formation of the [3+2] adduct

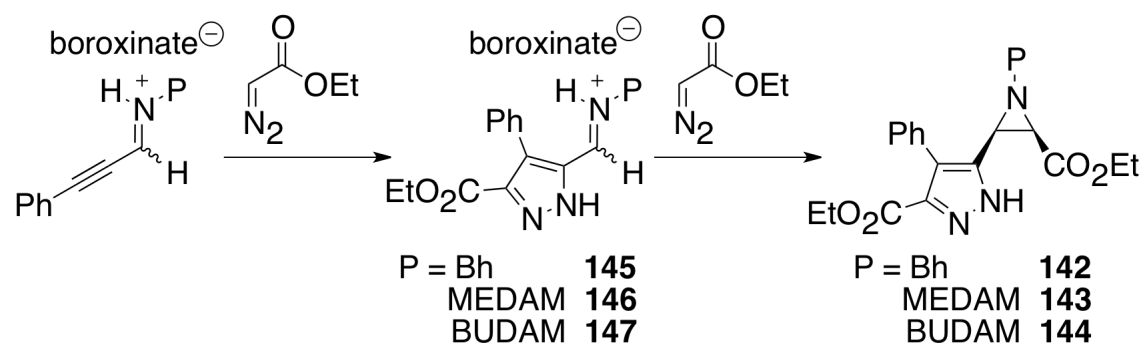


Table 2.6 Catalytic asymmetric synthesis of alkynyl aziridines with ethyl diazoacetate^a

	136	30		139		144	
entry	R	imine	ligand	AZ	% yield	% ee	%
					AZ ^b	AZ ^c	yield ^d
1	Me ₃ Si	136b	(<i>S</i>)-VAPOL	139b	86	95	-
2	C ₆ H ₅	136c	(<i>S</i>)-VAPOL	139c	66	97	18
3	C ₆ H ₅	136c	(<i>R</i>)-VANOL	139c	49	-85 ^e	17
4	4-MeOC ₆ H ₄	136d	(<i>S</i>)-VAPOL	139d	45	96	27
5	4-MeOC ₆ H ₄	136d	(<i>R</i>)-VANOL	139d	24	-83 ^e	11
6	4-BrC ₆ H ₄	136e	(<i>S</i>)-VAPOL	139e	54	97	24
7	4-BrC ₆ H ₄	136e	(<i>R</i>)-VANOL	139e	25	-53 ^e	5
8	4-MeO ₂ CC ₆ H ₄	136f	(<i>S</i>)-VAPOL	139f	57	94	19
9	4-MeO ₂ CC ₆ H ₄	136f	(<i>R</i>)-VANOL	139f	30	-54 ^e	5

Table 2.6 (cont'd)

10	4-NO ₂ C ₆ H ₄	136g	(<i>S</i>)-VAPOL	139g	35	88	22
11	4-NO ₂ C ₆ H ₄	136g	(<i>R</i>)-VANOL	139g	8	−41 ^e	3
12	<i>n</i> -butyl	136k	(<i>S</i>)-VAPOL	139k	nd ^f	nd	nd
13	cyclohexyl	136l	(<i>S</i>)-VAPOL	139l	nd ^f	nd	nd

^a Unless otherwise specified, all reactions were performed at 0.5 M in ether with 1.2 equiv EDA at −20 °C for 24 h with 10 mol% catalyst. The catalyst was prepared as described in Table 2.3.

nd = not determined. No *trans*-aziridine was detected in any reaction. ^b Isolated yield after chromatography on silica gel. ^c Determined on purified *cis*-aziridine **139** by HPLC. ^d Determined from ¹H NMR spectrum of the crude reaction mixture and based on isolated yield of *cis*-aziridine. ^e Enantiomer of **139** is formed. ^f Complex mixture of products was formed. The ratio of **139:144** was ~ 1:1 but neither was the major species.

Based on those observations, we believe that the [3+2] cycloaddition should occur before the aziridination (Scheme 2.33).

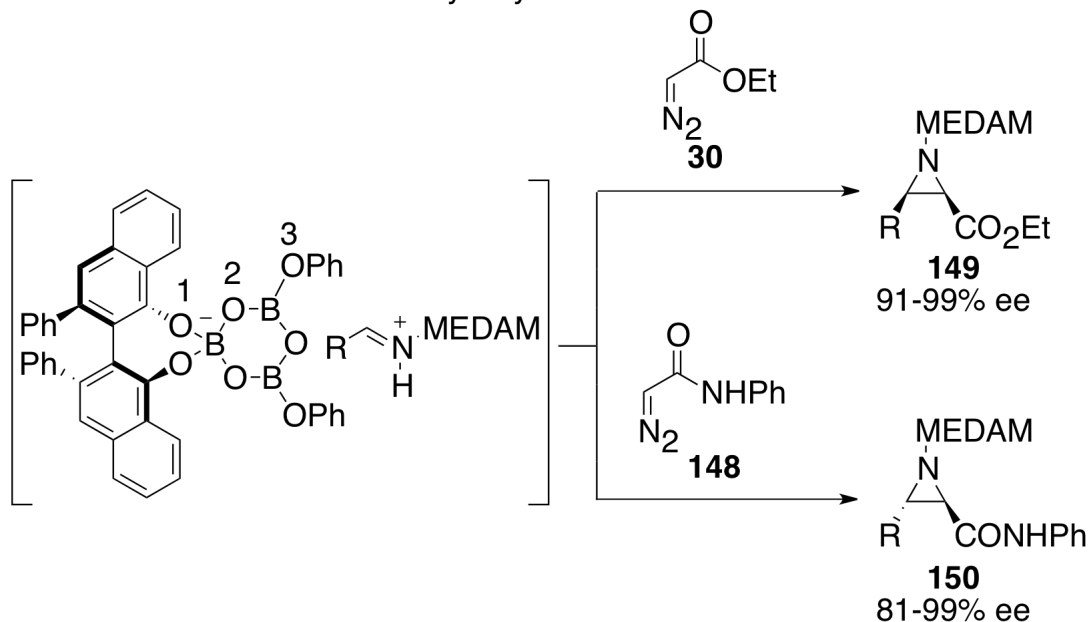
With the optimal condition established, the scope of the transformation was developed (Table 2.6). VAPOL gave uniformly superior performance in terms of both asymmetric induction and yield. Excellent enantioselectivities and good yields were obtained with aryl and silyl substituted alkynyl imines. In the case of aryl substituted alkynyl imines, pyrrazoles were observed in small amounts. However, no such side product was observed with silyl substituted alkynyl imines.

Aliphatic substituted alkynyl imines gave complicated reaction mixtures which were not characterized (Table 2.6, entries 12 and 13).

2.3.2 Aziridinations with diazoacetamide

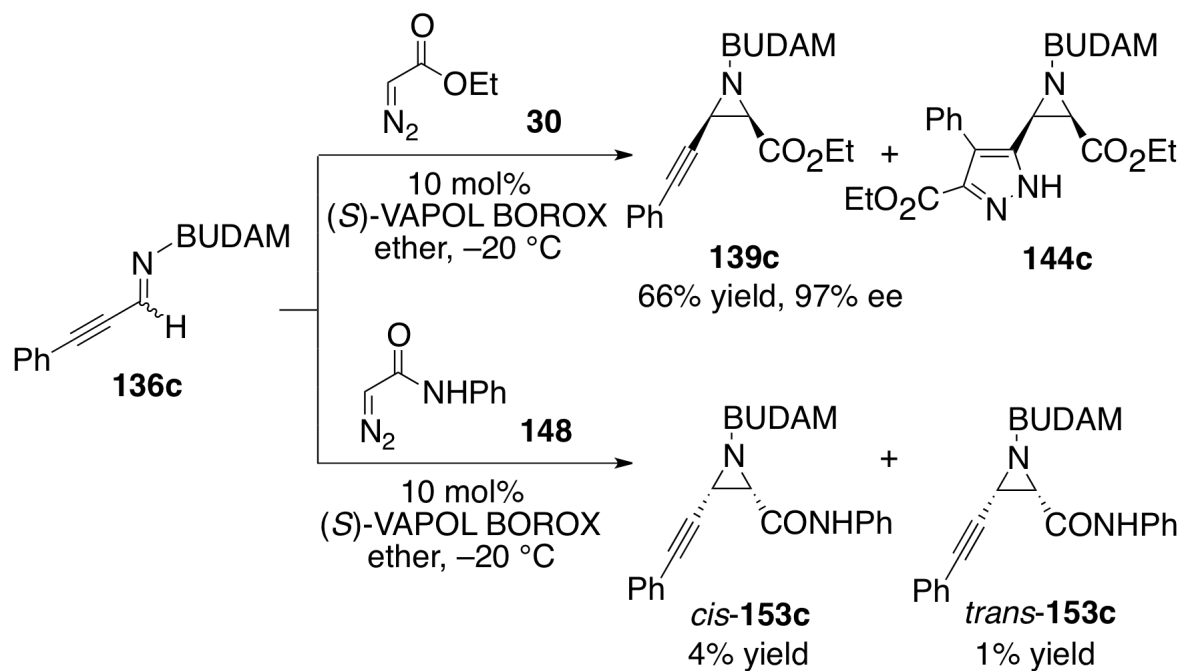
Recently, we reported that *trans*-aziridines could be obtained from the same imines and same BORO-X catalyst by switching from a diazo ester to a diazoacetamide (Scheme 2.34).^{27a} Computational studies suggest that in case of *cis*-aziridine formation, the protonated imine is H-bonded to O-1 of the boroxinate core and ethyl acetate is H-bonded to O-2.^{27b} While in the course of *trans*-aziridine formation, the protonated imine is H-bonded to O-3 and diazoacetamide is H-bonded to O-1 and O-2. The reversed binding sequence contributes to the opposite diastereochemical outcome.

Scheme 2.34 A universal catalyst system for both *cis*- and *trans*-aziridines



It was originally expected that the azidination of the same alkynyl imines with diazoacetamide would lead to *trans*-alkynyl aziridines. However, very little amounts of aziridines were observed (Scheme 2.35) under the conditions that were optimized for the ethyl diazoacetate **30** (Table 2.6). The reaction of alkynyl imine **136c** with diazoacetamide **148** under the identical condition with ethyl diazoacetate **30** gave the *cis*-aziridine **153c** in 4% yield (¹H NMR yield) and the *trans*-aziridine **153c** in 1% yield (¹H NMR yield), and no starting imine remained. VANOL gave a better result (16% *cis*-aziridine **153c** and 13% *trans*-aziridine **153c**) under the same conditions (Table 2.7, entry 12 vs 13).

Scheme 2.35 Aziridinations of alkynyl imines with diazo acetate and acetamide



When switching the *N*-substituent of the imine from BUDAM to benzhydryl and MEDAM, promising results were obtained. Benzhydryl alkynyl aziridine **151c** was produced in 77% yield and 90% ee (Table 2.7, entry 2) and the MEDAM alkynyl aziridine **152c** was obtained in 77% yield and 90% ee (Table 2.7, entry 4). VANOL is a better ligand than either VAPOL or

7,7'-di-*t*-butylVANOL (Table 2.7, entry 3 vs 4 and 5). Further optimization on temperature, catalyst loading, reaction time and solvent was carried out. The optimal conditions are with 5 mol% catalyst in toluene at $-40\text{ }^{\circ}\text{C}$ with a reaction time of 4 h, from which the aziridine **152c** could be obtained in 91% yield and 97% ee (*cis/trans* = 50:1) (Table 2.7, entry 16).

Table 2.7 Optimization of the catalytic asymmetric aziridination of phenylpropynyl imines with diazoacetate **148**^a

entry	ligand	P	temp ($^{\circ}\text{C}$)	mol% cat	time (h)	% conv ^b	<i>cis</i> / <i>trans</i> ^b	% yield AZ ^c	% ee AZ ^d
1	(<i>S</i>)-VANOL	Bh	0	10	24	100	25:1	77	89
2	(<i>R</i>)-VAPOL	Bh	0	10	24	100	20:1	77	-90
3	(<i>S</i>)-VANOL	MEDAM	0	10	24	100	12:1	78	94
4	(<i>R</i>)-VAPOL	MEDAM	0	10	24	100	20:1	77	-90
5	(<i>S</i>)- <i>t</i> Bu ₂ - -VANOL ^e	MEDAM	0	10	24	100	14:1	84	59
6	(<i>S</i>)-VANOL	BUDAM	0	10	24	100	2:1	34 ^f	71
7	(<i>R</i>)-VAPOL	BUDAM	0	10	24	100	2:1	nd ^{f,g}	nd
8	(<i>S</i>)-VANOL	MEDAM	-20	10	24	100	20:1	84	96

Table 2.7 (cont'd)

9	(<i>S</i>)-VANOL	MEDAM	−20	5	24	100	20:1	86	96
10	(<i>S</i>)-VANOL	MEDAM	−20	5	1	100	17:1	82	97
11	(<i>S</i>)-VANOL	MEDAM	−20	2	1	100	>100:1	44	98
12	(<i>S</i>)-VANOL	BUDAM	−20	10	24	100	1.2:1	16 ^{h,i}	nd
13	(<i>R</i>)-VAPOL	BUDAM	−20	10	24	100	4:1	4 ^{h,i}	nd
14	(<i>S</i>)-VANOL	Bh	−40	5	4	22	>100:1	nd	nd
15	(<i>R</i>)-VAPOL	Bh	−40	5	4	46	20:1	nd	nd
16	(<i>S</i>)-VANOL	MEDAM	−40	5	4	100	50:1	91	97
17	(<i>S</i>)-VANOL	MEDAM	−40	5	4	100	17:1	83 ^h	92
18	(<i>S</i>)-VANOL	BUDAM	−40	5	4	12	2:1	nd	nd
19	(<i>R</i>)-VAPOL	BUDAM	−40	5	4	0	-	-	-
20	(<i>S</i>)-VANOL	MEDAM	−78	5	4	14	>100:1	nd	nd

^a Unless otherwise specified, all reactions were performed on 0.2 mmol in toluene at 0.2 M imine with 1.4 equiv of diazoacetamide for 4 h and went to 100% conversion. The catalyst was prepared by heating a mixture of 1 equiv of the ligand, 3 equiv BH₃•SMe₂, 2 equiv phenol, 3 equiv H₂O in toluene at 100 °C for 1 h. The volatiles were then removed under vacuum (0.1 mm Hg) at 100 °C for 1 h. nd = not determined. ^b Determined from ¹H NMR spectrum of the crude reaction mixture. ^c Yield of isolated pure *cis*-aziridine after silica gel chromatography. ^d Determined by HPLC on pure *cis*-aziridine. ^e 7,7'-di-*t*-butylVANOL. ^f A number of other

Table 2.7 (cont'd)

unidentified products formed in this reaction.^g The amount of *cis*-aziridine is much less than in entry 6.^h Reaction performed in ether.ⁱ Determined from ¹H NMR spectrum of the crude reaction mixture with Ph₃CH as internal standard.

The optimal conditions were then examined with twelve additional alkynyl imines (Table 2.8). In all cases, high asymmetric inductions were achieved. The reactions of aryl substituted alkynyl imines went to completion with 5 mol% catalyst at –40 °C within 4 h. All gave 96-99% ee, regardless of various functional groups at different positions on the aryl ring (Table 2.8, entries 5 to 19). The reactions of n-butyl and cyclohexyl substituted alkynyl imines needed a higher temperature (–20 °C) to finish in 4 h and also went with excellent enantioselectivities (Table 2.8, entries 20 to 24). The reaction of the *t*-butyl substituted alkynyl imine **135k** was slower and needed 24 h to go to completion. Lower induction (91%) and lower *cis/trans* ratio (4:1) were obtained (Table 2.8, entries 25 to 26). The reaction of the trimethylsilyl substituted alkynyl imine **135b** also gave lower induction (83%) and lower *cis/trans* ratio (5:1) (Table 2.8, entries 3 & 4). Fortunately, the reaction of the triisopropylsilyl substituted alkynyl imine **135a** gave 86% yield and 98% ee with an excellent *cis/trans* ratio (50:1) (Table 2.8, entries 1 & 2).

Table 2.8 Catalytic asymmetric synthesis of alkynyl aziridines with diazo acetamide **148**^a

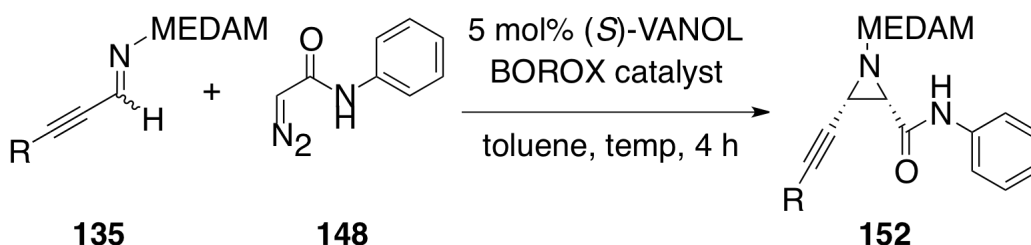
								
entry	R	Ligand	imine	temp (°C)	<i>cis</i> / <i>trans</i> ^b	AZ	% yield AZ ^c	% ee AZ ^d
1	<i>i</i> -Pr ₃ Si	(<i>S</i>)-VANOL	135a	−20	50:1	152a	86	98
2	<i>i</i> -Pr ₃ Si	(<i>R</i>)-VANOL	135a	−20	100:1	152a	87	98
3	Me ₃ Si	(<i>S</i>)-VANOL	135b	−20	5:1	152b	80	83
4	Me ₃ Si	(<i>R</i>)-VANOL	135b	−20	5:1	152b	80	86
5	C ₆ H ₅	(<i>S</i>)-VANOL	135c	−40	50:1	152c	91	97
6	4-MeOC ₆ H ₄	(<i>S</i>)-VANOL	135d	−40	>100:1	152d	90	99
7	4-MeOC ₆ H ₄	(<i>R</i>)-VANOL	135d	−40	>100:1	152d	89	99
8	4-BrC ₆ H ₄	(<i>S</i>)-VANOL	135e	−40	>100:1	152e	93	98
9	4-BrC ₆ H ₄	(<i>R</i>)-VANOL	135e	−40	>100:1	152e	92	99
10	4-MeO ₂ CC ₆ H ₄	(<i>S</i>)-VANOL	135f	−40	25:1	152f	90	96
11	4-MeO ₂ CC ₆ H ₄	(<i>R</i>)-VANOL	135f	−40	20:1	152f	89	95
12	4-NO ₂ C ₆ H ₄	(<i>S</i>)-VANOL	135g	−40	25:1	152g	91	95
13	4-NO ₂ C ₆ H ₄	(<i>R</i>)-VANOL	135g	−40	25:1	152g	89	96
14	3-MeC ₆ H ₄	(<i>S</i>)-VANOL	135h	−40	33:1	152h	89	96

Table 2.8 (cont'd)

15	3-MeC ₆ H ₄	(<i>R</i>)-VANOL	135h	−40	33:1	152h	90	96
16	2-MeC ₆ H ₄	(<i>S</i>)-VANOL	135i	−40	33:1	152i	95	95
17	2-MeC ₆ H ₄	(<i>R</i>)-VANOL	135i	−40	33:1	152i	94	98
18	1-naphthyl	(<i>S</i>)-VANOL	135j	−40	33:1	152j	95	97
19	1-naphthyl	(<i>R</i>)-VANOL	135j	−40	25:1	152j	94	99
20	<i>n</i> -butyl	(<i>S</i>)-VANOL	135k	−20	25:1	152k	82	98
21	<i>n</i> -butyl	(<i>R</i>)-VANOL	135k	−20	>100:1	152k	81	98
22	cyclohexyl	(<i>S</i>)-VANOL	135l	0	9:1	152l	73	91
23	cyclohexyl	(<i>S</i>)-VANOL	135l	−20	25:1	152l	84	97
24 ^e	cyclohexyl	(<i>S</i>)-VANOL	135l	−40	>100:1	152l	78	99
25 ^f	<i>t</i> -butyl	(<i>S</i>)-VANOL	135m	−20	4:1	152m	77	91
26 ^f	<i>t</i> -butyl	(<i>R</i>)-VANOL	135m	−20	4:1	152m	78	91

^a Unless otherwise specified, all reactions were performed on 0.2 mmol in toluene at 0.2 M imine with 1.4 equiv of diazoacetamide **148** for 4h and went to 100% conversion. The catalyst was prepared as described in Table 2.7. ^b Determined from ¹H NMR spectrum of the crude reaction mixture. ^c Yield of isolated pure *cis*-aziridine after silica gel chromatography. ^d Determined by HPLC on pure *cis*-aziridine. ^e Reaction went to 81% completion. ^f Reaction time was 24 h.

When the more soluble *N*-*n*-butyl diazoacetamide **154** was employed, slightly lower yield (86%) and lower induction (95%) were observed with imine **135c** (Table 2.9), compared to the results from *N*-phenyl diazoacetamide **148** under the identical conditions (Table 2.8, entry 5).

Table 2.9 Catalytic asymmetric aziridination of alkynyl imines with *N*-*n*-butyl diazoacetamide **154**^a

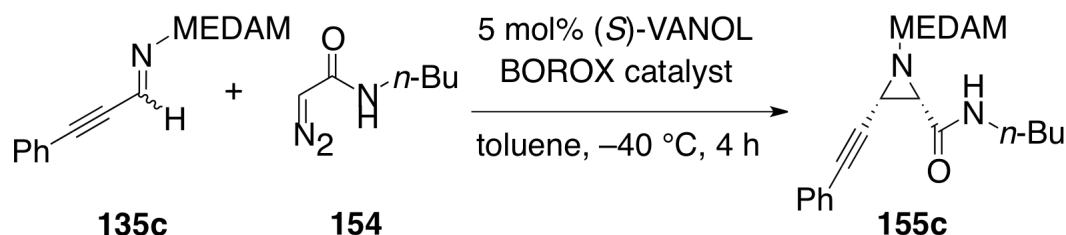


Table 2.9 (cont'd)

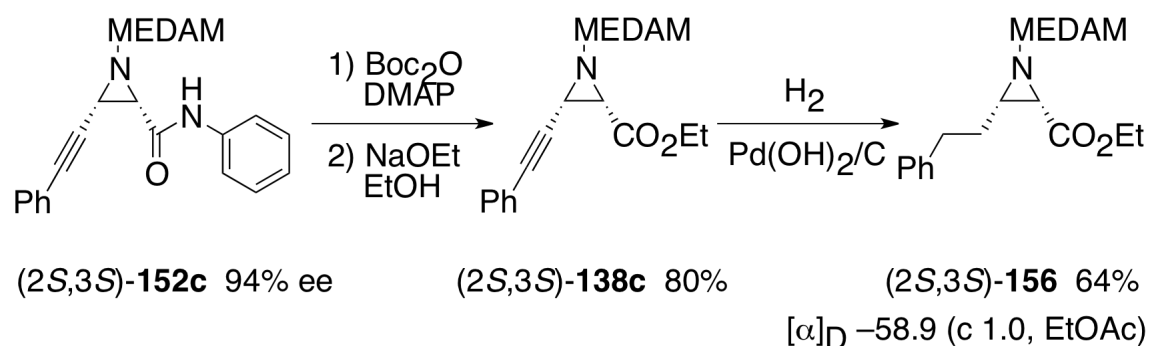
entry	ligand	<i>cis/trans</i> ^b	% yield AZ ^c	% ee AZ ^d
1	(<i>S</i>)-VANOL	33:1	84	94
2	(<i>R</i>)-VANOL	50:1	86	95

^a Unless otherwise specified, all reactions were performed on 0.2 mmol in toluene at 0.2 M imine with 1.4 equiv of diazoacetamide **154** for 4 h and went to 100% conversion. The catalyst was prepared as described in Table 2.7. ^b Determined from ¹H NMR spectrum of the crude mixture. ^c Yield of isolated pure *cis*-aziridine after silica gel chromatography. ^d Determined by HPLC on pure *cis*-aziridine.

After transforming amide **152c** into ester **138c**, it was found that this compound had an optical rotation that had a sign opposite to that for *cis*-aziridine **138c** synthesized from imine **135c** with ethyl diazoacetate **30** with the same enantiomer of the ligand (Table 2.5). In other words, by using a ligand with the same chirality, the reaction of diazoacetamide **148** gave the

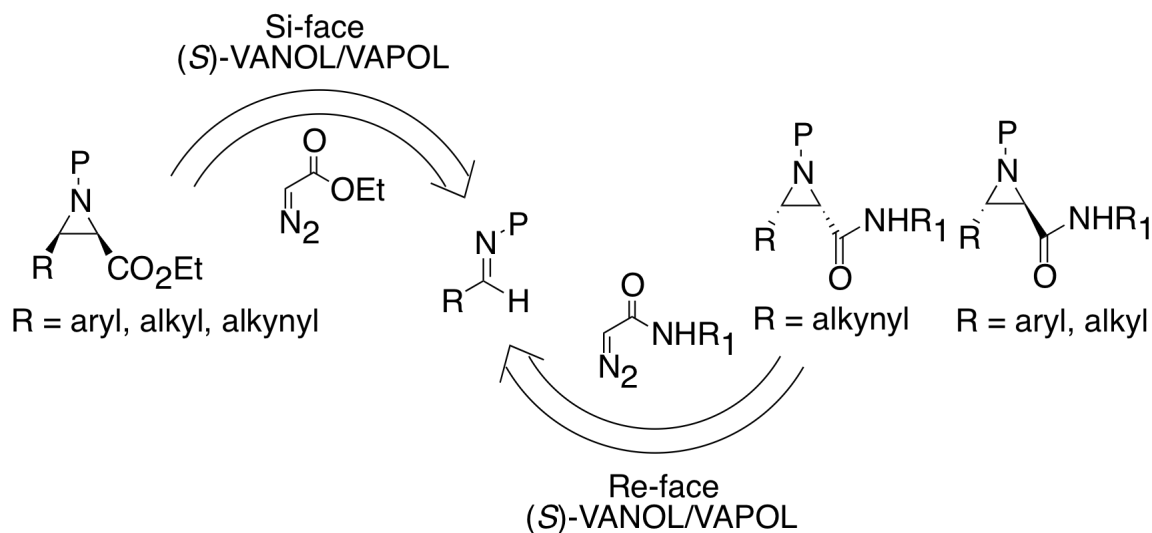
pseudoenantiomer of the product from the reaction of diazoacetate **30**. Thus, the chirality of the products from the aziridination reaction are reagent dependent. Pearlman's catalyst promoted hydrogenation of *cis*-aziridine **138c** prepared from amide **152c** afforded the known aziridine **156**

Scheme 2.36 Absolute configuration of alkynyl aziridines **152c** and **138c**



the facial selectivities of the Wulff aziridination reactions can be summarized as shown in Scheme 2.37. With the (*S*)-ligand, Si-face addition of diazoacetates to the imine is observed while Re-face addition of diazoacetamides to the imine is preferred. In the case of 2° diazoacetamides, alkynyl imines give *cis*-aziridines while aryl and alkyl imines afford *trans*-aziridines.

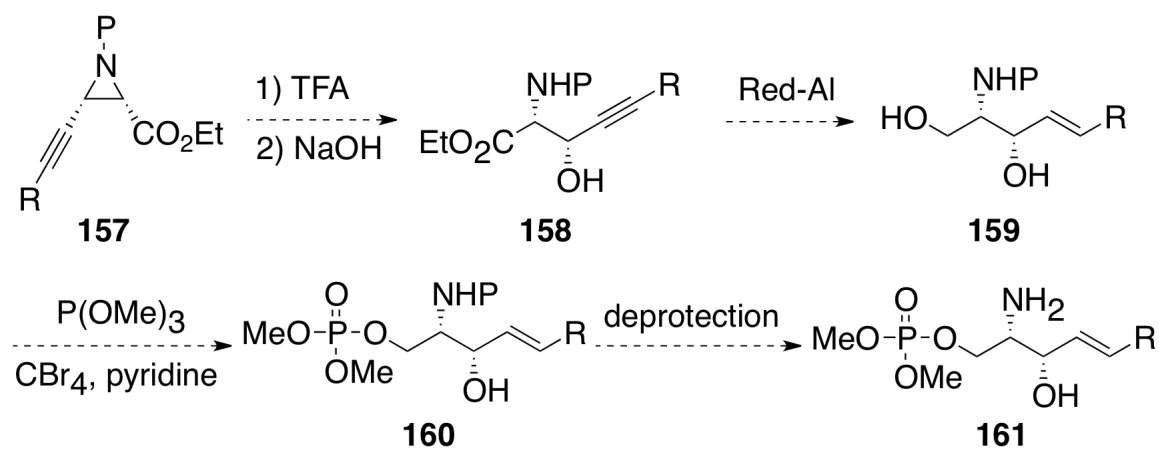
Scheme 2.37 Facial selectivities in the aziridination reactions



2.4 Future plan

One potential application of the above chemistry is the synthesis of sphingosine and its analogues. The proposed synthetic route is shown in Scheme 2.38.

Scheme 2.38 Proposed synthetic route of sphingosine analogues



2.5 Conclusion

We have successfully developed the first highly enantioselective catalytic synthesis of *cis*-alkynyl aziridine-2-carboxylate esters or amides in excellent yields with very high diastereoselectivities. Several important features of this work are: a) the induction of the aziridine is independent of the geometry of the imine; b) the reactions of alkynyl imines with ethyl diazoacetate give *cis*-aziridines with excellent asymmetric inductions but in moderate yields due in part to the competing formation of [3+2] pyrazole side products; c) In contrast to previous *trans*-aziridinations from aryl or alkyl imines, the reactions of alkynyl imines with diazoacetamides afford *cis*-aziridines in excellent yields with excellent enantioselectivities; d) *cis*-aziridines obtained with diazoacetates and diazoacetamides are opposite enantiomers when the same enantiomer of the catalyst is used.

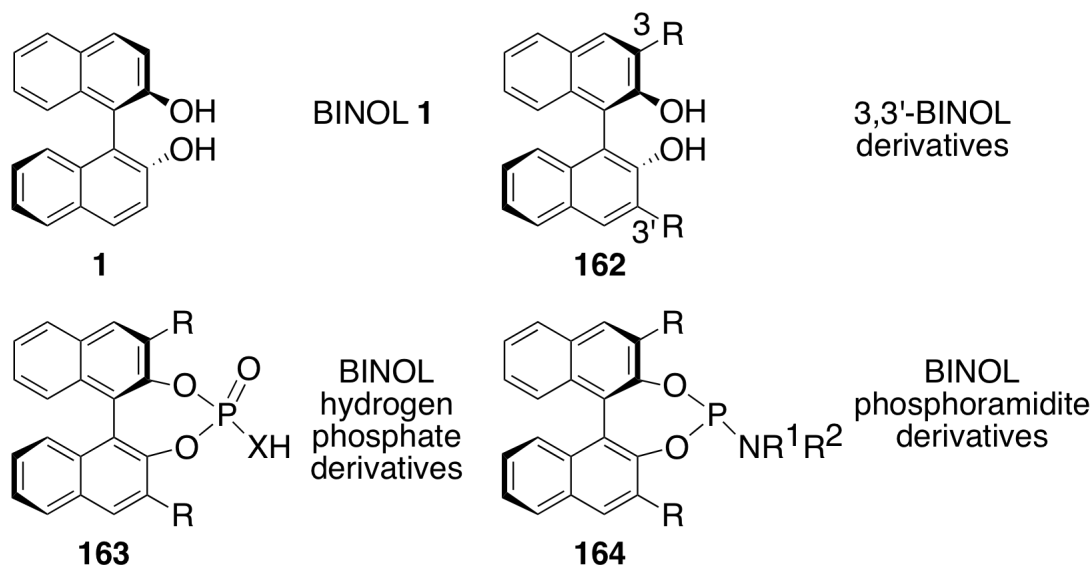
CHAPTER THREE

CONVERGENT SYNTHESIS OF 7,7'-DISUBSTITUTED VANOL LIGANDS AND A CONSENSUS IN THE AZIRIDINATION REACTION

3.1 Introduction

In the general introduction in Chapter 1, we have learned that VANOL and VAPOL are the members of the vaulted biaryls which is a new class of “privileged ligands” as judged by their increasing new applications in asymmetric catalysis. The substrates in an organic reaction may possess an enormous molecular diversity that drives the demand for structurally diverse catalysts. Chiral ligands, which serve an important role in tuning the electronics of the active site and in defining the chiral environment of the catalysts, should be of a collection flexible enough to offer the maximum potential of discovering the optimal platform for transforming a given substrate.

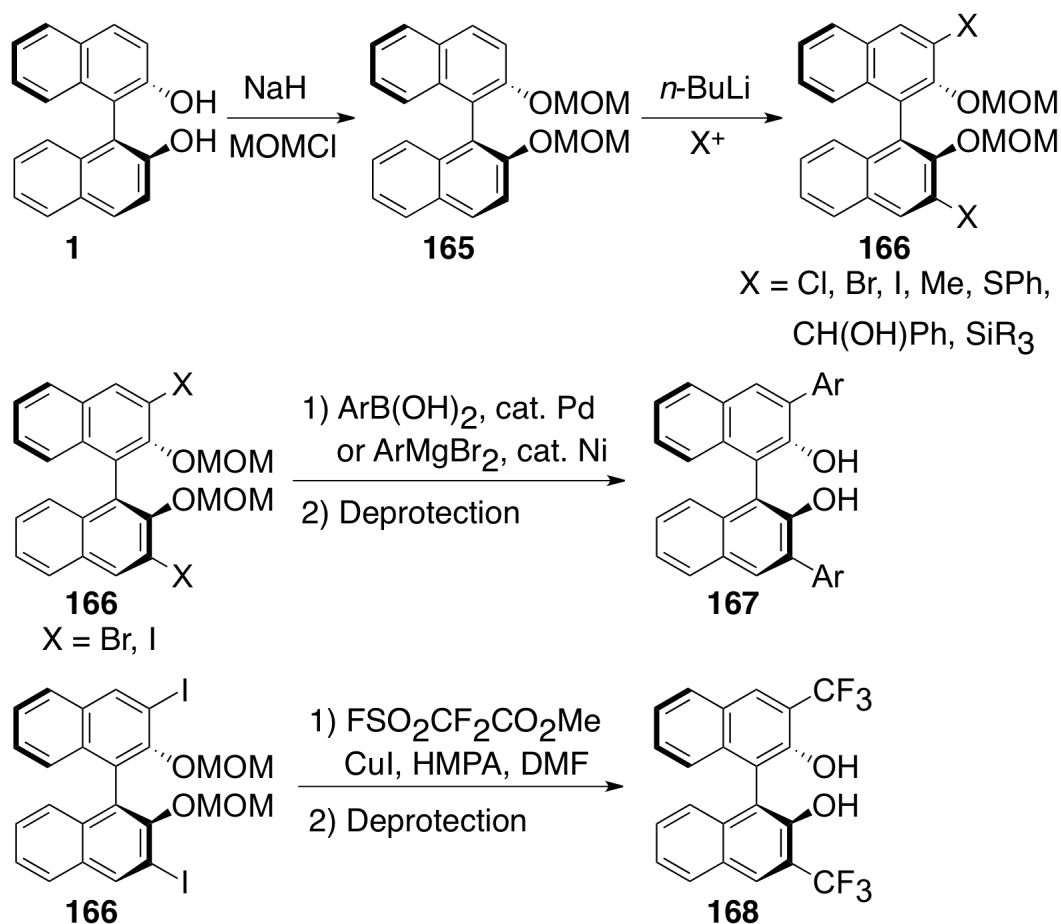
Scheme 3.1 BINOL and BINOL derivatives



The chemistry of BINOL has been extensively developed not only due to the early recognition of its catalysis potential but also the ease and flexibility with which it was possible to form a

library of BINOL derivatives. The vast majority of BINOL derivatives are those that have substituents in the 3- and 3'-positions (Scheme 3.1).¹¹ And from those 3,3'-BINOL derivatives, functionalization of the phenol substituents leads to the phosphate derivatives, as well as to the phosphoramidite derivatives.⁶⁵⁻⁶⁹

Scheme 3.2 Synthesis of 3,3'-BINOL derivatives



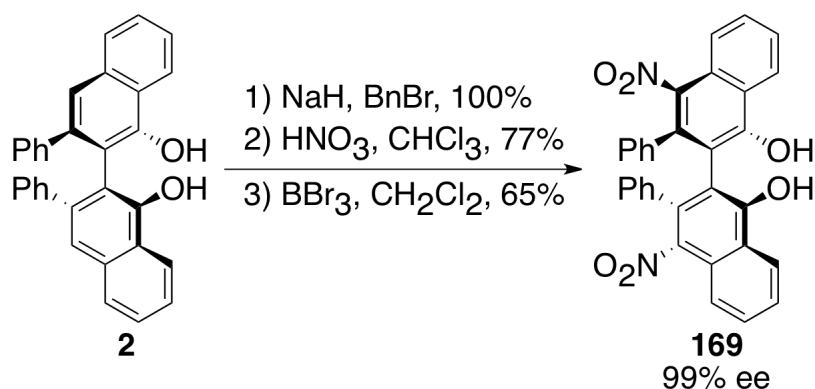
Some of the most common methods for the introduction of different groups in the 3- and 3'-positions are outlined in Scheme 3.2. Different functional groups (i.e. Me, CH(OH)Ph, SPh, Br, Cl, I, SiR₃) could be accessed through ortho lithiation of 2,2'-oxygen-based directed metalation groups followed by electrophile quench.⁷⁰ Treatment of 3,3'-dibromo or 3,3'-iodo BINOL derivatives with various boronic acids under Suzuki cross coupling conditions furnishes

3,3'-diaryl BINOL derivatives. Trifluoromethylation can be achieved with $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}$ mediated by CuI .⁷¹

3.2 Background

Compared to the well-established methods for preparing BINOL derivatives, the approaches to VANOL and VAPOL derivatives are limited and not well explored. There are two general ways to modify VANOL/VAPOL: 1) by replacing a certain hydrogen atom(s) in one of the rings in an existing molecule of VANOL/VAPOL or 2) by synthesizing substituted monomers prior to dimerization followed by resolution or deracemization.

Scheme 3.3 Synthesis of 4,4'-dinitroVANOL



The first approach appears to be more direct and convenient. The easiest way is via electrophilic aromatic substitution reactions. 4,4'-Dinitro VANOL was prepared by Dr. Hu from our group via nitration of the naphthol rings which are activated and directed by the phenol groups (Scheme 3.3).⁷²

Scheme 3.4 Attempted directed lithiation-substitution of unprotected VANOL

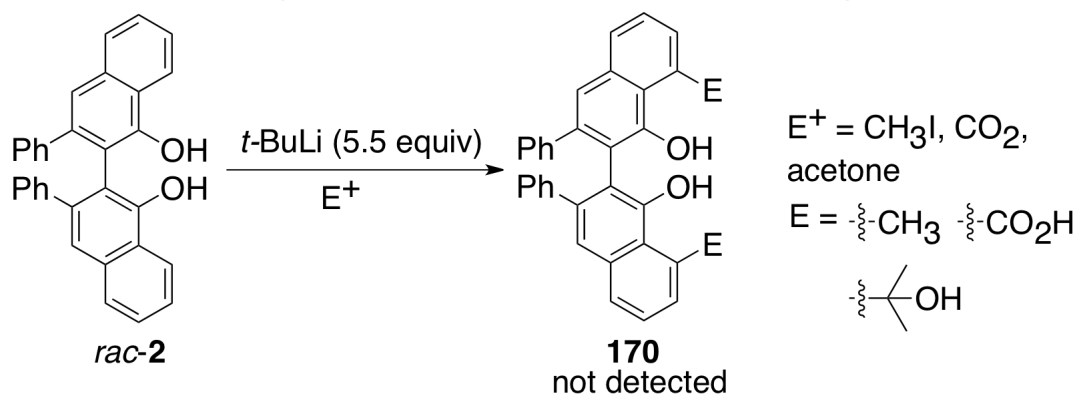
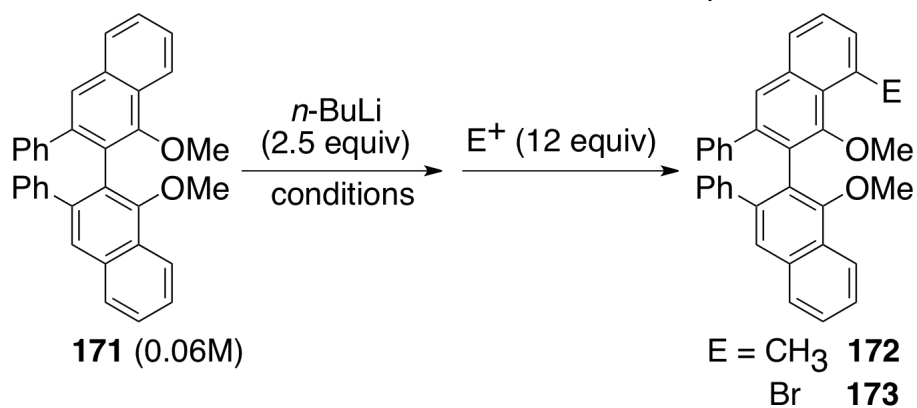


Table 3.1 Directed mono lithiation-substitution of protected VANOL



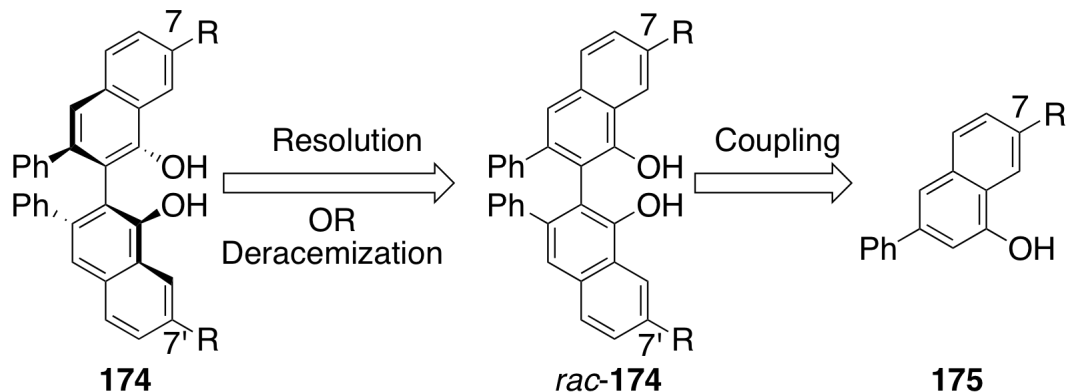
entry	E^+	solvent	E	conditions	TMEDA (eq)	% yield ^c
1	CH_3I	ether	CH_3	25 °C, 35 h	0	nd ^a
2	CH_3I	ether	CH_3	45 °C, 2 h	0	40 ^b
3	CH_3I	ether	CH_3	50 °C, 24 h	0	100 ^b
4	CH_3I	ether	CH_3	25 °C, 24 h	2.5	44.2 (100 ^b)
5	CH_3I	hexanes	CH_3	25 °C, 24 h	2.5	nd ^a
6	$\text{BrCH}_2\text{CH}_2\text{Br}$	ether	Br	25 °C, 3 h	2.5	31.5 (65 ^d)

^a nd = not detected, **171** was recovered. ^b conversion based on ^1H NMR spectrum of the crude reaction mixture. ^c isolated yield by chromatography on silica gel. ^d **171** (34.8%) was recovered.

Due to the close proximity of the 8 and 8' positions to the hydroxyl functions, an ortho-lithiation/electrophile quench sequence was investigated by Dr. Ding from our group (Scheme 3.4).⁷³ However, only starting material was recovered.

The same sequence was then carried out on VANOL protected as its bis-methyl ether. With MeI as the electrophile, 8-methylated VANOL **172** was obtained (Table 3.1). Similarly, bromination led to 8-bromo VANOL upon treatment with 1,2-dibromoethane.⁷³ However, introduction of substituents in the 8,8'-positions leads to decreased yields and inductions (Chapter 4). Therefore, the second route seemed to be the method of choice to introduce substituents in the 7,7'-positions (Scheme 3.5).

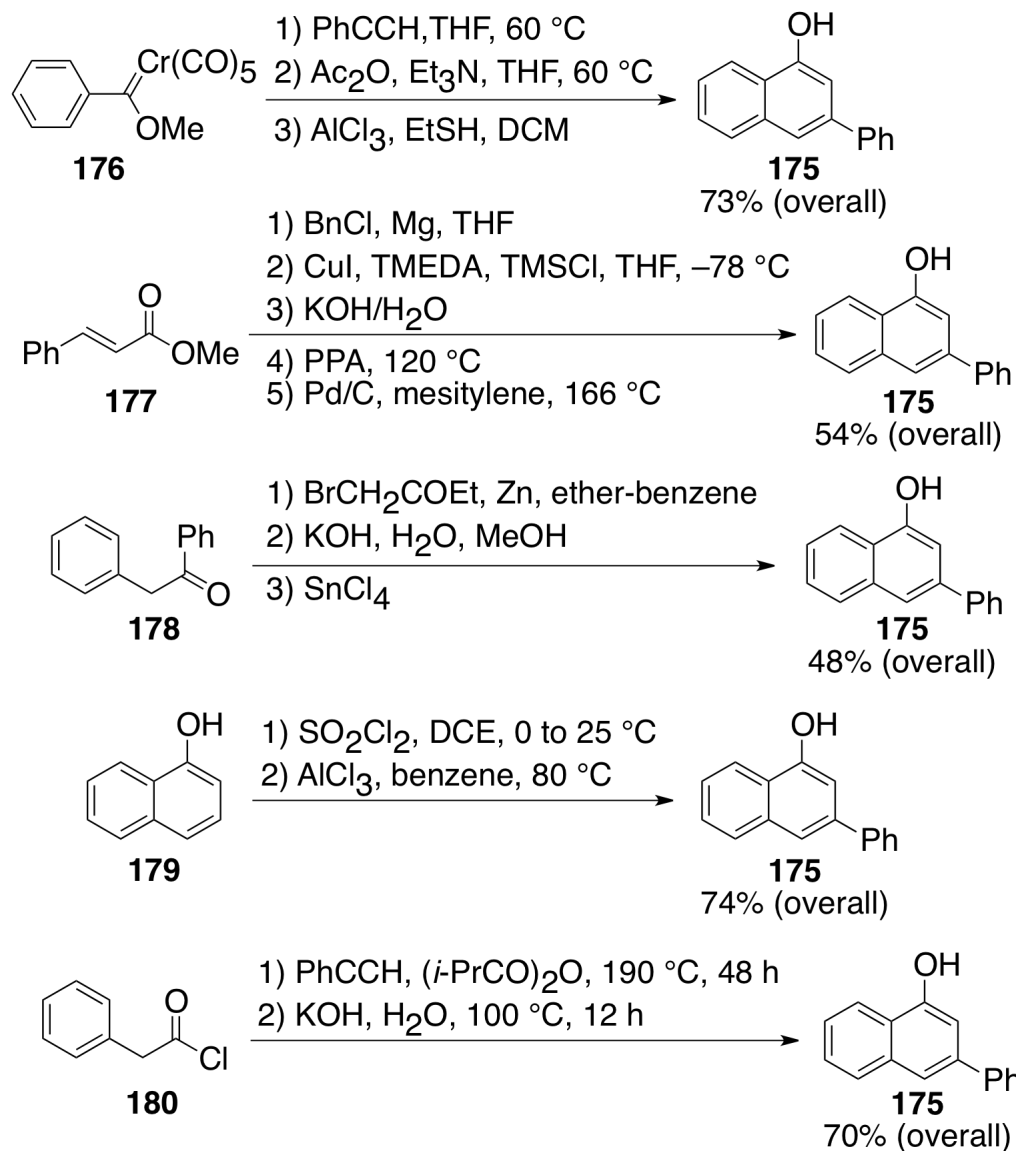
Scheme 3.5 Retrosynthetic analysis of 7,7'-disubstituted VANOL



There are a number of ways to synthesize 3-phenyl-1-naphthol as VANOL monomer. Dr. Ding instigated the investigations into several ways to prepare this key intermediate (Scheme 3.6).^{13f,13g,73} The first route is benzannulation pathway. Benzannulation of the phenyl carbene complex with phenylacetylene, followed by exposure to EtSH in the presence of AlCl₃, affords the monomer **175** in 73% overall yield. The second route involves Michael addition of a benzyl

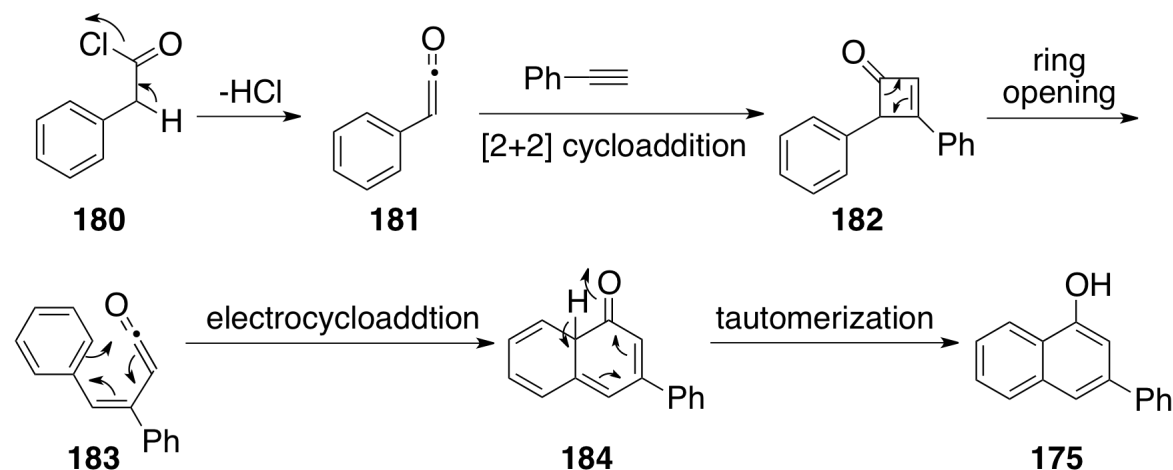
Grignard to methyl cinnamate, followed by intramolecular Friedel-Craft reaction. Dehydrogenation of the resulting tetralone yields the monomer **175** in 54% overall yield. The third route is a Reformatsky reaction/cycloacylation sequence, giving the monomer **175** in 48% overall yield. The fourth route features a dienone-phenol rearrangement of a 4-aryl-1-tetralenone generated in-situ from the reaction of a chlorination product of 1-naphthol with AlCl_3 and benzene. The overall yield is 74%. The last route is ketene pathway. The key step is a cycloaddition/electrocyclic ring-opening/electrocyclic ring closure/tautomerization (CAEC) cascade. This last route tolerates more function groups and many phenyl acetic acid derivatives are commercially available. Therefore, the CAEC cascade is the method of choice.

Scheme 3.6 Various routes for the synthesis of 3-phenyl-1-naphthol



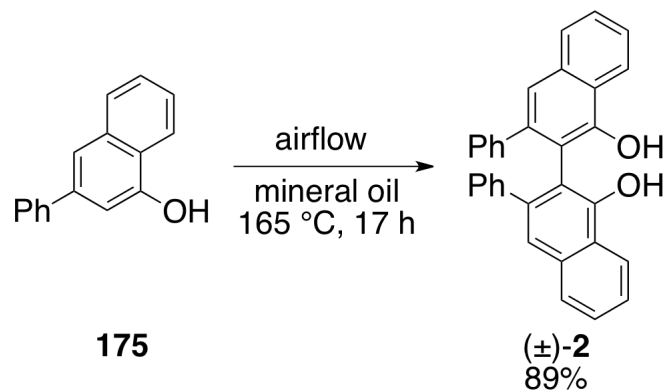
The mechanism of the CAEC cascade is presented in Scheme 3.8. Pyrolysis of phenylacetyl chloride gives ketene **181**, which undergoes [2+2] cycloaddition with phenylacetylene. Electrocyclic ring-opening of the adduct **182**, followed by electrocyclic ring closure and subsequent tautomerization, gives the monomer **175** in a one-pot fashion.

Scheme 3.7 Mechanism of the CAEC cascade



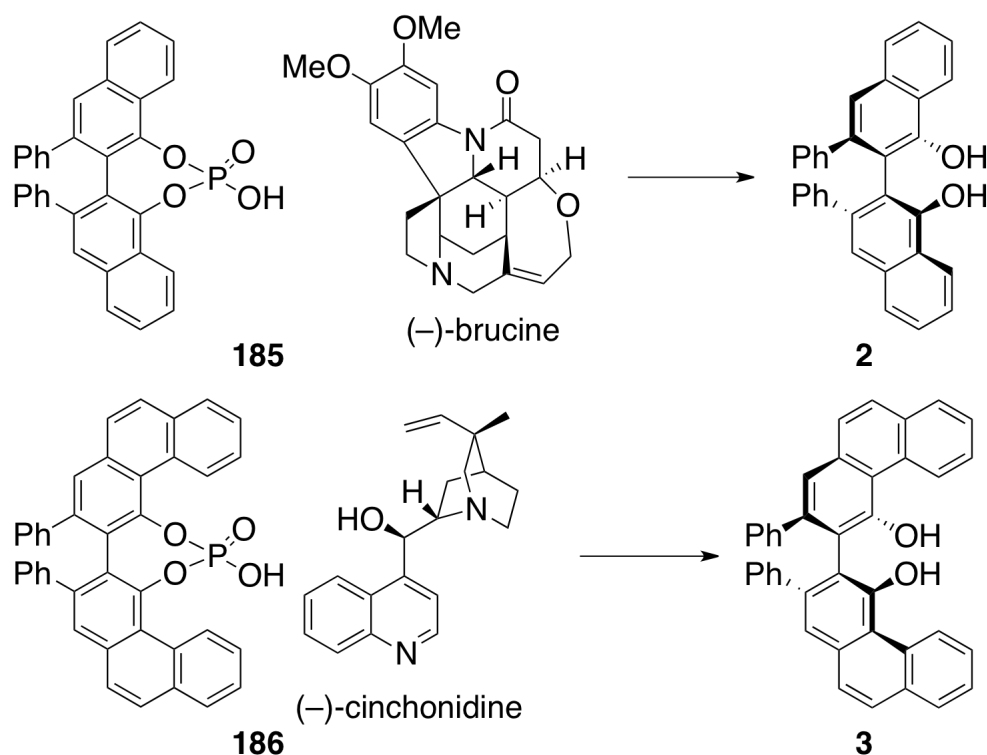
The first synthesis of racemic VANOL was performed by heating **175** (1 g scale) in a test tube in the presence of air at 190 °C to give an 87% yield of racemic VANOL.^{13a} The major drawback of this method is that VANOL solidifies during the process and traps the monomer which results in incomplete conversion. Dr. Ding optimized the coupling step by choosing various solvents and temperatures with different concentrations and found that by heating the monomer as a 0.92 M solution in mineral oil at 165 °C for 17 h, the pure racemate was obtained in 89% yield (Scheme 3.9).⁷³ Thus, this optimal procedure for the oxidative coupling is method of choice for the work in this thesis.

Scheme 3.8 Synthesis of *rac*-VANOL



There are two general ways of preparing optical pure VANOL and VAPOL from the racemates. The first way is by resolution (Scheme 3.9).^{13a,13g,73} The resolution of VANOL is based on the separation of diastereomeric salts formed from the reaction of its racemic VANOL hydrogen phosphate with (–)-brucine. The resolution of VAPOL is related to that of VANOL but employs (–)-cinchonidine instead of (–)-brucine. Resolution is good for large scale synthesis. However, it might not be a facile way to synthesis a large number of VANOL derivatives.

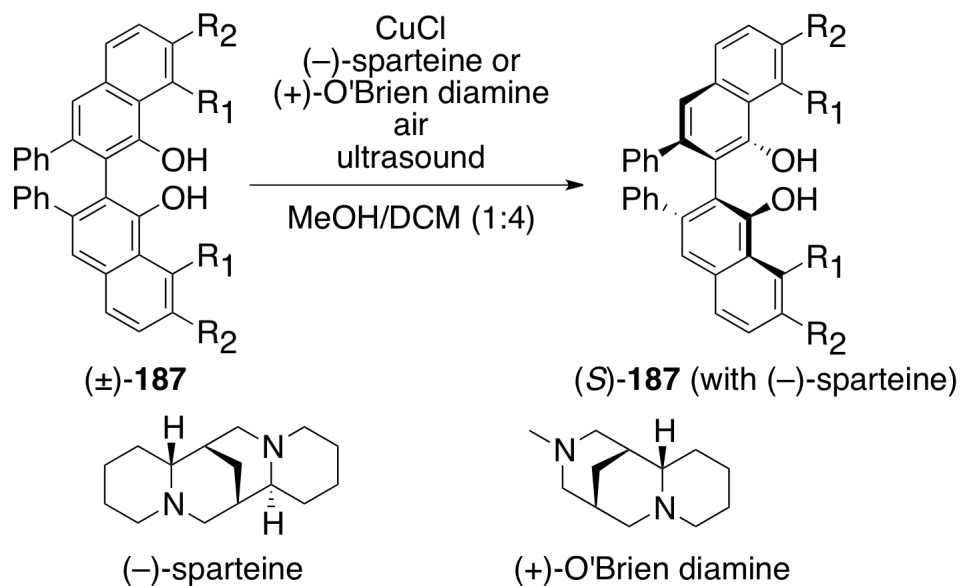
Scheme 3.9 Resolution of *rac*-VANOL/VAPOL



The second way for securing optical pure VANOL and VAPOL is by deracemization. Dr. Hu developed a more reliable procedure for the deracemization of VANOL/VAPOL mediated by copper (II)/diamine complexes (Scheme 3.10).^{13c} While the use of a copper complex of (–)-sparteine gives (*S*)-enantiomers of BINOL, VANOL and VAPOL, the use of a copper

complex of (+)-O'Brien diamine gives the (*R*)-enantiomeric series. This process may be more suitable for small scale synthesis and fast access to a library of VANOL derivatives.

Scheme 3.10 Deracemization of *rac*-VANOL/VAPOL



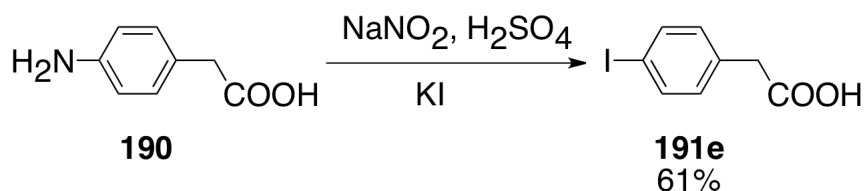
3.3 Results and discussion

3.3.1 Preparation of 4-substituted phenylacetic acids

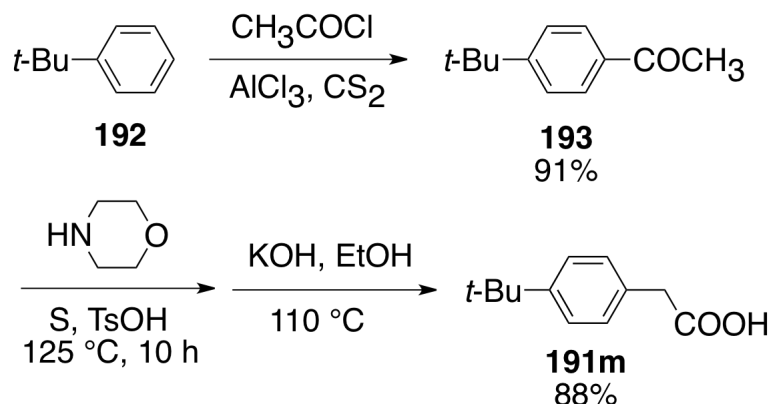
From the above discussion, the optimized route to the optical pure VANOL has already been developed. This route is short, efficient, cost effective and capable of generating a large number of VANOL derivatives in a convergent manner. The best and easiest position for diversity proliferation is in the 7- and 7'-positions of VANOL.

Though most of the required 4-substituted phenylacetic acids are commercially available, two acids were prepared from relative inexpensive starting materials. Sandmeyer reaction of 4-aminophenylacetic acid with NaNO_2 and H_2SO_4 , followed by KI yields 4-iodophenylacetic acid in 61% yield (Scheme 3.11).⁷⁴

Scheme 3.11 Synthesis of 4-iodophenylacetic acid

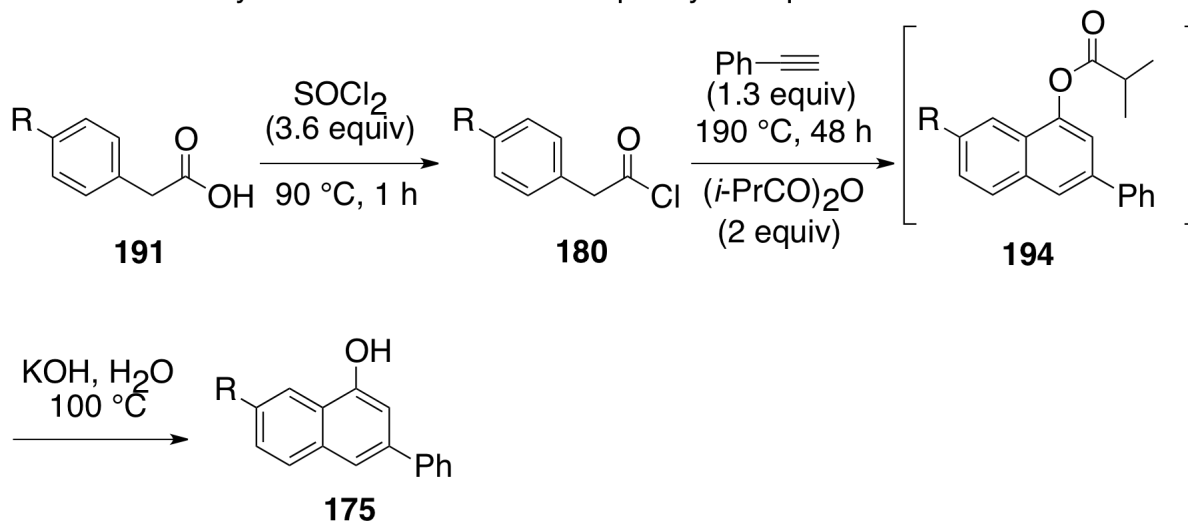


Friedel-Crafts acylation of *t*-butylbenzene with acetyl chloride in the presence of AlCl_3 afforded 4-*t*-butylacetophenone in 91% yield (Scheme 3.12).⁷⁵ Willgerodt-Kindler reaction of 4-*t*-butylacetophenone and subsequent hydrolysis gave 4-*tert*-butyl-phenylacetic acid in 88% yield in a one-pot process.^{76,77} This sequence involves only one column chromatography separation of the final product **191m**.

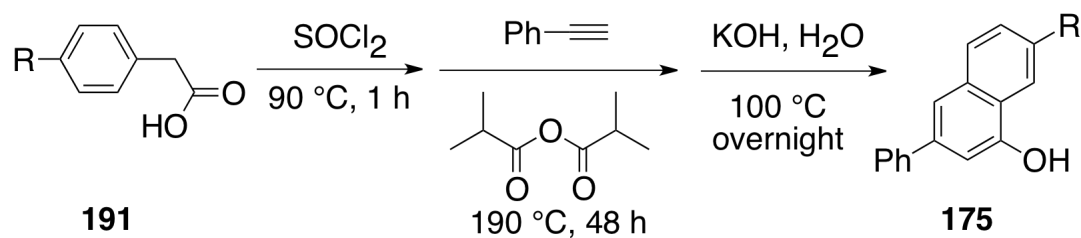
Scheme 3.12 Synthesis of 4-*tert*-butyl-phenylacetic acid**3.3.2 Preparation of 7-substituted 3-phenyl-1-naphthols**

The synthesis of various monomers was carried out via the CAEC cascade (Scheme 3.13).^{13g}

The *iso*-butyric anhydride is used to trap the product naphthols to prevent them from reacting with phenyl ketene, which in its absence would necessarily result in a much lower yield.

Scheme 3.13 Synthesis of 7-substituted 3-phenyl-1-naphthols via the CAEC cascade

It was pleased to find that various halogen groups, 1°, 2°, 3° alkyls, and OMe survive the CAEC cascade (Table 3.2). The reactions with phenyl acetic acids bearing CF_3 , NMe_2 or NO_2 groups in the para-position gave non-separable mixtures.

Table 3.2 Synthesis of 7-substituted 3-phenyl-1-naphthol

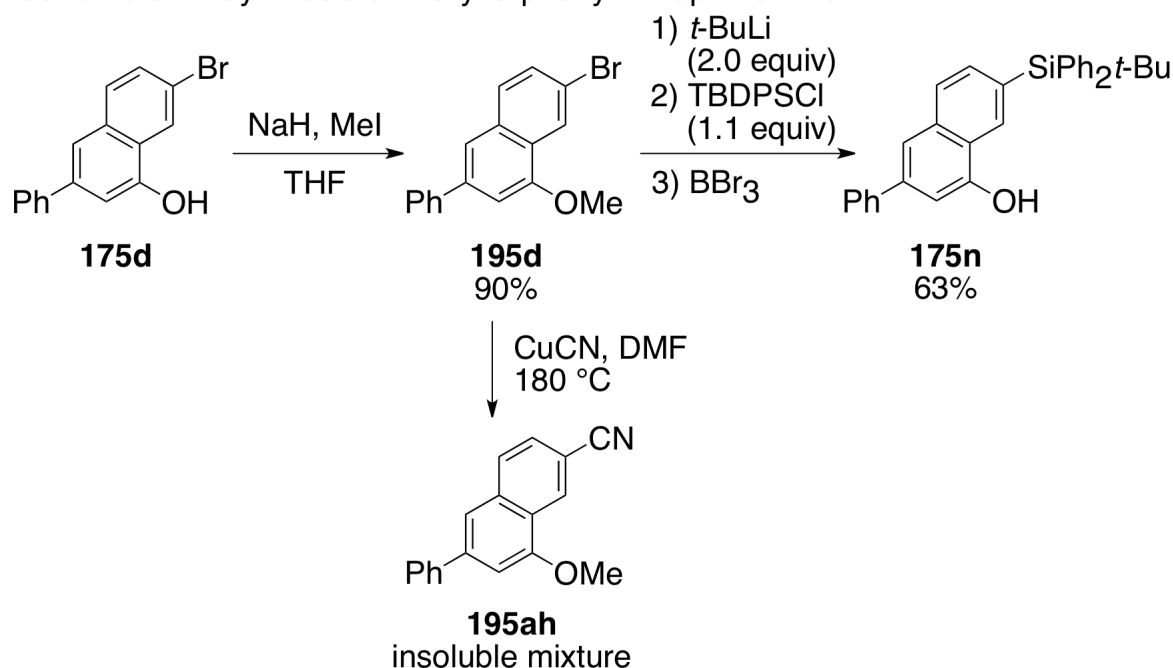
entry	series	R	% yield ^a
1	b	F	65
2	c	Cl	71
3	d	Br	67
4	e	I	52
5	g	OMe	50
6	h	Me	56
7	k	<i>i</i> -Pr	61
8	m	<i>t</i> -Bu	51
9	ag	Ph	65
10	aj	NMe ₂	nd
11	f	CF ₃	nd
12	ai	NO ₂	nd

^a isolated yield by chromatography on silica gel. nd = not determined

Lithiation of the protected bromo naphthol **195d**, and then quenched with

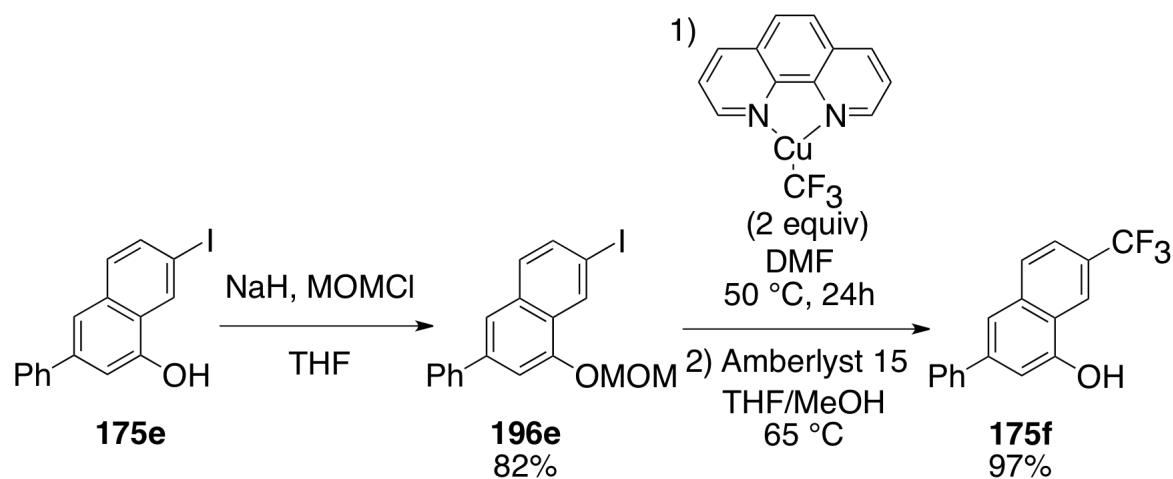
tert-butyl(chloro)diphenylsilane, followed by deprotection afforded silyl-substituted naphthol **175n** in 63% yield (Scheme 3.14).¹⁵ Treatment of the protected bromo naphthol **195d** by the Shechter modification of the Rosenmund-Van Braun reaction gave insoluble mixture of products that was not further characterized.⁷⁸

Scheme 3.14 Synthesis of 7-silyl 3-phenyl-1-naphthol **175n**



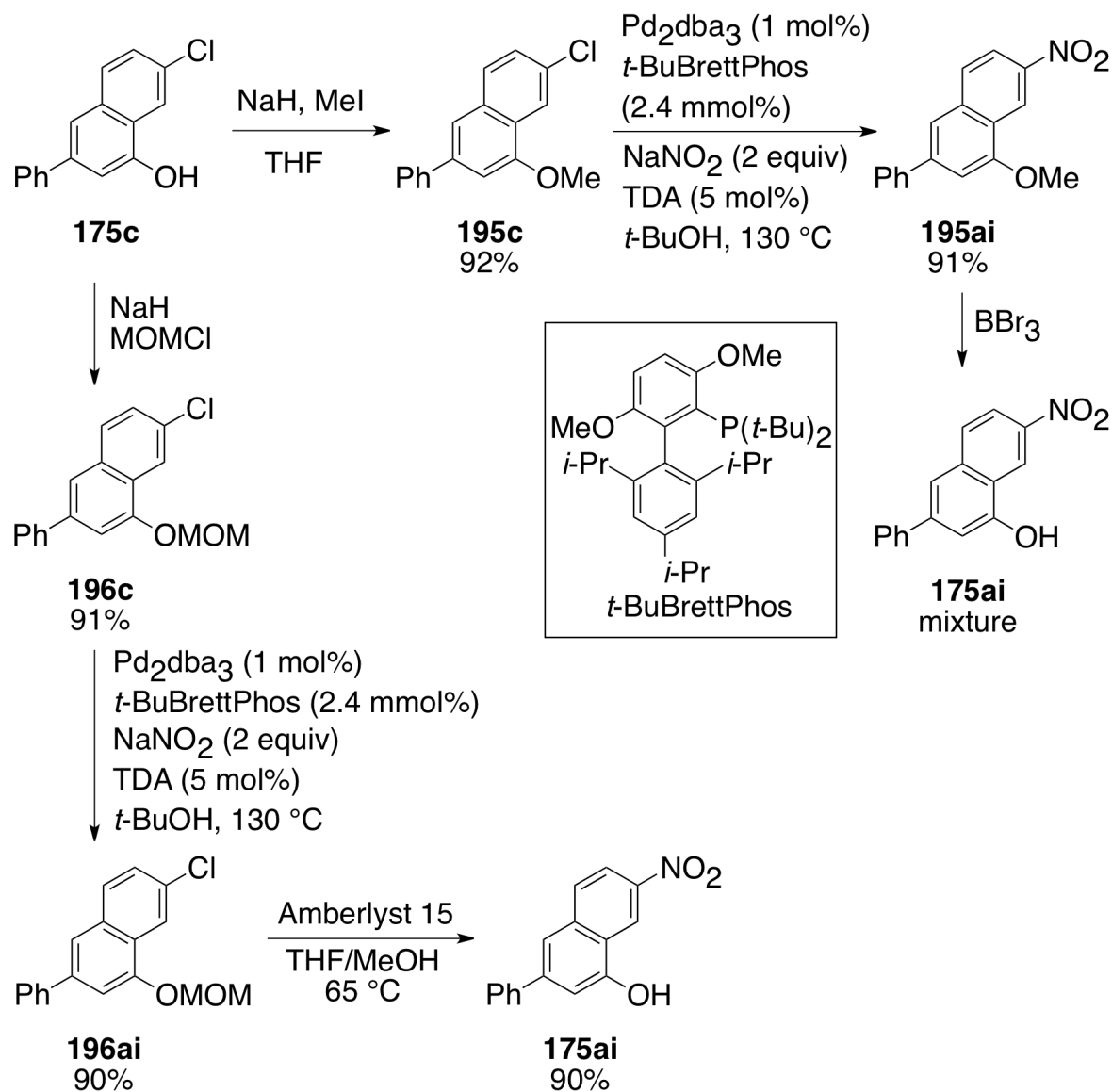
Coupling of the MOM protected iodonaphthol **196e** with the phenanthroline complex of trifluoromethyl copper developed by Hartwig and coworkers, followed by deprotection generated the trifluoromethyl naphthol **175f** in 97% yield (Scheme 3.15).⁷⁹

Scheme 3.15 Synthesis of 7-trifluoromethyl-3-phenyl-1-naphthol **175f**



The nitro naphthol **175ai** was successfully accessed by employing a process developed by Buchwald and coworkers (Scheme 3.16).⁵ Pd and *t*-buBrettPhos could promote the conversion of protected chloro naphthol **195c** or **196c** to the nitro naphthol **195ai** or **196ai**. Demethylation of the nitroaromatic methyl ether **195ai** with BBr₃ failed to give a clean product, which was disappointing. To our delight, removal of the MOM group of **196ai** with Amberlyst 15 gave the desired nitro naphthol **175ai** in 90% yield.

Scheme 3.16 Synthesis of 7-nitro-3-phenyl-1-naphthol **175ai**



3.3.3 Oxidative coupling and deracemization

The oxidative coupling procedure was then applied to the 7-substituted-3-phenyl-1-naphthols described above (Table 3.3). Different halogen groups, alkyl groups, and a silyl group survived the coupling conditions and the resulting racemic VANOL derivatives were available for the deracemization process. The racemic 7,7'-dimethoxyl VANOL **174g** has low solubility that

obstructs purification and further processing. The oxidative couplings of 7-nitro- and 7-phenyl-3-phenyl-1-naphthol failed, giving complicated mixtures. It was delightful to find that all of the new VANOL derivatives could be brought to >99% ee in the (*S*)-enantiomer with the (–)-sparteine-copper complex which isomerizes the (*R*)-enantiomer in good to excellent yield. (*R*)-VANOL derivatives with >99% ee were obtained when the (+)-sparteine-copper complex was used.

Table 3.3 Synthesis of optically pure 7,7'-disubstituted VANOL derivatives

175		(±)-174		(S)-174	
entry	series	R	% yield (±)-174	% yield (S)-174	% ee (S)-174
1	b	F	91	45	>99
2	c	Cl	73 ^a	83	>99
3	d	Br	84	83	>99
4	d	Br	84	98	>99 ^b
5	e	I	86	76	>99
6	f	CF ₃	51 ^c	79	>99 ^b
7	g	OMe	86 ^d	-	-

Table 3.3 (cont'd)

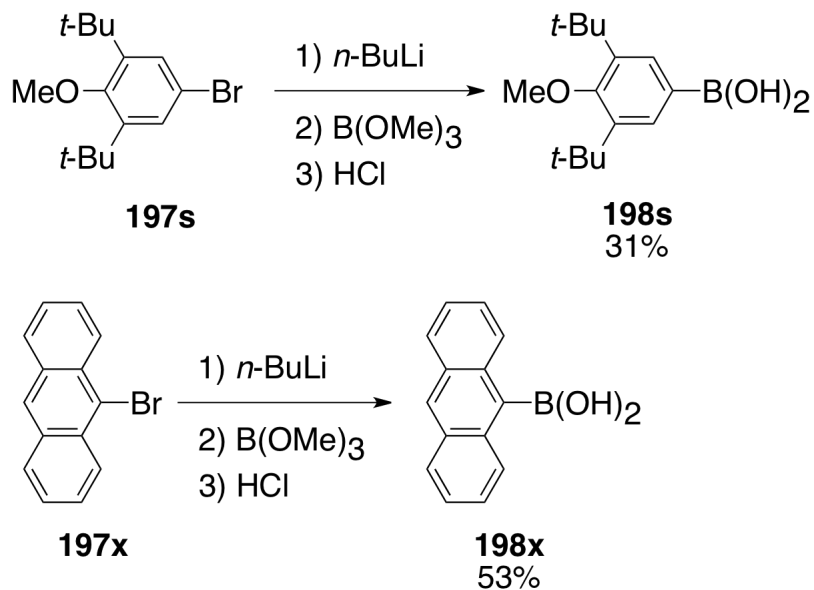
8	h	Me	54	55	>99
9	k	<i>i</i> -Pr	82 ^c	72	>99 ^b
10	m	<i>t</i> -Bu	72 ^e	77	>99
11	n	SiPh ₂ <i>t</i> -Bu	84	80	>99
12	ag	Ph	-		
13	ai	NO ₂	-		

^a phenol coupling for 48 h. ^b (*R*)-**174** obtained upon deracemization with (+)-sparteine. ^c phenol coupling at 160 °C for 48 h. ^d low solubility. ^e phenol coupling at 150 °C.

3.3.4 Synthesis of 7,7'-VANOL derivatives via Suzuki coupling

The convergent synthesis of various 7,7'-VANOL derivatives could in principle be realized by a number of different types of coupling reactions. The Suzuki coupling of different aryl boronic acids with the enantiopure 7,7'-dibromoVANOL could lead to a variety of 7,7'-diaryl VANOL derivatives. The two aryl boronic acids **198s** and **198x** were synthesized via lithiation of the corresponding aryl bromides and then borylation. Hydrolysis gave the corresponding aryl boronic acids in decent yields (Scheme 3.17).^{80,81}

Scheme 3.17 Synthesis of aryl boronic acids



Several Suzuki conditions with the unprotected 7,7'-dibromoVANOL (*S*)-**174d** were screened and the optimal conditions were established (Table 3.4, entry 2).¹⁵

Table 3.4 Suzuki couplings of 7,7'-dibromo VANOL

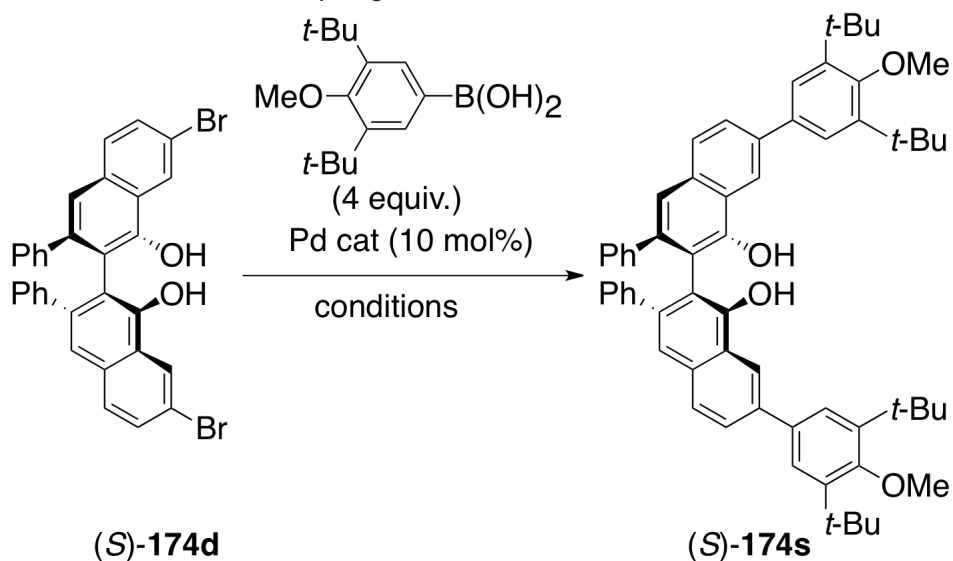


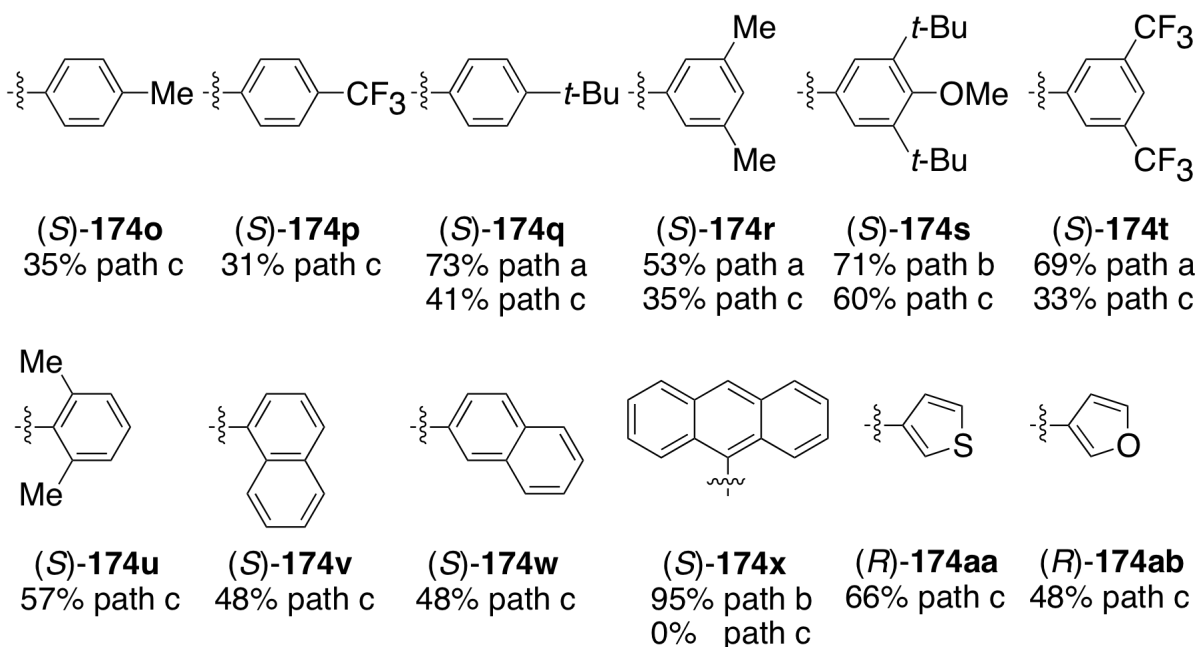
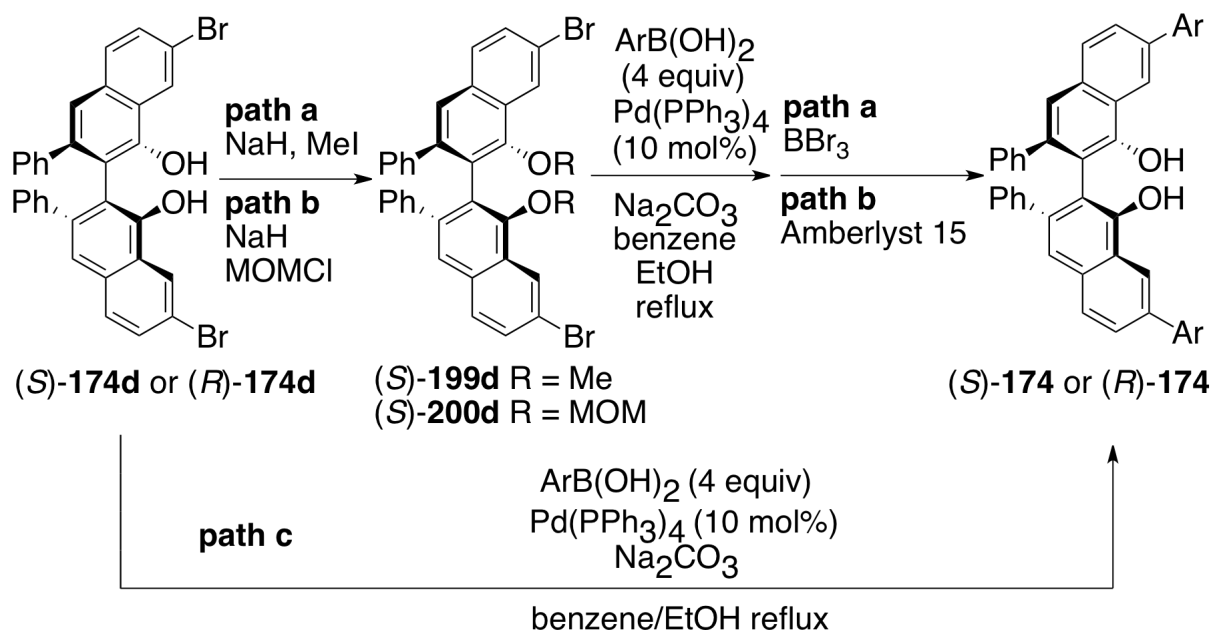
Table 3.4 (cont'd)

entry	Pd cat	base	solvent	% yield (<i>S</i>)- 174s ^a
1	Pd(PPh ₃) ₄	Na ₂ CO ₃	DME/H ₂ O	42
2	Pd(PPh ₃) ₄	Na ₂ CO ₃	benzene/EtOH/H ₂ O	60
3	PdCl ₂ •dppf•CH ₂ Cl ₂	K ₃ PO ₄ •2H ₂ O	DME	42

^a isolated yield by chromatography on silica gel.

Three different protocols were employed in the Suzuki coupling reactions (Scheme 3.18). Higher overall yields were obtained with a protection/Suzuki coupling/deprotection sequence than with a one-step method in which no protection is employed. For instance, 7,7'-bis-(*para-t*-butylphenyl)VANOL (*S*)-**174g** could be generated in 41% yield by direct Suzuki coupling, while the three-step method gave a 73% overall yield. However, the one-step method is simple, direct and fast. Homocoupling of the boronic acids and the formation of a considerable amount of base-line material might be the cause of the relatively lower yields of the one-step method. Polyaromatics (1-naphthyl, 2-naphthyl and 9-anthracenyl) and heterocycles (3-thiophenyl and 3-furyl) were successfully introduced by Suzuki couplings as well.

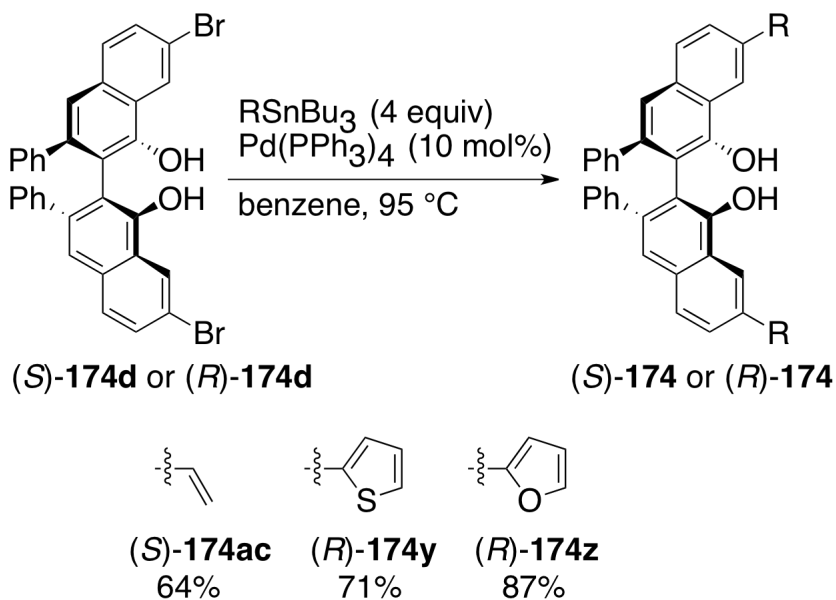
Scheme 3.18 Synthesis of 7,7'-diaryl VANOLs via Suzuki coupling



3.3.5 Synthesis of 7,7'-VANOL derivatives via Stille coupling

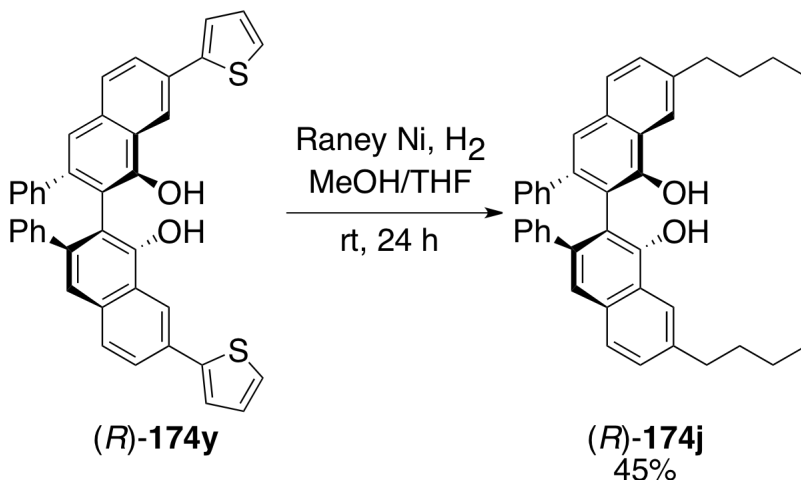
The convergent synthesis of VANOL derivatives could also employ the Stille coupling reaction.⁸² The Stille coupling of 7,7'-dibromoVANOL with various stannanes was used to produce 7,7'-divinylVANOL, 7,7'-bis-(2-thiophenyl)VANOL and 7,7'-bis-(2-furyl)VANOL in good to excellent yields (Scheme 3.19).

Scheme 3.19 Synthesis of 7,7'-disubstituted VANOL via Stille coupling



Hydrogenation of 7,7'-bis-(2-thiophenyl)VANOL (**(R)-174y**) with Raney Ni and H_2 at room temperature afforded 7,7'-di-*n*-butylVANOL (**(R)-174j**) in 45% yield (Scheme 3.20).⁸³

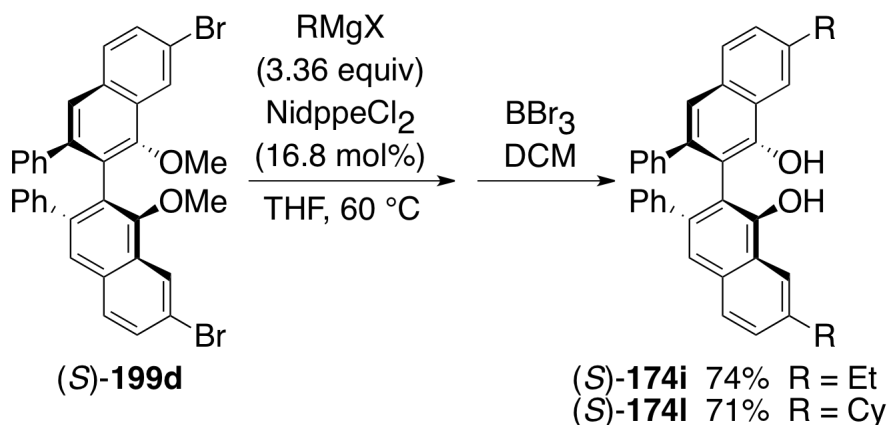
Scheme 3.20 Synthesis of 7,7'-di-*n*-butylVANOL



3.3.6 Synthesis of 7,7'-VANOL derivatives via Kumada coupling

The Kumada coupling reaction also adds to the convergent synthesis of VANOL derivatives. Reactions of the protected 7,7'-dibromoVANOL (*S*)-**199d** with the proper Grignard reagents (1° or 2° alkyls) catalyzed by Ni(dpppe)Cl_2 , followed by deprotection gave 7,7-diethyl- or 7,7-dicyclohexylVANOL in good yields (Scheme 3.21).¹⁵ The Kumada couplings of the unprotected 7,7'-dibromoVANOL (*S*)-**174d** with the Grignard reagents under the same conditions failed, leading to the recovery of the starting material.

Scheme 3.21 Synthesis of 7,7'-dialkyl VANOL via Kumada coupling

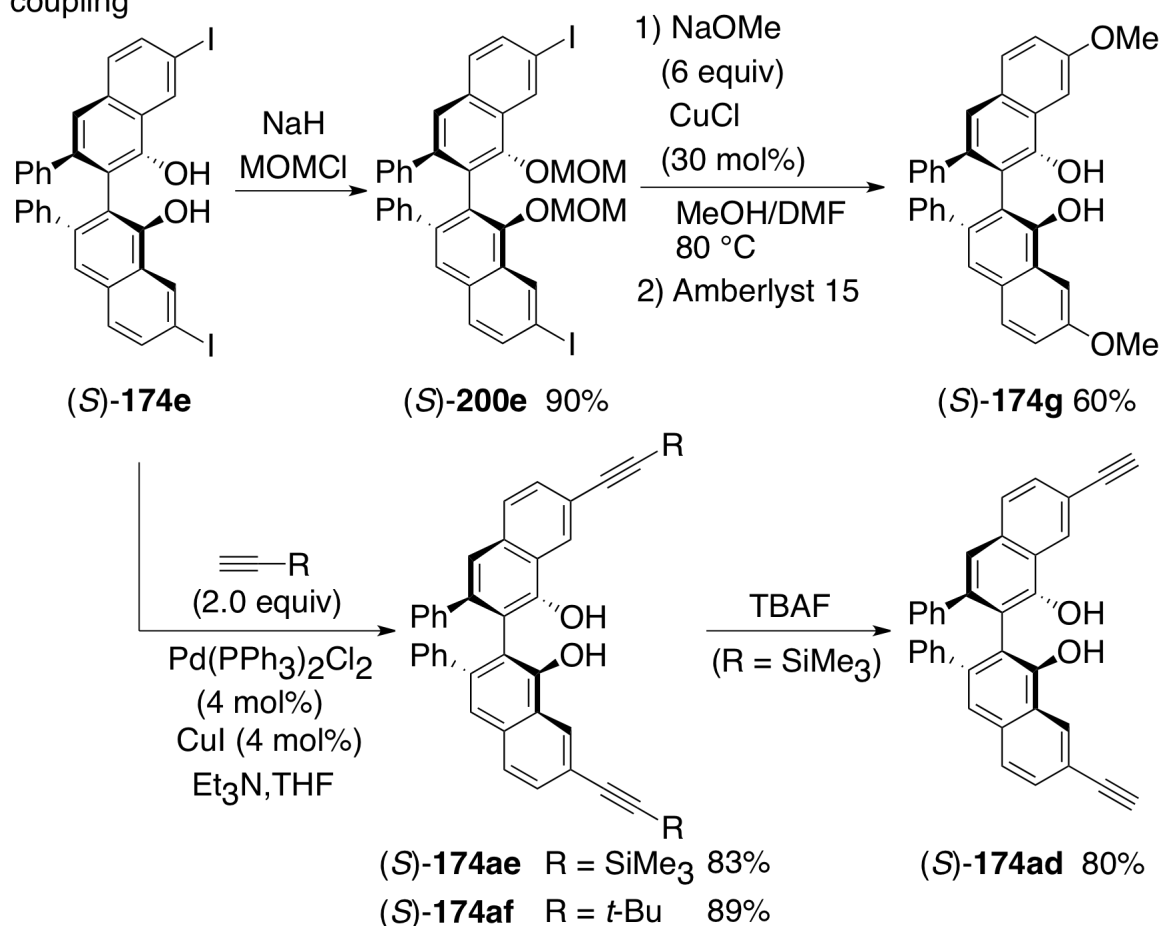


3.3.7 Synthesis of 7,7'-VANOL derivatives via Sonogashira and Ullman coupling reactions

Direct Sonogashira couplings of the 7,7'-diiodoVANOL (*S*)-**174e** were of highly efficiency as well. The coupling with trimethylsilyl acetylene afforded (*S*)-**174ae** in 83% yield and that with *t*-butylacetylene afforded (*S*)-**174af** in 89% yield (Scheme 3.22).^{63c} Removal of the trimethylsilyl group in the former with TBAF gave the alkynyl ligand (*S*)-**174ad** in 80% yield. Since the deracemization of racemic 7,7'-dimethoxyVANOL failed, conversion of

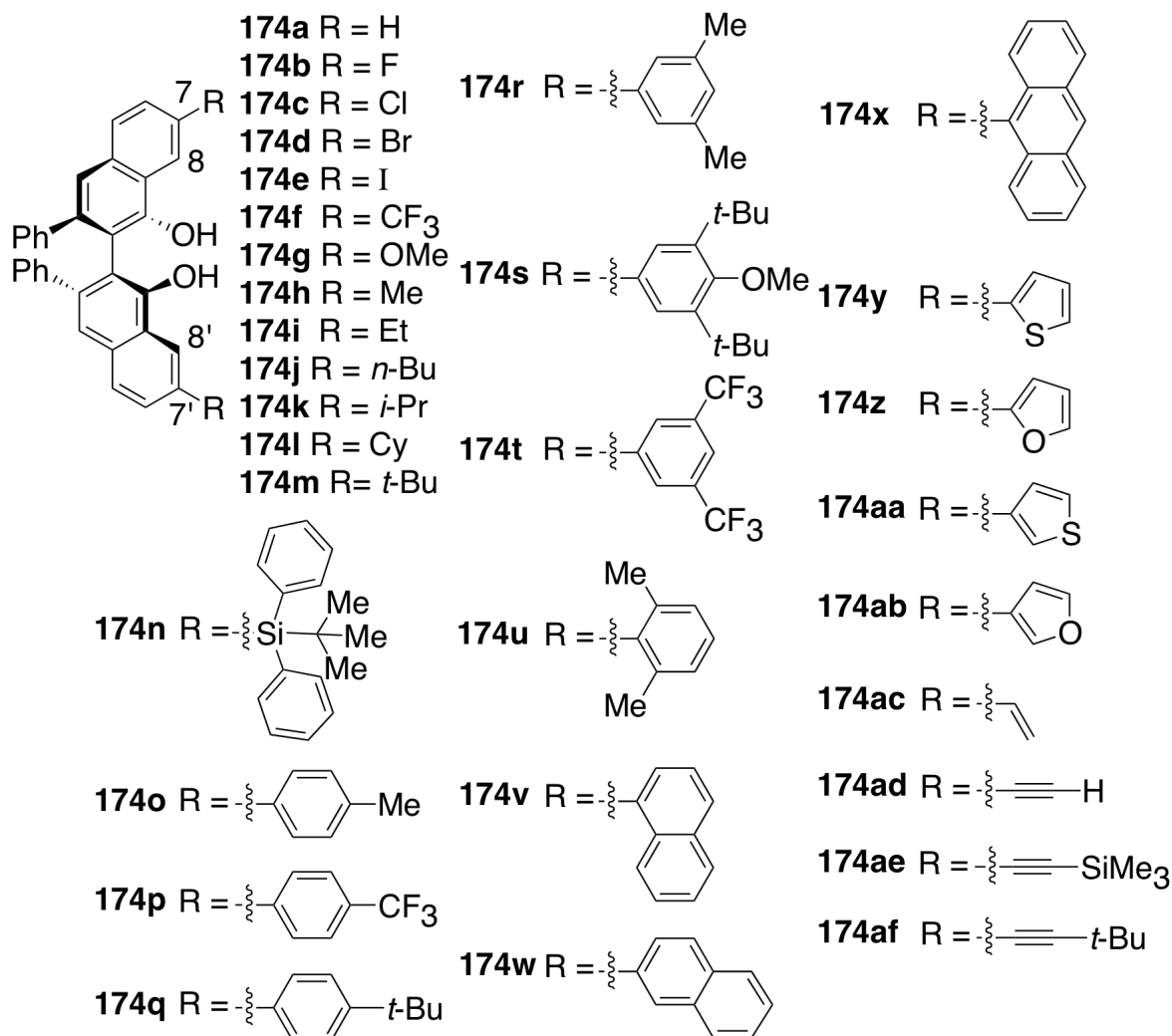
7,7'-diiodoVANOL (*S*)-**174e** to the 7,7'-dimethoxyIVANOL (*S*)-**174g** was investigated with several protocols. The phenol functions in the 7,7'-diiodoVANOL were protected as methoxymethyl ethers in order to realize orthogonal functionalization of the two pairs of the four phenols in the coupling product. The copper mediated coupling with sodium methoxide was successful in introducing the methoxy functions in the 7,7'-positions of VANOL.⁸⁴ Removal of the MOM groups with Amberlyst 15 gave the desired 7,7'-dimethoxyIVANOL (*S*)-**174g** in 54% yield over three steps.

Scheme 3.22 Synthesis of 7,7'-disubstituted VANOL via Sonogashira and Ullman coupling



Thus, a direct and convergent synthesis of 7,7'-disubstituted VANOL derivatives has been accomplished, resulting in the successful construction of a library of 31 ligands (Scheme 3.23).

Scheme 3.23 The library of 7,7'-disubstituted VANOL derivatives

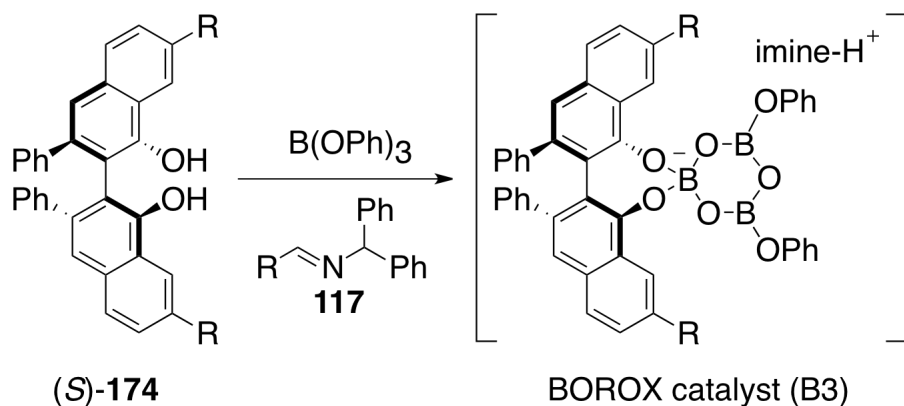
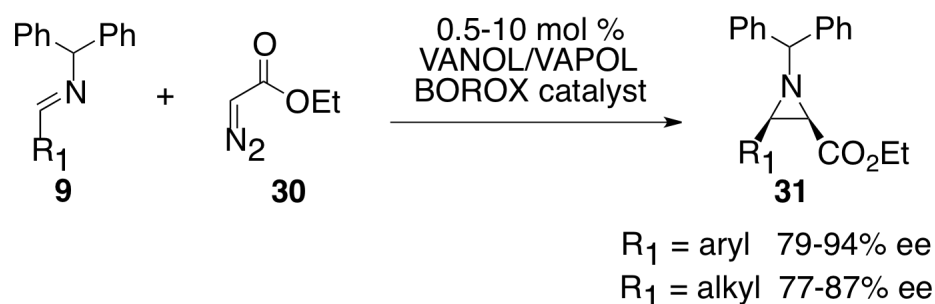


3.3.8 Screen of 7,7'-VANOL derivatives in the Wulff *cis*-aziridination reaction

Our group reported the first highly diastereoselective and enantioselective catalytic asymmetric synthesis of aziridines (Wulff *cis*-aziridination reaction) in 1999 (Scheme 3.24).²⁶ The reactions of aryl imines prepared from aryl aldehydes and benzhydryl amine give aziridines in 79-94% ee with both VANOL and VAPOL derived catalysts, and those from aliphatic aldehydes give aziridines in 77-87% ee. Of all the substituted benzhydryl imines examined, MEDAM imines are

the optimal, giving 96-99% ee for aryl aziridines and 86-92% ee for alkyl aziridines. However, MEDAM-NH₂ is not commercially available. Thus, it would be important to improve the asymmetric inductions with simple benzhydryl imines from commercially available benzyhydrl amine. In addition, it would be of mechanistic interest to investigate the effect of the different substituents in each of the 31 ligands on the Wulff *cis*-aziridination reaction with benzhydryl imines.

Scheme 3.24 Wulff *cis*-aziridination reaction



The first round of screening of the 31 ligands was performed with the imine **9i**, synthesized from cyclohexane carboxaldehyde, since this imine only gives 81% ee with VANOL derived BOROX catalyst, leaving much room for improvement (Table 3.5). It was found that catalysts from most of the ligands gave a higher asymmetric induction than that from the parent VANOL ligand. The halogen groups have generally small positive effects (F, 82% ee; Br, 85% ee; I, 88% ee) except

for Cl which has a small negative effect (78% ee) and it seems that size rather than an inductive electron-withdrawing effect predominates the asymmetric induction. That OMe gives a higher induction than 1° or 2° alkyl groups indicates that there is a positive component to an electron-releasing effect. The series of aryl groups reveals that the interplay between sterics and electronics of the aryl group is quite delicate and complicated. The 4-methylphenyl group gives 90% ee and the 4-*t*-butylphenyl group gives 93% ee, big jumps from 81% ee with VANOL. However, the increase is more than negated by a 4-trifluoromethylphenyl group (78% ee). A similar trend is observed where the 3,5-dimethylphenyl group gives 92% ee, a jump from 81% ee with VANOL, whereas this increase is again negated by a 3,5-bis-trifluoromethylphenyl group (80% ee). The advantage of a phenyl group is lost when *ortho*-groups are introduced on the phenyl ring. For example the 2,6-dimethylphenyl group gives 82% ee, the 2-naphthyl group gives 81% ee and the 9-anthracenyl group gives 63% ee. Most of the 1° and 2° alkyl groups give similar asymmetric inductions (Me, 87% ee; Et, 87% ee; *n*-Bu, 89% ee; *i*-Pr, 89% ee; Cy, 87% ee). The *t*-Bu group gives 94% ee and turns out to be the optimal among all of the 31 ligands

Table 3.5 Ligand screen on the *cis*-aziridination reaction of phenyl imine **9i**^a

Reaction scheme: Phenyl imine **9i** (cyclohexyl-CH=N-CH(Ph)₂) + ethyl diazoacetate **30** (CH₂=N₂-CO₂Et) → **31i** (cis-aziridine with cyclohexyl, N-CH(Ph)₂, and CO₂Et groups).

entry	ligand	R	% yield ^b	% ee ^c
1	3	H	78	82 VAPOL

Table 3.5 (cont'd)

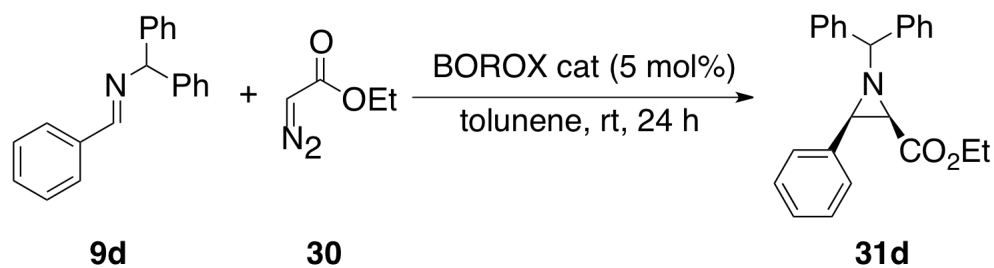
2	174a	H	77	81	VANOL
3	174b	F	76	82	
4	174c	Cl	83	78	
5	174d	Br	78	85	
6	174e	I	80	88	
7	174f	CF ₃	88	85	
8	174g	OMe	88	92	
9	174h	Me	83	87	
10	174i	Et	91	87	
11	174j	<i>n</i> -Bu	91	89	
12	174k	<i>i</i> -Pr	91	89	
13	174l	Cy	90	87	
14	174m	<i>t</i> -Bu	88	94	
15	174n	SiPh ₂ <i>t</i> -Bu	72	79	
16	174o	4-MeC ₆ H ₄	89	90	
17	174p	4-CF ₃ C ₆ H ₄	93	78	
18	174q	4- <i>t</i> -BuC ₆ H ₄	83	93	
19	174r	3,5-Me ₂ C ₆ H ₃	88	92	
20	174s	3,5-(<i>t</i> -Bu) ₂ -4-MeOC ₆ H ₂	77	86	

Table 3.5 (cont'd)

21	174t	3,5-(CF ₃) ₂ C ₆ H ₃	90	80
22	174u	2,6-Me ₂ C ₆ H ₃	72	82
23	174v	1-naphthyl	87	81
24	174w	2-naphthyl	94	90
25	174x	9-anthracenyl	72	63
26	174y	2-C ₄ H ₃ S	90	88
27	174z	2-C ₄ H ₃ O	77	76
28	174aa	3-C ₄ H ₃ S	91	90
29	174ab	3-C ₄ H ₃ O	90	89
30	174ac	-CH=CH ₂	90	82
31	174ad	-CCH	85	84
32	174ae	-CCSiMe ₃	79	88
33	174af	-CC- <i>t</i> -Bu	87	87

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The catalyst was prepared from 1 equiv ligand, 4 equiv B(OPh)₃ and 1 equiv H₂O at 80 °C in toluene for 1 h, followed by removal of volatiles under vacuum (0.5 mm Hg) at 80 °C for 0.5 h. ^b yield of isolated *cis*-aziridine by chromatography on silica gel. ^c determined by HPLC on a Chiralcel OD-H column.

The second round of screening of the 31 ligands was performed with the imine **9d** synthesized from benzaldehyde (Table 3.6). Many of the trends in asymmetric induction observed for the cyclohexyl imine **9i** were also observed for the phenyl imine **9d**. Electron releasing groups generally give increased inductions (OMe, 96% ee) compared to VANOL (92% ee) while electron withdrawing substituents lead to decrease inductions (F, 83% ee; Cl, 89% ee; Br, 89% ee; CF₃, 86% ee). The 4-methylphenyl group gives 96% ee and 4-*t*-butylphenyl group gives 97% ee. The increase is again more than negated by a 4-trifluoromethylphenyl group (84% ee). One contrast is that the 3,5-bis-trifluoromethylphenyl group gives an increased induction (95% ee) for the phenyl imine **9d** but a decreased induction (78% ee) for the cyclohexyl imine **9i**, compared to VANOL. The advantage of a phenyl group is again lost when *ortho*-groups are introduced on the phenyl ring. Et, *n*-Bu and Cy groups give the same asymmetric induction (94%) but the *i*-Pr group gives 97% ee and the *t*-Bu group gives 98% ee. The best ligand for the cyclohexyl imine is also the best ligand for the phenyl imine. All reactions were carried out for 24 h in order to ensure that any differences in rates for the different ligands could be accommodated. The reaction of the phenyl imine **9d** with the catalyst from 7,7'-di-*t*-butylVANOL (5 mol%) was repeated and stopped after 4 h. The reaction was complete and gave aziridine **31d** in 89% yield with 97.4% ee. The sample of the ligand used in this reaction has been stored in the refrigerator under N₂ for two years subsequent to the first run indicated in Table 3.6.

Table 3.6 Ligand screen on the *cis*-aziridination reaction of phenyl imine **9d**^a

entry	ligand	R	% yield ^b	% ee ^c
1	3	H	76	93 VAPOL
2	174a	H	84	92 VANOL
3	174b	F	80	83
4	174c	Cl	91	89
5	174d	Br	89 ^d	89 ^d
6	174e	I	85	92
7	174f	CF ₃	96	86
8	174g	OMe	86	96
9	174h	Me	82 ^e	86 ^e
10	174i	Et	90	94
11	174j	<i>n</i> -Bu	95	94
12	174k	<i>i</i> -Pr	93	97
13	174l	Cy	94	94
14	174m	<i>t</i> -Bu	82 ^f	98 ^f
15	174n	SiPh ₂ <i>t</i> -Bu	77	94

Table 3.6 (cont'd)

16	174o	4-MeC ₆ H ₄	94	96
17	174p	4-CF ₃ C ₆ H ₄	92	84
18	174q	4- <i>t</i> -BuC ₆ H ₄	85	97
19	174r	3,5-Me ₂ C ₆ H ₃	82	95
20	174s	3,5-(<i>t</i> -Bu) ₂ -4-MeOC ₆ H ₂	85	97
21	174t	3,5-(CF ₃) ₂ C ₆ H ₃	94	95
22	174u	2,6-Me ₂ C ₆ H ₃	77	91
23	174v	1-naphthyl	92	92
24	174w	2-naphthyl	91	95
25	174x	9-anthracenyl	88	84
26	174y	2-C ₄ H ₃ S	96	95
27	174z	2-C ₄ H ₃ O	95	96
28	174aa	3-C ₄ H ₃ S	96	96
29	174ab	3-C ₄ H ₃ O	98	95
30	174ac	-CH=CH ₂	91	93
31	174ad	-CCH	86	93
32	174ae	-CCSiMe ₃	86	92
33	174af	-CC- <i>t</i> -Bu	94	94

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst.

The catalyst was prepared as indicated in Table 3.5. ^b yield of isolated *cis*-aziridine by chromatography on silica gel. ^c determined by HPLC on a Chiralcel OD-H column. ^d a repeat of this reaction on 1.0 mmol scale gave 80% yield and 88% ee. ^e a repeat of this reaction on 1.0 mmol scale gave 87% yield and 86% ee. ^f a repeat of this reaction revealed that it was complete in 4 h to give 89% yield and 97.4% ee.

Given the fact that the 7,7'-di-*t*-butylVANOL was the best ligand for both of the benzhydryl imines **9d** and **9i**, ten benzhydryl imines were then examined with the catalyst generated from 7,7'-di-*t*-butylVANOL (Table 3.7). All of these imines have been previously examined with catalysts prepared from VANOL and VAPOL.^{26g} For all the ten imines, 7,7'-di-*t*-butylVANOL gives higher asymmetric inductions and yields than either VANOL or VAPOL. For aryl imines, 7,7'-di-*t*-butylVANOL gives 95-99% ee, while VAPOL gives 79-94% ee and VANOL gives 87-94% ee. For 1°, 2° and 3° alkyl imines, 7,7'-di-*t*-butylVANOL gives 94-96% ee, while VAPOL gives 81-87% ee and VANOL gives 77-85% ee. 7,7'-Di-*t*-butylVANOL gives both a much higher average yield and asymmetric induction (85% yield, 97% ee) than VANOL (74% yield, 87% ee) or VAPOL (65% yield, 86% ee). The improvement on some challenging substrates is much more obvious. For instance, the reaction of the 2-bromophenyl imine **9c** with the VAPOL catalyst gives a 1.6:1 mixture of *cis* and *trans* isomers (82% ee for the *cis* isomer), and the VANOL catalyst gives a 1.9:1 mixture of *cis* and *trans* isomers (82% ee for the *cis* isomer), whereas, the 7,7'-di-*t*-butylVANOL catalyst gives an 8:1 mixture of *cis* and *trans* isomers (95% ee for the *cis* isomer). Improved diastereoselectivity is also observed for the 2-methylphenyl

imine **9f** with *cis:trans* ratios increasing from 10:1 to 12: 1 to >100:1 for the VAPOL, VANOL and 7,7'-di-*t*-butylVANOL catalysts, respectively. A decrease in the amount of enamine side-products and an increase in the *cis:trans* ratio together account for the increase in efficiency in the formation of the *cis*-aziridine. The 7,7'-di-*t*-butylVANOL catalyst solves several of the long-standing problems in the Wulff *cis*-aziridination reactions of benzhydryl imines, providing excellent diastereoselectivities and enantioselectivities.

Table 3.7 Substrate scope comparison of di-*t*-Bu-VANOL with VANOL and VAPOL^a

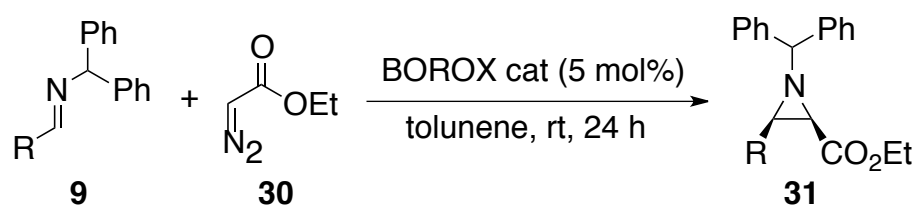
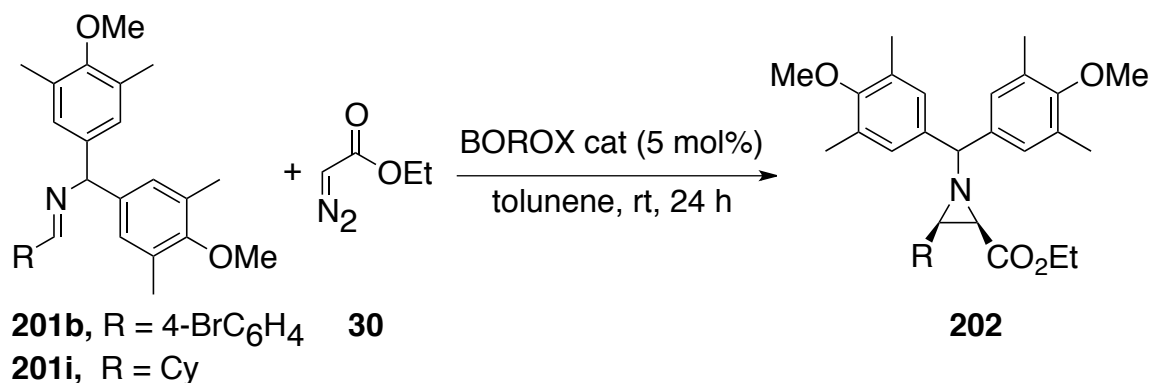
							
series	R	VAPOL catalyst ^b		VANOL catalyst ^b		<i>t</i> -Bu ₂ VANOL catalyst	
		% yield	% ee	% yield	% ee	% yield	% ee
		AZ ^c	AZ ^d	AZ ^c	AZ ^d	AZ ^c	AZ ^d
a	4-NO ₂ C ₆ H ₄	79	79	86	89	96	98
b	4-BrC ₆ H ₄	78	90	86	94	90	98
c	2-BrC ₆ H ₄	37 ^e	82	43 ^f	82	78 ^g	95
d	C ₆ H ₅	82	94	87	93	82	98
e	1-naphthyl	76	93	80	93	91	99
f	2-MeC ₆ H ₄	63 ^h	91	67 ⁱ	90	92 ^j	97
g	4-MeOC ₆ H ₄	51	86	67	87	71	98
h	<i>n</i> -propyl	40	81	54	77	77	94

Table 3.7 (cont'd)

i	cyclohexyl	73	81	79	82	88	94
j	<i>t</i> -butyl	72	87	89	85	89	96
	average	65	86	74	87	85	97

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The catalyst was prepared as indicated in Table 3.5. ^b data taken from ref 26g. ^c yield of isolated *cis*-aziridine by chromatography on silica gel. ^d determined by HPLC on a Chiralcel OD-H column. ^e plus 23% yield *trans*-**31c** (*cis/trans* = 1.6:1). ^f plus 23% yield *trans*-**31c** (*cis/trans* = 1.9:1). ^g plus 10% yield *trans*-**31f** (*cis/trans* = 8:1). ^h plus 6% yield *trans*-**31f** (*cis/trans* = 10:1). ⁱ plus 6% yield *trans* (*cis/trans* = 12:1). ^j *cis/trans* > 100:1.

Given the success of with benzhydryl imines, 7,7'-di-*t*-butylVANOL was then examined with MEDAM imines (Table 3.8). The reaction of the 4-bromophenyl imine **201b** with the VANOL catalyst affords aziridine **202b** in 95% yield and 97% ee and the reaction with the 7,7'-di-*t*-butylVANOL catalyst affords aziridine **202b** in 95% yield and 99% ee. The reaction of the cyclohexyl imine **201i** with the VANOL catalyst affords aziridine **202i** in 95% yield and 91% ee and with 7,7'-di-*t*-butylVANOL catalyst aziridine **202b** is obtained in 92% yield and 97% ee. Thus 7,7'-di-*t*-butylVANOL can further improve the performance of MEDAM imines in term of asymmetric induction.

Table 3.8 *Cis*-aziridination reaction of imines **201** with VANOL and di-*t*-Bu-VANOL^a

entry	R	VANOL catalyst ^b		<i>t</i> -Bu ₂ VANOL catalyst	
		% yield AZ ^c	% ee AZ ^d	% yield AZ ^c	% ee AZ ^d
1	4-BrC ₆ H ₄	95	97	95	99
2	cyclohexyl	95	91	92	97

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst.

The catalyst was prepared as indicated in Table 3.5. ^b data taken from ref 26j. ^c yield of isolated *cis*-aziridine by chromatography on silica gel. ^d determined by HPLC.

3.3.9 Utility of 7,7'-di-*t*-butylVANOL in the Wulff *trans*-aziridination reaction

It was found that 7,7'-di-*t*-butylVANOL catalyst outperforms that from VANOL in the Wulff *trans*-aziridination reaction as well at least for the two substrates shown in Table 3.9. The reaction of the ethyl imine **203k** with the VANOL catalyst affords aziridine **204k** in 67% yield and 85% ee and that with the 7,7'-di-*t*-butylVANOL catalyst affords aziridine **204k** in 65% yield and 90% ee. The reaction of the *n*-propyl imine **203l** with the VANOL catalyst affords aziridine

204l in 70% yield and 71% ee and that with the 7,7'-di-*t*-butylVANOL catalyst affords aziridine **204l** in 69% yield and 85% ee. Though the reaction of the phenyl imine **204d** with the 7,7'-di-*t*-butylVANOL catalyst affords no desired *trans*-aziridines.

Table 3.9 *Trans*-aziridination reaction of imine **203** with VANOL and di-*t*-Bu-VANOL^a

203d, R = Ph
203k, R = Et
203k, R = *n*-Pr

148

BOROX cat (10 mol%)
 toluene, 0 °C, 24 h

204

		VANOL catalyst ^b		<i>t</i> -Bu ₂ VANOL catalyst	
entry	R	% yield AZ ^c	% ee AZ ^d	% yield AZ ^c	% ee AZ ^d
1	Ph	75	91	nd	nd
2	Et	67	82	65	90
3	<i>n</i> -Pr	70	71	69	85

^a Unless otherwise specified, all reactions were performed on 0.2 mmol scale in toluene at 0.2 M imine with 1.4 equiv of diazoacetamide for 24 h at 0 °C and went to 100% conversion. The catalyst was prepared by heating a mixture of 1 equiv of the ligand, 3 equiv BH₃•SMe₂, 2 equiv phenol, 3 equiv H₂O in toluene at 100 °C for 1 h. The volatiles were then removed under vacuum (0.1 mm Hg) at 100 °C for 1 h. nd = not determined. ^b data taken from ref 27a. ^c yield of isolated *trans*-aziridine by chromatography on silica gel. ^d determined by HPLC.

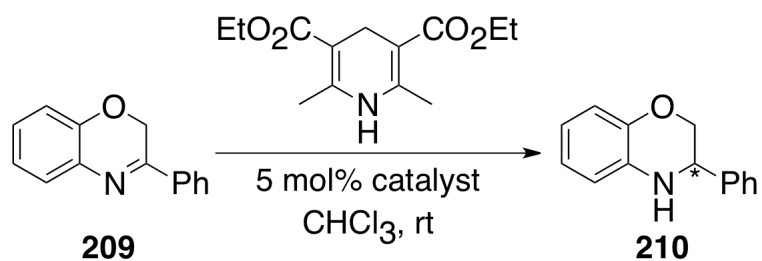
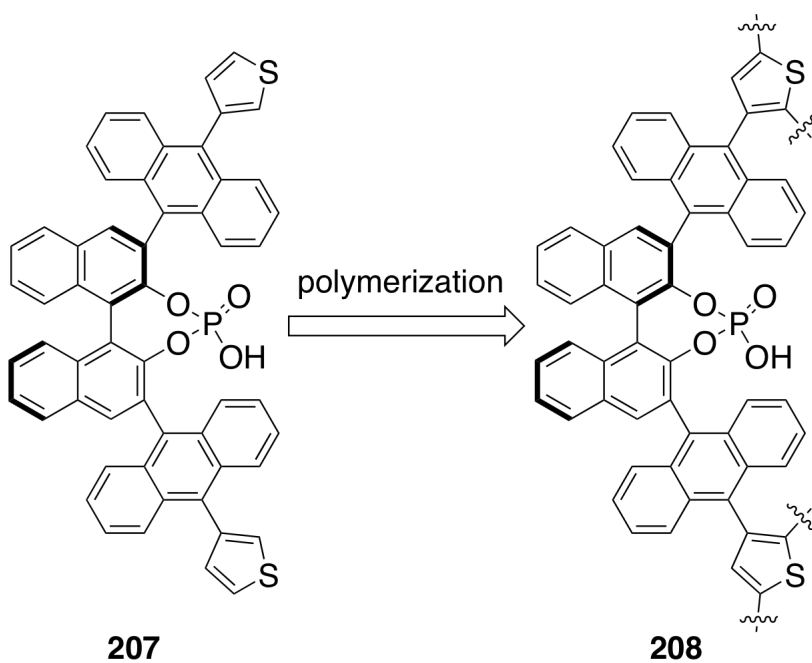
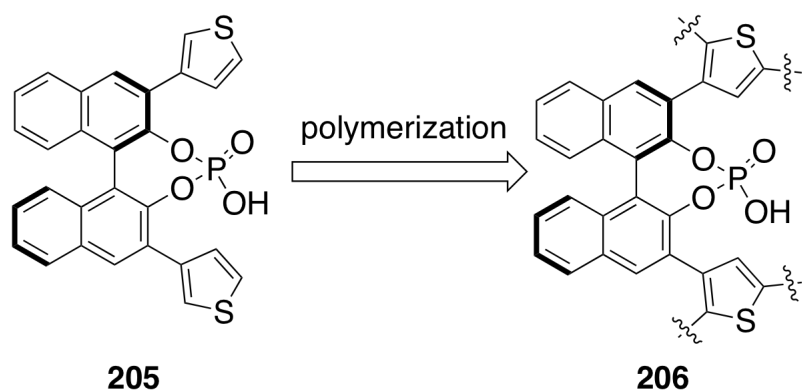
3.4 Future plan

With the set of thirty-one VANOL derivatives in hands, it would be of synthetic benefit to find a superior ligand to further improve the Wulff *trans*-aziridination developed by Dr. Desai and the catalytic asymmetric synthesis of trisubstituted aziridines developed by Dr. Huang.^{27a,29}

Blechert and coworkers introduced a new concept to immobilize an organocatalyst (Scheme 3.25).⁸⁵ They obtained several polymer networks **206** or **208** via the oxidative coupling of thienyl-functionalized BINOL derivatives in the form of the structure-directing monomers **205** or **207**. Microporosity, chirality and active centers are introduced in the polymer network. Those polymers can catalyze transfer hydrogenation of dihydro-2*H*-benzoxazine **209** with decent to excellent enantioselectivities. The catalysts could be recovered by centrifugation and reused for 10 runs without any loss in activity or selectivity. The reactions catalyzed by the heterogeneous catalysts show increased enantioselectivity compared to the homogeneous reactions.

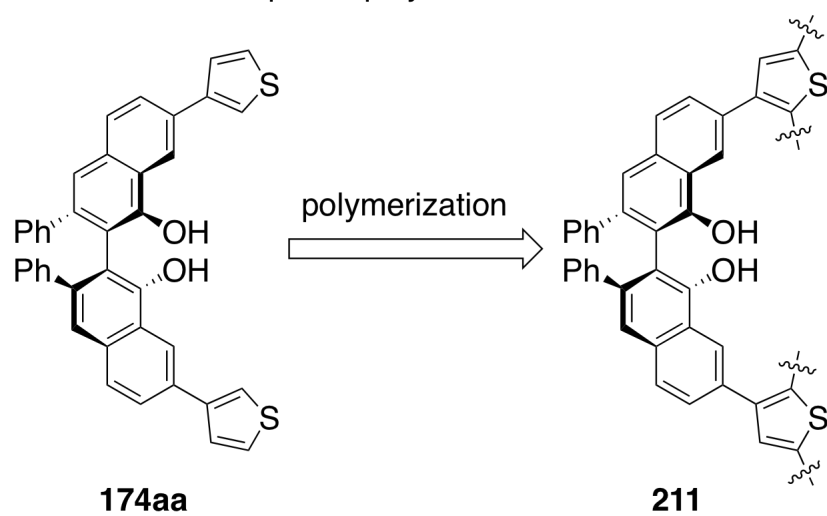
Inspired by their concept, we might be able to prepare a polymer network **211** from 7,7'-bis-(3-thienyl)VANOL **174aa**, a ligand from the 31 member VANOL library (Scheme 3.26). This homogeneous catalyst could be used in the Wulff aziridination reactions, as well as other reactions catalyzed by VANOL.

Scheme 3.25 Synthesis of polymer networks of BINOL derivatives



with **206**: >99% conv, 47% ee
with **208**: >99% conv, 98% ee

Scheme 3.26 Proposed polymer network of VANOL derivative **174aa**



3.5 Conclusion

The family of 7,7'-disubstituted VANOL ligands can be quickly and efficiently prepared in three steps from *p*-substituted phenylacetic acids and phenylacetylene via a cycloaddition/electrocyclic ring-opening/electrocyclic ring closure/tautomerization cascade, a phenol homo-coupling reaction and finally deracemization. A convergent synthesis of additional members of the family can be achieved via 7,7'-dibromoVANOL or 7,7'-diiodoVANOL via Suzuki, Stille, Kumada, Sonogashira, Hartwig and Ullman coupling reactions. A set of 31 7,7'-disubstituted VANOL ligands was then used to screen the *cis*-aziridination reaction of benzhydryl imines and ethyl diazoacetate. Phenyl and cyclohexyl imines were treated with boroxinate catalysts prepared from all 31 of the VANOL ligands. Asymmetric inductions varied from 63-98% ee. The best induction for the two imines was obtained with the same ligand: 7,7'-di-*t*-butylVANOL. This ligand was applied to the aziridination of ten different benzhydryl imines. For aryl imines, 7,7'-di-*t*-butylVANOL gave 95-99% ee, and for alkyl imines, it gave 94-96% ee. For every imine, 7,7'-di-*t*-butylVANOL afforded a higher induction than VANOL or VAPOL. Higher *cis/trans* selectivities were observed for *o*-substituted aryl imines with 7,7'-di-*t*-butylVANOL. 7,7'-di-*t*-butylVANOL is also compatible with other *N*-substituents, such as MEDAM and BUDAM. Moreover, it improves the asymmetric induction with alkyl imines in the *trans*-aziridination reaction.

CHAPTER FOUR

SYSTEMATIC EXPLORATION OF SINGLE-POINT AND DOUBLE-POINT

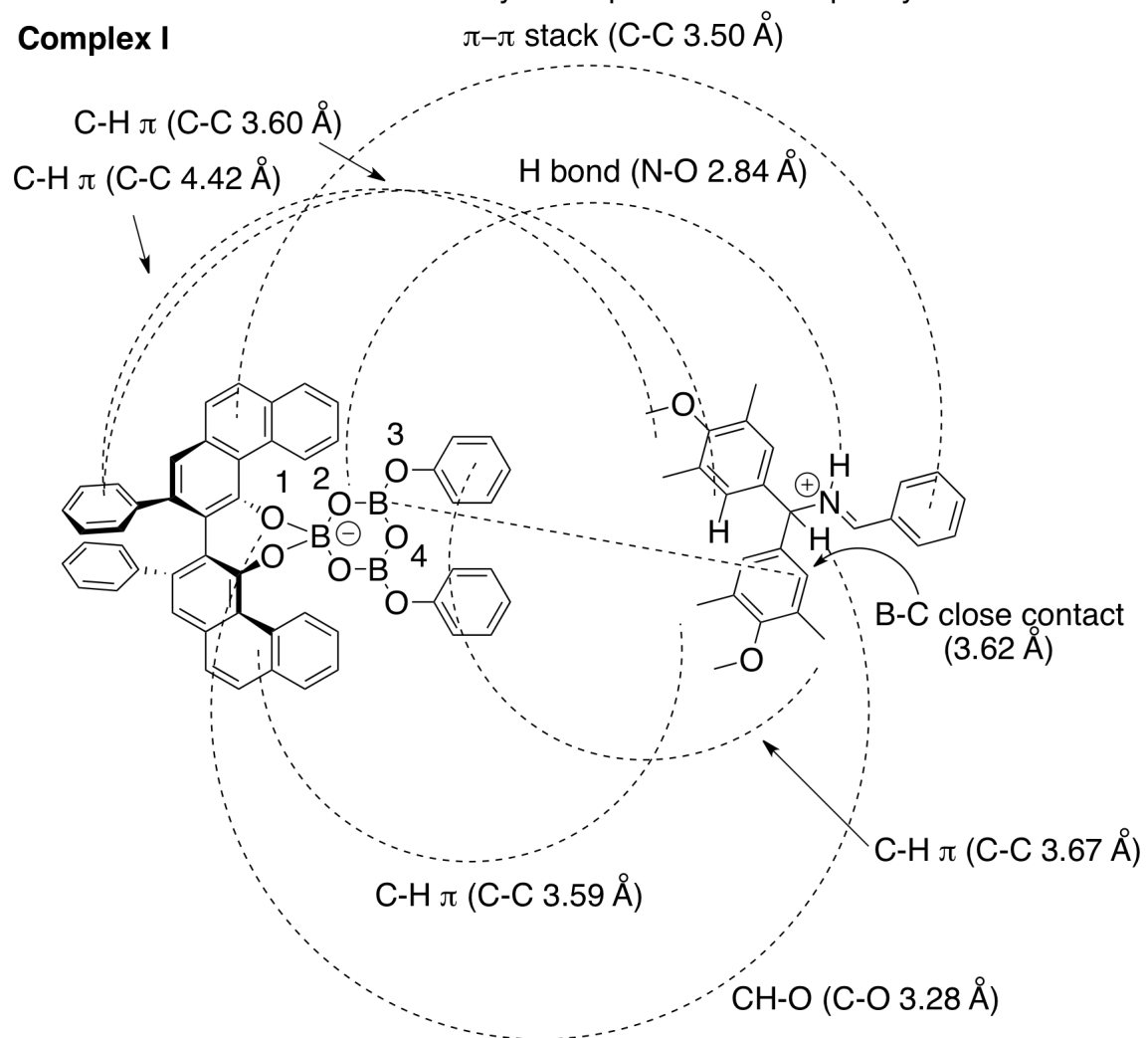
CHANGES TO VANOL BOROX CATALYST: STRUCTURE-ACTIVITY

RELATIONSHIP STUDY ON VANOL DERIVATIVES

4.1 Introduction

Our group developed the first highly enantioselective *cis*-aziridination reaction of imine and diazo compound.^{26a,26b} Originally the catalyst was thought to be a Lewis acids. Later on, Dr. Hu determined that this transformation actually is a Brønsted acid catalyzed reaction through extensive NMR and crystallographic studies.^{26i,26l} The crystal structure of the chemzyme-substrate complex revealed the unique boroxinate topology, self-assembled from VAPOL, B(OPh)₃, H₂O and the MEDAM imine of benzaldehyde (Scheme 4.1).^{26l} There is an H bonding between the hydrogen of the protonated imine and one of the oxygens of the boroxinate ring (N-O distance is 2.84 Å). In addition, there are several non-covalent catalyst-substrate contacts. There is a π - π stacking interaction between the phenyl group of the protonated imine and the central ring of the phenanthrene of the catalyst (3.50 Å). Four CH- π interactions could be identified. One of the methyl groups of the MEDAM imine is over the central ring of one of the phenanthrenes of the catalyst (3.59 Å). The other methyl group on the same phenyl group is over one of the phenoxy groups of the boroxinate core (3.67 Å). One of the *ortho*-H's of the other phenyl group of the imine is 3.60 Å away from the one of the phenyl groups (C3 phenyl) on the backside of VAPOL. The carbon of the methyl group next to this *ortho*-hydrogen is 4.42 Å away from the same phenyl ring (C3 phenyl).

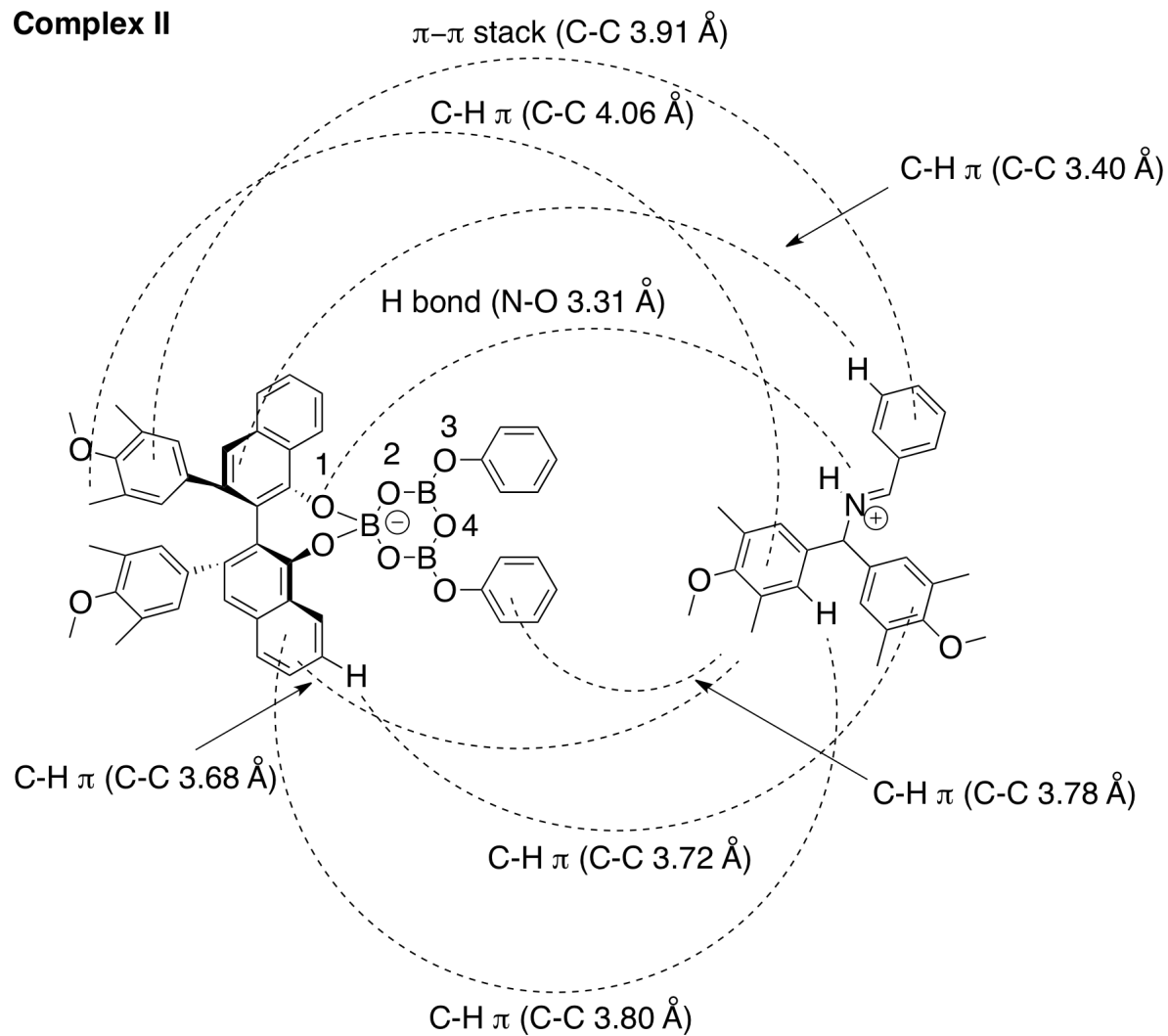
Scheme 4.1 VAPOL BOROX catalyst complexed with the phenyl MEDAM imine
Complex I



Zhenjie Lu from our group synthesized some VANOL derivatives with variation in the substituents on the C3 aryl group and was able to get a crystal structure of the BOROX catalyst from the VANOL derivative and the MEDAM imine of benzaldehyde (Scheme 4.2).⁶⁴ The binding of the catalyst and substrate was not the same as in the previous one (Scheme 4.1). The protonated imine is H-bonded to the boroxinate core in a different way and is H-bonded to O-1 not O-2. The H bonding distance is 3.31 Å. The π - π stacking is now between the phenyl group of the iminium cation and the 3,5-dimethyl-4-methoxyphenyl substituent (C3 aryl) of the ligand (3.91 Å). There are at least six CH- π interactions. The phenyl group of the iminium cation is rotated about 90° and has a CH- π interaction with the naphthalene ring of the ligand (3.40 Å). The other naphthalene ring is involved in CH- π interactions with an *ortho*-hydrogen (3.80 Å) and a methyl group (3.68 Å) of one of the 3,5-dimethyl-4-methoxyphenyl groups of the MEDAM imine. A hydrogen in the 7-position of one of the naphthalene rings of the ligand is over the other 3,5-dimethyl-4-methoxyphenyl groups of the MEDAM imine (3.72 Å). The methyl group on the same 3,5-dimethyl-4-methoxyphenyl group of the MEDAM imine is over one of the phenyl groups of the boroxinate core (3.78 Å). There is a CH- π interaction between the same 3,5-dimethyl-4-methoxyphenyl group of the MEDAM imine and the methyl group of the 3,5-dimethyl-4-methoxyphenyl group (C3 aryl) of the ligand (4.06 Å). The biggest difference in this crystal structure is that the methine hydrogen of the imine is pointing away from the catalyst and projecting into free space, while in the previous structure, the methine hydrogen is pointing towards the catalyst and is engaged in a CH-O interaction with the boroxinate core (3.28 Å).

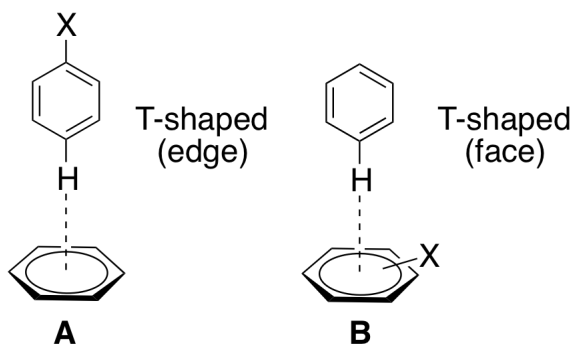
Scheme 4.2 VANOL ligand BOROX catalyst complexed with the phenyl MEDAM imine

Complex II



The hydrogen binding holds the catalyst and substrate together while the π - π and CH- π interactions organize the two parts and direct the path of the incoming diazo compound. Current but universally accepted thinking on CH- π interactions derives from experimental and computational studies and it is believed that an electron-withdrawing group on the edge ring will increase the interaction between face and edge rings (Scheme 4.3).^{97,98} Electron-donating groups on the face ring will also enhance the interaction, while electron-withdrawing groups on the face ring will have opposite effect.

Scheme 4.3 CH- π interaction



The CH- π interaction is enhanced when:
a) electron withdrawing group on the edge ring (A)
b) electron donating group on the face ring (B)

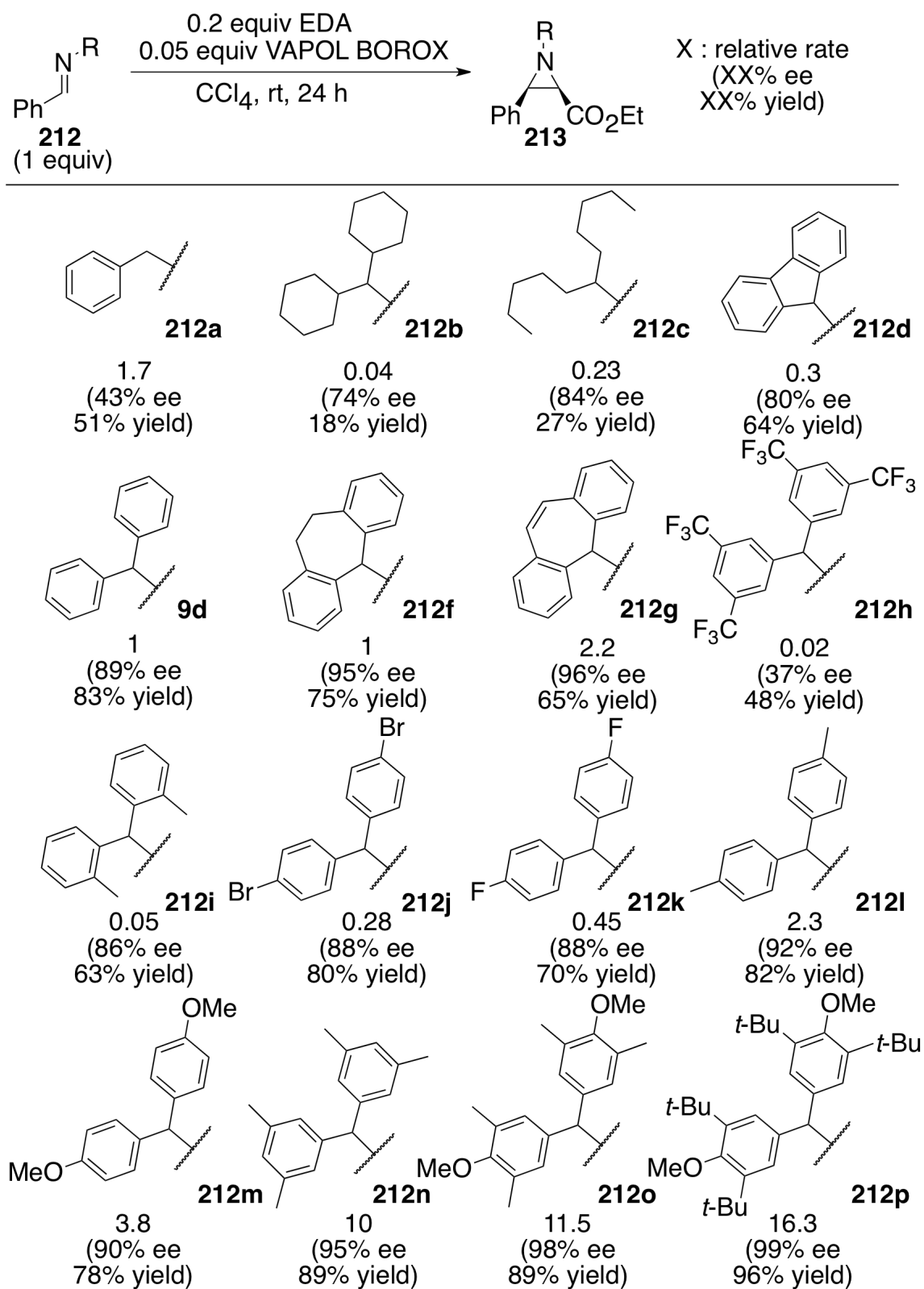
4.2 Background

4.2.1 Effect of the *N*-substituent on the imine

In order to understand the details of the aziridination reaction, our group has carried out a continuous study, examining the contribution of each component in turn.

Before the crystal structures discussed above were obtained and solved, Dr. Zhang and Dr. Lu investigated the interactions between the *N*-substituent and catalyst by changing the conformation, electronics and sterics of the *N*-substituent (Scheme 4.4).^{26h} The relative rate was determined in competition experiments in which 1.0 equiv of imine **9d** and 1.0 equiv of a competitor imine were reacted with 0.2 equiv of EDA in the presence of 5 mol % of VAPOL BOROX catalyst at 25 °C for 24 h. The *N*-alkyl and benzyl imines give lower induction than the benzhydryl imine, indicating the importance of the interactions of the two phenyl groups and the catalyst. The reactions with the imines **1d**, **1f**, and **1g** reveal that the orientation of the two phenyl groups is important. The increased reactivity and enantioselectivity of BUDAM imine **212o** and the MEDAM imine **212p** may be related to the CH- π interactions of methyl and *t*-butyl groups with the catalyst observed in the crystal structures of the MEDAM imines. Introduction of electron-withdrawing groups (Br or F) leads to slightly decreased induction, while that of electron-donating groups (Me or OMe) has opposite effect. The 3,5-bis(trifluoromethyl) analogue gives a much slower reaction rate and a much lower induction (37% ee). Those observations may be suggestive of the importance of the CH- π interaction between the phenyl group of the imine and the C3 phenyl of the ligand observed in the second crystal structure (Scheme 4.2).

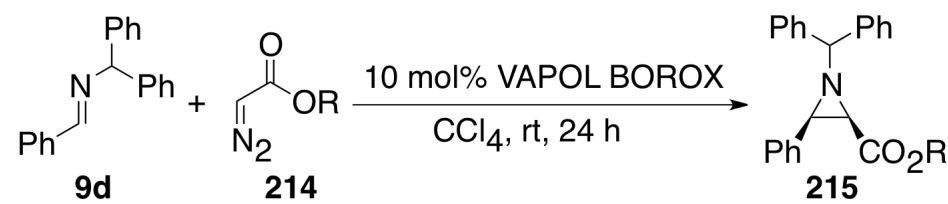
Scheme 4.4 Aziridination reaction of different *N*-substituted imines^{26h}



4.2.2 Effect of diazo compounds

Dr. Lu was the first to look at variation of the alcohol group in the ester group of the diazo acetate. The steric and electronic changes in the diazo acetates only affects the asymmetric inductions in the range of 1-4% ee and give comparable yields (Table 4.1).⁶⁴ The most sterically hindered *t*-butyl diazo acetate gives lowest enantioselectivity (89% ee). The electron-withdrawing phenyl diazo acetate leads to lower induction (91% ee) as well.

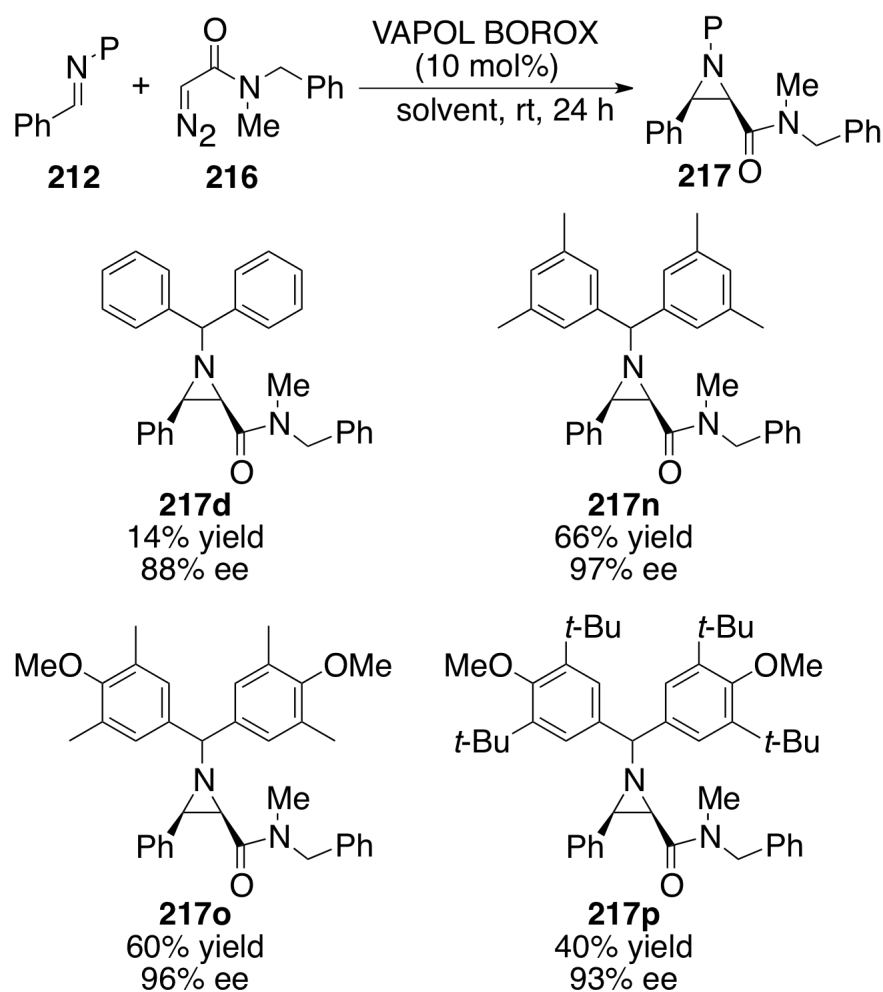
Table 4.1 Aziridination reaction of different diazo acetates^a

				
entry	R	series of 214	% yield AZ ^b	% ee AZ ^c
1	Me	a	90	91
2	Et	b	84	93
3	<i>i</i> -Pr	c	86	92
4	<i>t</i> -Bu	d	95	89
5	Ph	e	88	91

^a Unless otherwise specified, all reactions was carried out at 0.5 M in imine in CCl₄ with 10 mol% catalyst loading. The catalyst were prepared from 1 equiv VAPOL, 3 equiv B(OPh)₃ at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. ^b Isolated yield after silica gel chromatography. ^c Determined from chiral HPLC on a Chiralcel OD-H column.

The reaction of imines and the 3° diazoacetamide **216** give *cis*-aziridines (Scheme 4.5).^{26j} The nature of the *N*-substituent on the imine influences the yield and induction. The yields vary from 14-66% and the inductions vary from 88-97%.

Scheme 4.5 Aziridination reaction of 3° diazoacetamide



When switching to 2° diazoacetamide, the reaction gives *trans*-aziridines.²⁷ Dr.Vetticatt performed a computational study on those observations. It is suggested that for *cis*-aziridine

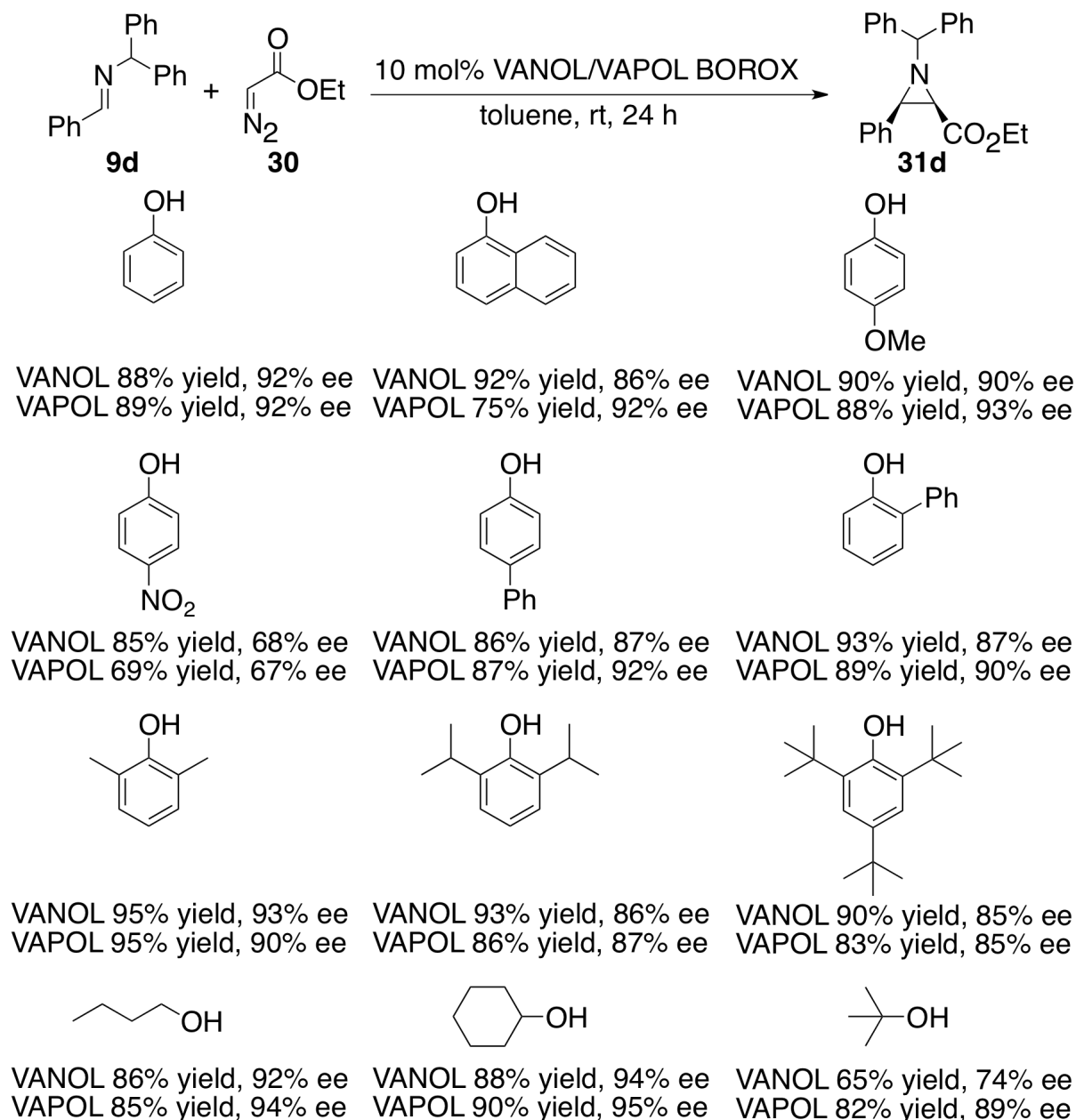
formation, the protonated imine is H bonding to O-1 of the boroxinate core and the diazoactate or 3° acetamide H bonds to O-2; while for *trans*-aziridine formation, the protonated imine is H bonded to O-3 of the boroxinate core and the 2° acetamide is H bonded to O-1 and O-2.

4.2.3 Effect of phenols

Our catalyst could also be prepared by self-assembly from the ligand, $\text{BH}_3 \cdot \text{SMe}_2$, a phenol, H_2O and the imine. As discussed above, a CH- π interaction between the phenoxy group of the boroxinate ring and the phenyl rings of the benzhydryl group of the imine is observed in both the crystal structures (Scheme 4.1 and 4.2). Therefore, an investigation of the electronic and steric effects of this phenoxy group on asymmetric inductions in the aziridination reactions and thus on the interactions between the catalysts and the phenyl imine **9d** was carried out by Dr. Lu and Dr. Osminski.^{64,86} Phenol with *para*-electron-withdrawing group (OMe) gives lower enantioselectivity, while phenol with *para*-electron-donating group (NO_2) gives comparable enantioselectivity to phenol itself (Scheme 4.6). A diminished CH- π interaction between the phenoxy ring of the boroxinate (face) and the phenyl ring of the benzhydryl group (edge) would be consistent with the low induction observed for EWG on the phenol. Steric hindrance in the *ortho* position has a small negative effect on the asymmetric induction. Increased steric bulk on the *para*-position of the phenol has almost no effect on the asymmetric induction, and this is not surprising as this position is quite far away from the sites of interaction in the catalyst-imine complex. Aliphatic alcohols can also be incorporated into the boroxinate to give an effective

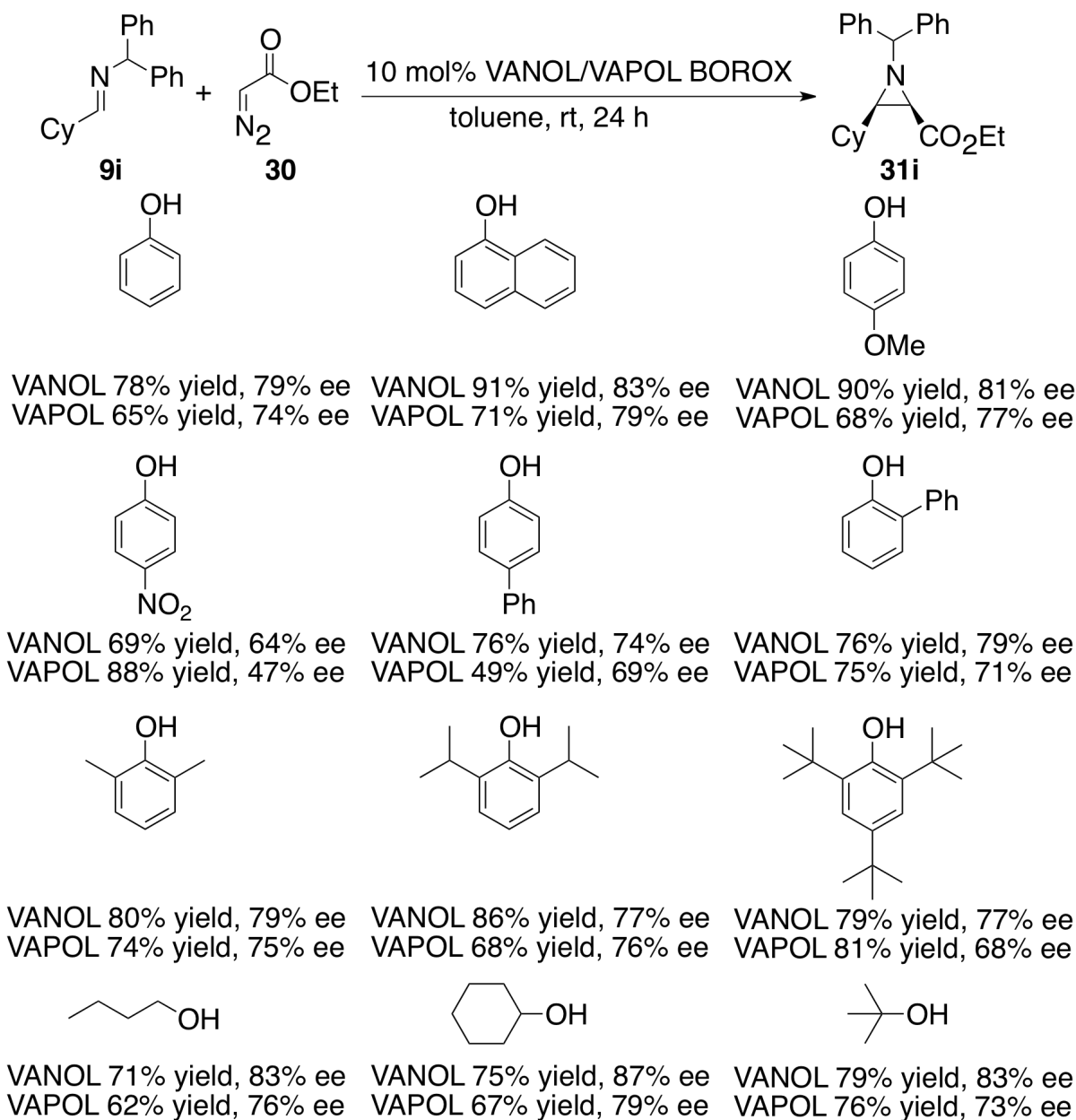
catalyst for the aziridination reaction, indicating that a CH- π interaction between the phenoxy ring of the boroxinate (face) and the phenyl ring of the benzhydryl group (edge) is not necessary for BOROX catalyst to function. Cyclohexanol turns out to be the optimal alcohol. The cyclohexyl imine **9i** was catalysts prepared from the same set of phenols and alcohols and similar trends were observed (Scheme 4.7). Interestingly, cyclohexanol turns out to be the optimal alcohol for this imine as well.

Scheme 4.6 Effect of phenols on the aziridination of the phenyl imine **9d**^a



^a Unless otherwise specified, all reactions were run in toluene in 0.5 M of imine with 1.1 equiv EDA **30** and 10 mol% catalyst loading. The catalyst was prepared by heating 1 equiv ligand, 3 equiv $\text{BH}_3\cdot\text{SMe}_2$, 2 equiv phenol or alcohol, and 1 equiv H_2O in toluene at 100 °C for 1 h and then exposure to high vacuum (0.5 mm Hg) for 0.5 h at 100 °C.

Scheme 4.7 Effect of phenols on the aziridination of the phenyl imine **9i**^a

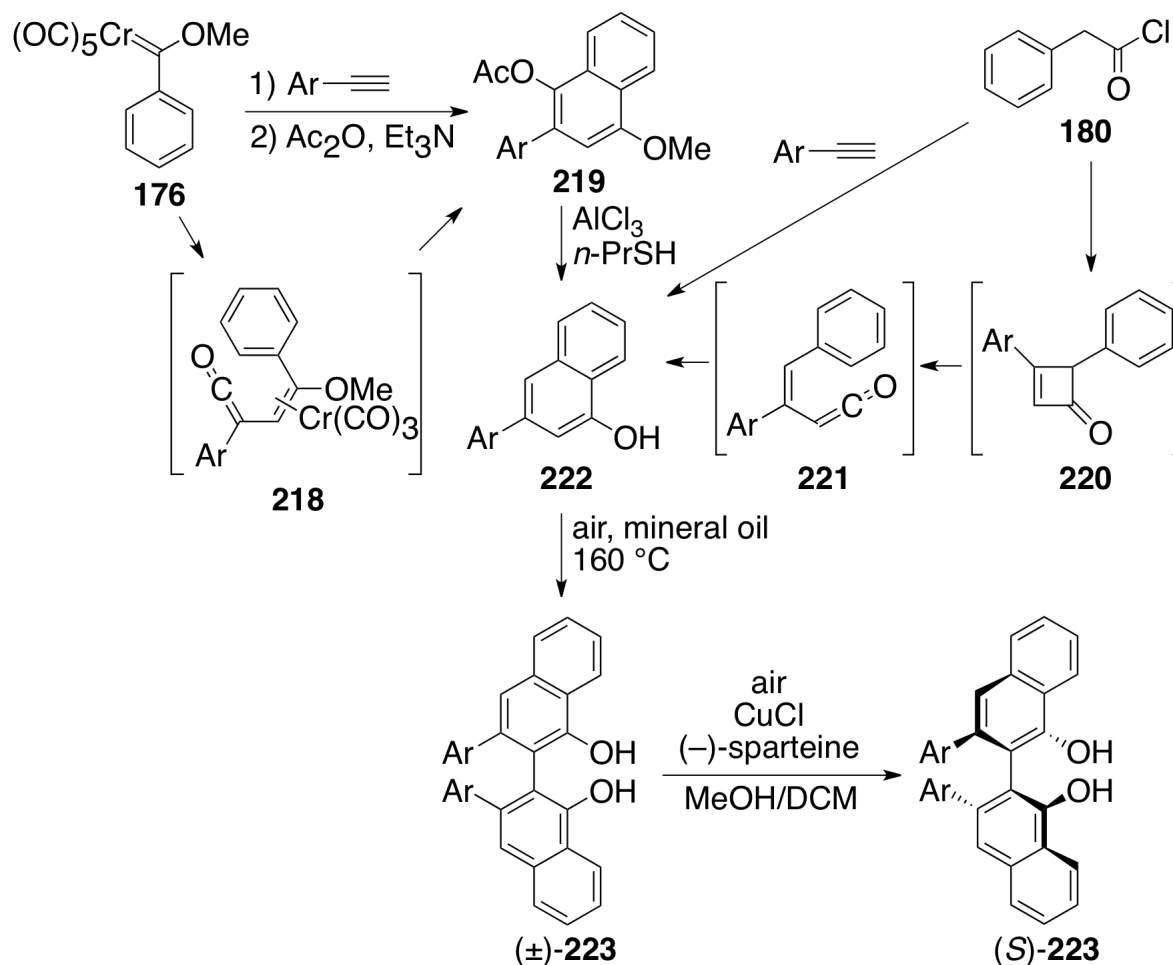


^a Unless otherwise specified, all reactions were run in toluene in 0.5 M of imine with 1.1 equiv EDA **30** and 10 mol% catalyst loading. The catalyst was prepared by heating 1 equiv ligand, 3 equiv $\text{BH}_3\cdot\text{SMe}_2$, 2 equiv phenol or alcohol, and 1 equiv H_2O in toluene at 100 °C for 1 h and then exposure to high vacuum (0.5 mm Hg) for 0.5 h at 100 °C.

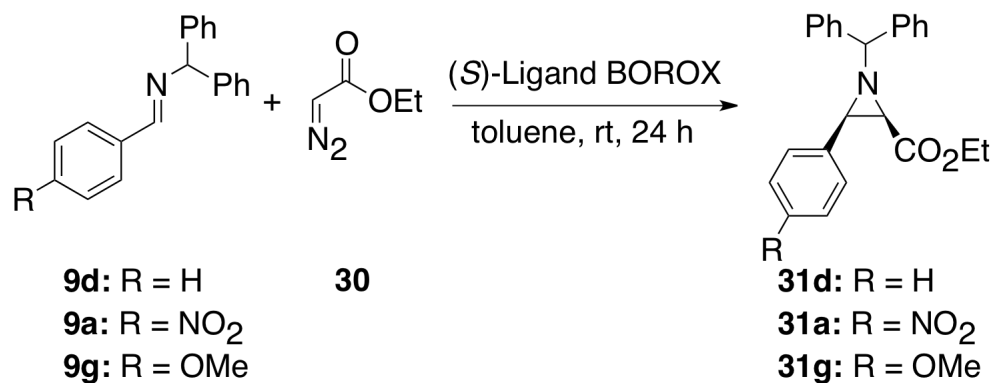
4.2.4 Effect of C3 aryl group

The first crystal structure (Scheme 4.1) reveals a possible CH- π interaction between the C3 phenyl group of the VAPOL ligand and the *ortho* hydrogen of the MEDAM group of the imine (4.42 Å). While in the second crystal structure (Scheme 4.2), there is a π - π stacking interaction between the phenyl group of the iminium cation and the 3,5-dimethyl-4-methoxyphenyl substituent of the C3 aryl group of the ligand (3.91 Å). Dr. Lu started an investigation on the dependence of various substituents in the C3 aryl group on VANOL with the asymmetric inductions in the aziridination reaction.⁶⁴ Her investigation focused on changing both the electronic and steric properties of the C3 phenyl group on VANOL with the hope that changes in the asymmetric induction might shed some light on the catalyst-substrate interactions.

Scheme 4.8 Synthetic routes of C3-aryl VANOL derivatives **223**



The monomer **222** could be synthesized either via the benzannulation pathway (I) or the ketene insertion pathway (II) (Scheme 4.8). The thermal coupling of the monomer **222** in the presence of air gives the racemic ligand **223**, which can be converted into (*S*)-**223** via a Cu(II)-(-)-sparteine complex mediated deracemization procedure.

Table 4.2 Aziridination reaction catalyzed by ligand BOROX catalyst^a

entry	mol% cat	imine	Ar	ligand	% yield ^b	% ee ^c
1	10	9d	C ₆ H ₅	VANOL	87	93
2	10	9d	4-BrC ₆ H ₄	223g	92	91
3	10	9d	4-PhC ₆ H ₄	223h	92	89
4	10	9d	3,5-Me ₂ C ₆ H ₃	223c	91	94
5	10	9d	3,5-Me ₂ -4-MeOC ₆ H ₂	223e	84	96
6	10	9d	4-EtOC ₆ H ₄	223o	81	94
7	5	9a	C ₆ H ₅	VANOL	86	89
8	5	9a	4-BrC ₆ H ₄	223g	86	89
9	5	9a	3,5-Me ₂ C ₆ H ₃	223c	85	88
10	5	9g	C ₆ H ₅	VANOL	61	87
11	5	9g	4-BrC ₆ H ₄	223g	68	85
12	5	9g	3,5-Me ₂ C ₆ H ₃	223c	54	92
13	5	9g	3,5-Me ₂ -4-MeOC ₆ H ₂	223e	62	96
14	5	9g	4-EtOC ₆ H ₄	223o	58	88

Table 4.2 (cont'd)

^a Unless otherwise specified, all reactions were carried out at 0.5 M in imine in toluene at 25 °C for 24 h with 1.1 equiv EDA **13**. The catalyst was generated from 1 equiv ligand, 4 equiv B(OPh)₃, and 1 equiv H₂O at 85 °C for 1 h, then 0.5 mm Hg vacuum was applied at 85 °C for 0.5 h. ^b Isolated yield after silica gel chromatography. ^c Determined from HPLC on a Chiralcel OD-H column.

Five chiral VANOL derivatives were prepared by Dr. Lu and examined for an evaluation of the interactions of C3 phenyl group (Table 4.2). The phenyl imine **9d** was used as the standard imine in the aziridination reactions. To span a broader range of catalyst-substrate interactions, the *para*-nitrophenyl imine **9a** and the *para*-methoxyphenyl imine **9g** were also examined with some ligands. There was a small but measurable variation in the asymmetric inductions (89-96% ee) and the lowest enantioselectivities were observed with imine **9d** (Table 4.2, entry 2 and entry 3) for the ligands with the most electron withdrawing groups on C3 phenyl group, which might be due to the weakened CH- π interaction in the complex I (Scheme 4.1) or π - π interaction in the complex II (Scheme 4.2). Ligands **223c** and **223e** enhance the enantioselectivity to a significant degree giving the highest asymmetric inductions for both imines **9d** and **9g**. This may be the result of enhanced CH- π interactions.

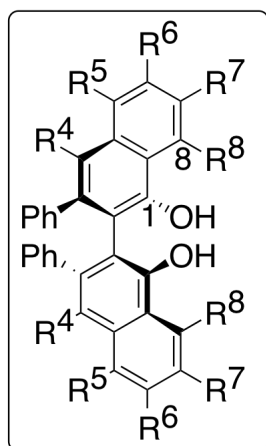
Dr. Lu obtained the 4,4'-di-nitro-VANOL **169** from Dr. Hu and it gave racemic aziridine **31d** but in comparable yield (73%).

4.3 Results and discussion

4.3.1 Effect of substitution on the naphthalene core

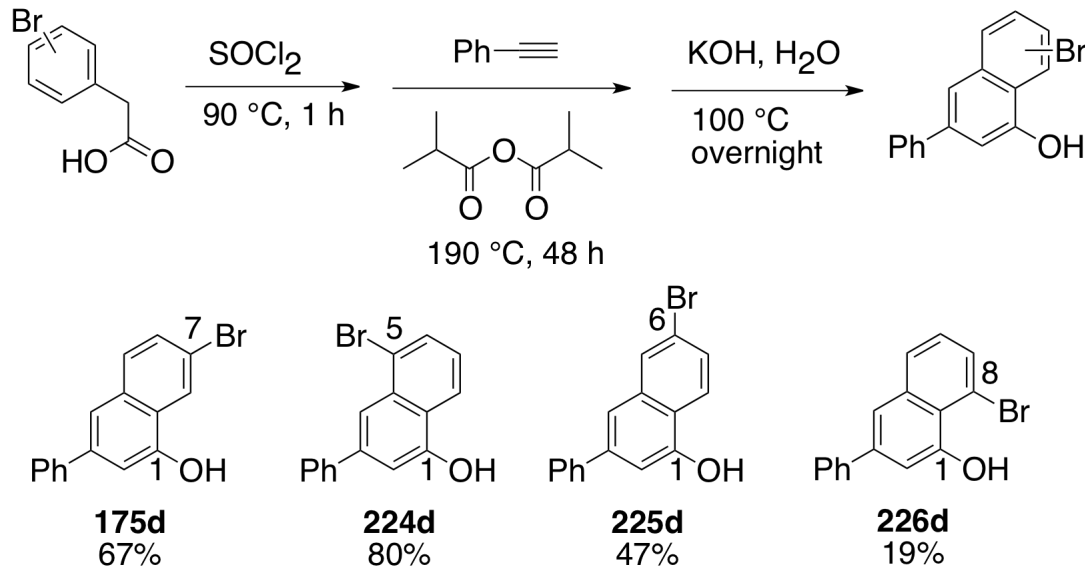
In Chapter 3, an intensive study that evaluated various groups in the 7,7'-positions of VANOL in BOROX catalyst for the aziridination reaction was compiled. Given the strength of the effect that substituents in this position had, it would be of interest to evaluate the effects that substituents in all the positions of the naphthalene ring have on the aziridination reaction (Scheme 4.9).

Scheme 4.9 Substituents on naphthalene core



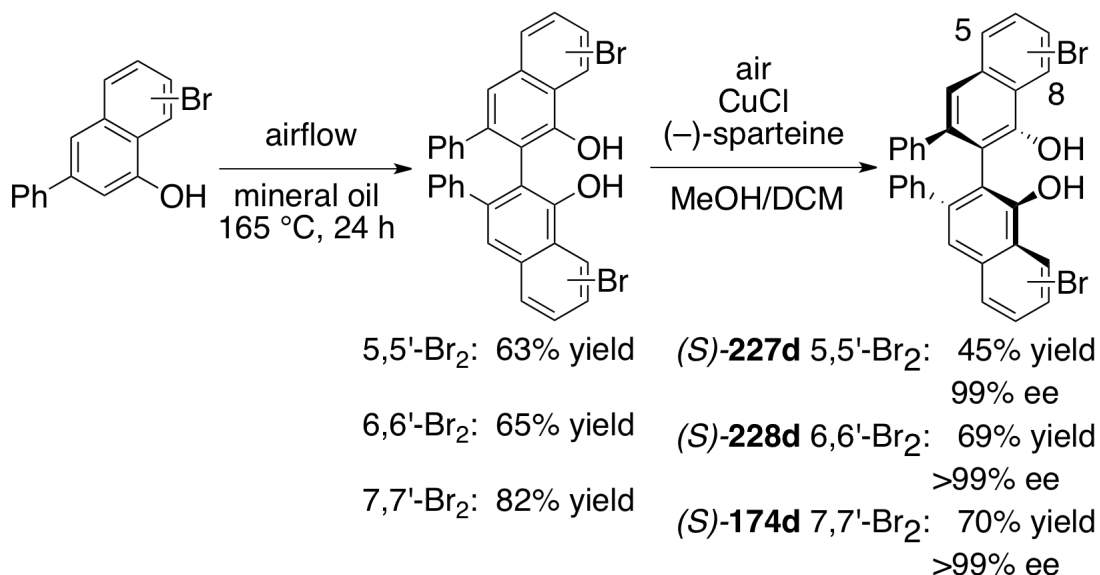
The reactions of 2-, 3- and 4-bromo phenylacetic acids with phenylacetylene were carried out under the optimal conditions for the CAEC cascade (Scheme 4.10). 4-bromo phenylacetic acid gives 7-bromo-3-phenyl-1-naphthol **175d** in 67% yield and 2-bromo phenylacetic acid yields 5-bromo monomer **224d** in 80% yield while 3-bromo phenylacetic acid affords the two regioisomers, 6-bromo-3-phenyl-1-naphthol **225d** (47%) and 8-bromo monomer **226d** (19%).

Scheme 4.10 CAEC cascade reactions of 2-, 3- and 4-bromo phenylacetic acids



The thermal coupling of the those monomers **175d**, **224d** and **225d** in the presence of air, followed by a Cu(II) -(-)-sparteine complex mediated deracemization procedure, generated the optically pure dibromo ligands with $\geq 99\%$ ee (Scheme 4.11).

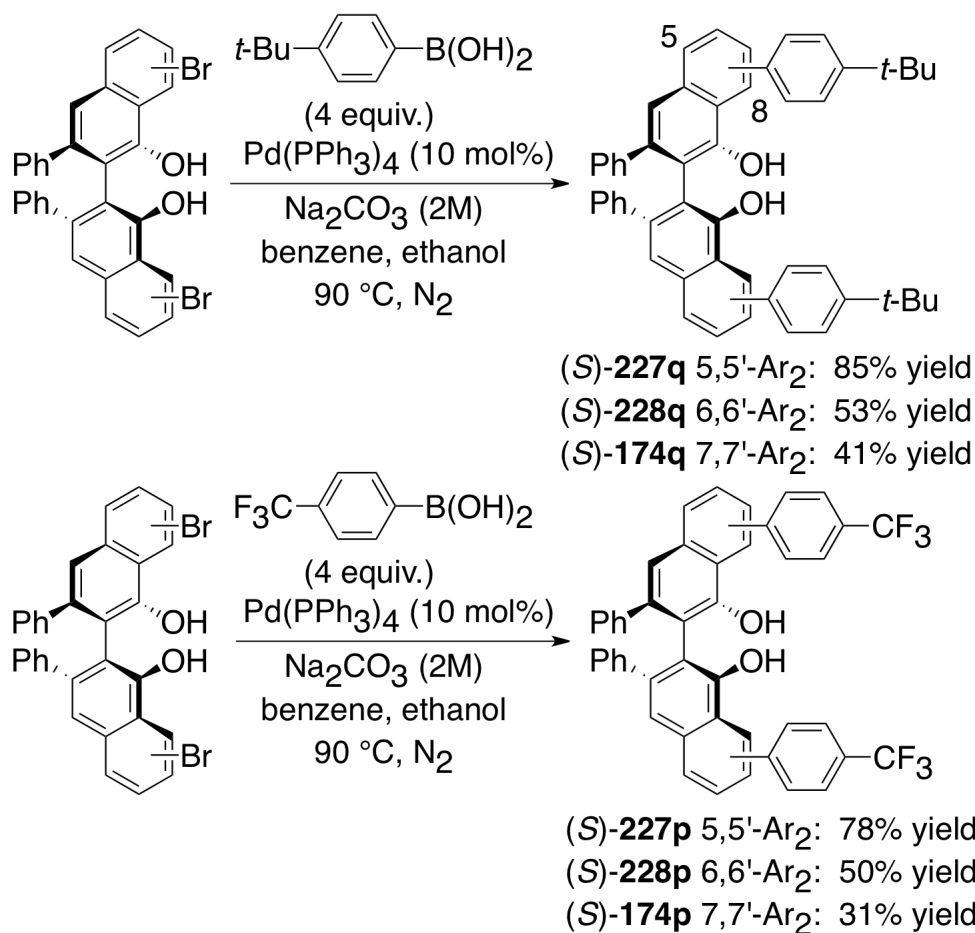
Scheme 4.11 Synthesis of dibromo VANOL ligands



The above three dibromo ligands were each converted to two sets of diaryl ligands via Suzuki coupling with 4-*tert*-butylphenylboronic acid and 4-(trifluoromethyl)phenylboronic acid,

respectively (Scheme 4.12). These set of substituents were chosen since the 4-*tert*-butylphenyl was among the best and 4-trifluoromethylphenyl was one the worst substituents for the aziridination reaction (Chapter 2).

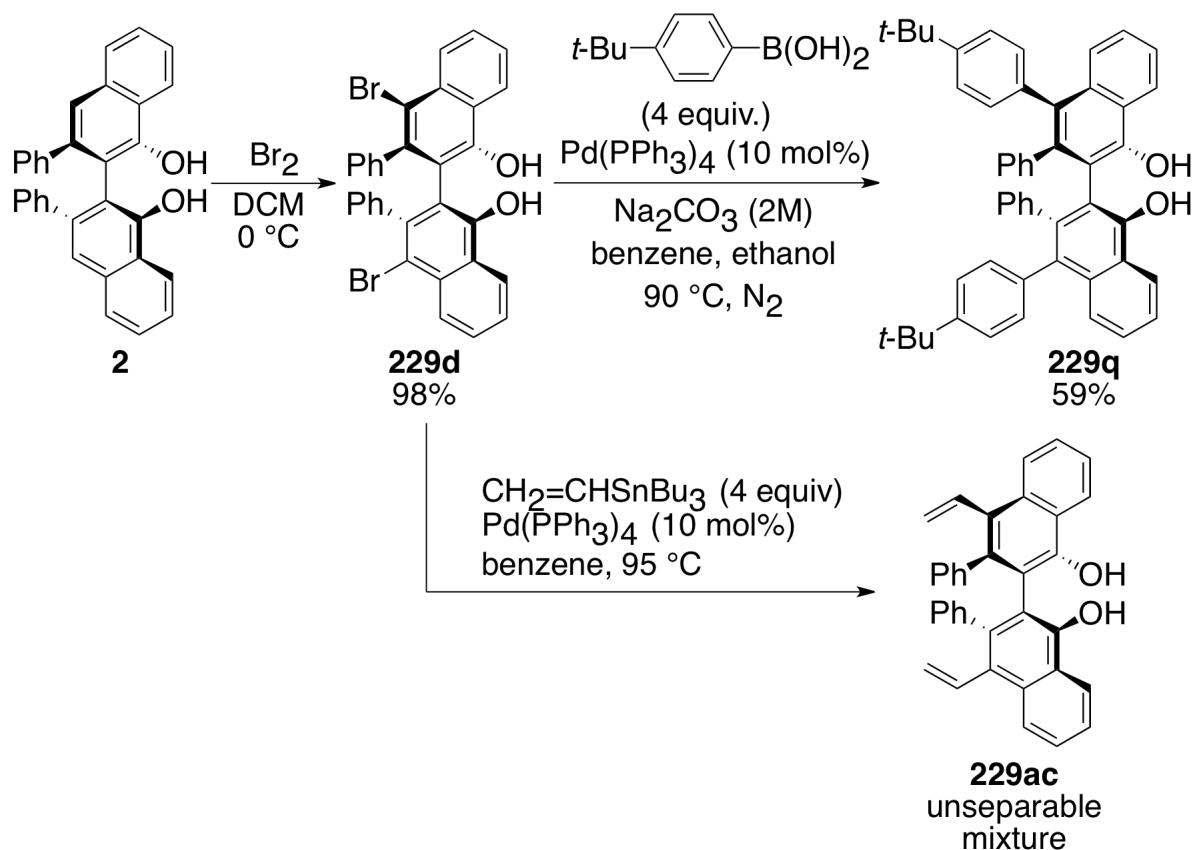
Scheme 4.12 Synthesis of diaryl VANOL ligands



Access to the 4,4'-disubstituted VANOL derivatives was achieved by direct bromination of optically pure VANOL with bromine which gave 4,4'-dibromo VANOL in a quite high yield (98%) (Scheme 4.13).⁸⁷ Suzuki coupling of 4,4'-dibromo VANOL **229d** with 4-*tert*-butylphenylboronic acid gave the 4,4'-diaryl VANOL **229q** in 59% yield. Since the azidation reaction with **229q** gave racemic products, 4-trifluoromethylphenyl was not

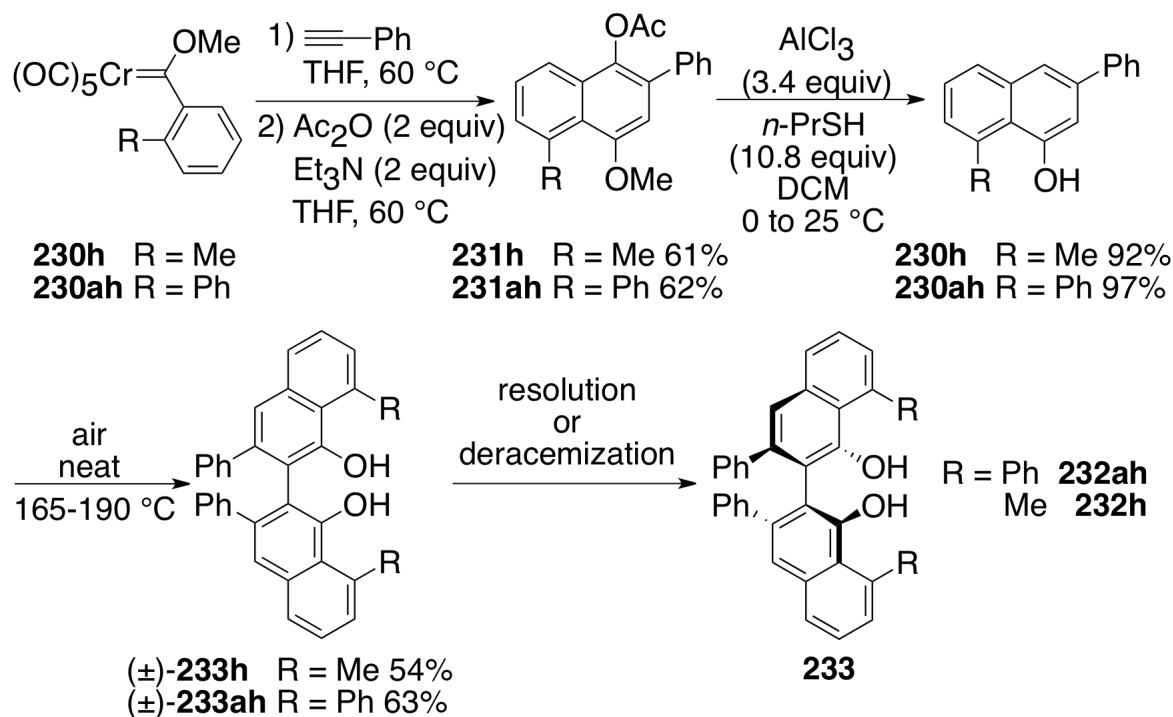
introduced. The Stille coupling with tributylstannylethylene gave an unseparable mixture of compounds that was not further characterized.

Scheme 4.13 Synthesis of 4,4'-disubstituted VANOL ligands



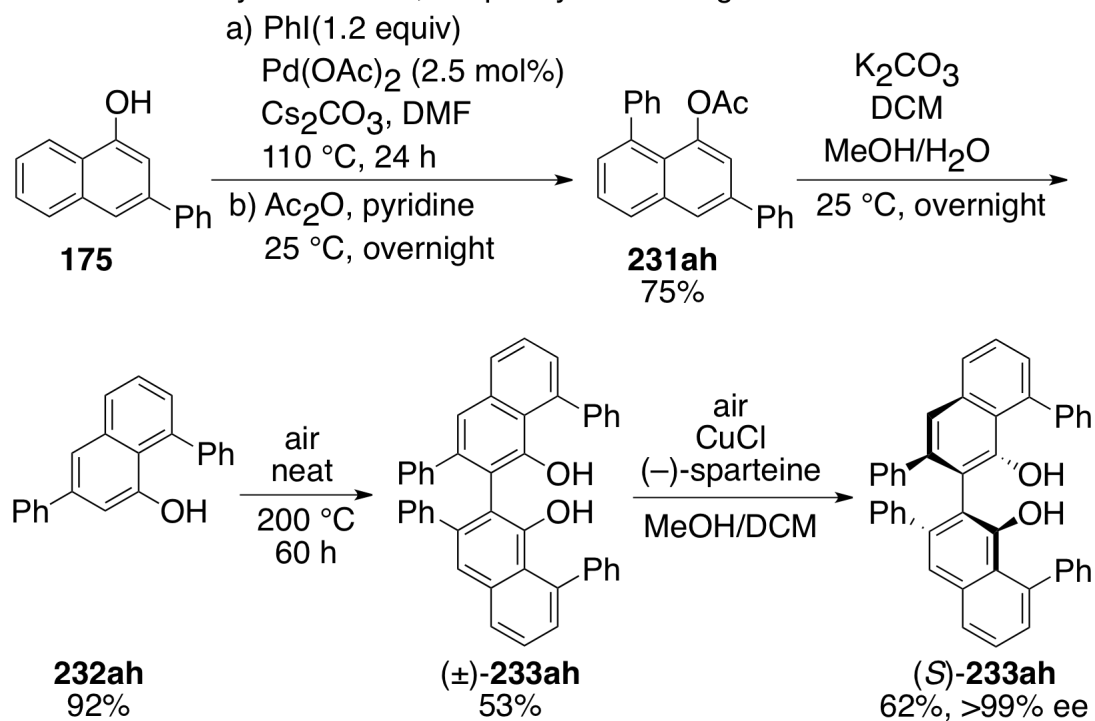
Gang Hu prepared the 8,8'-dimethyl and 8,8'-phenyl VANOL via the benzannulation pathway (Scheme 4.14).^{13d} Benzannulation reactions of the Fischer carbene complexes **230** with phenylacetylene, followed by deprotection gave the desired monomer **232**. Resolution or deracemization of the oxidative coupling intermediates from the monomer afforded the optically pure ligands **233**.

Scheme 4.14 Synthesis of 8,8'-disubstituted VANOL ligands



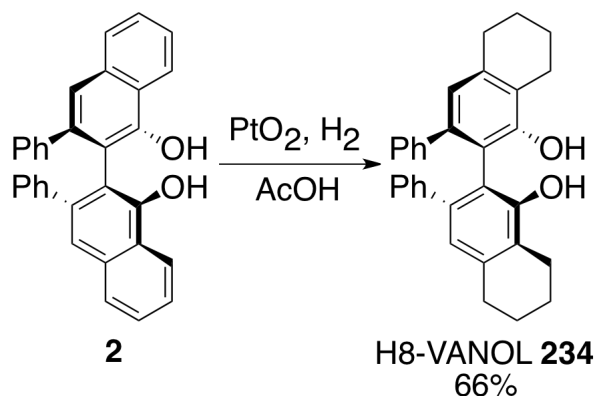
Aman Desai also synthesized 8,8'-phenyl VANOL **232ah** by another route (Scheme 4.15). The major difference is that the monomer was prepared via a phenoxy-directed palladium-mediated C–H activation/coupling protocol from the simple VANOL monomer.^{13e}

Scheme 4.15 Synthesis of 8,8'-diphenyl VANOL ligands



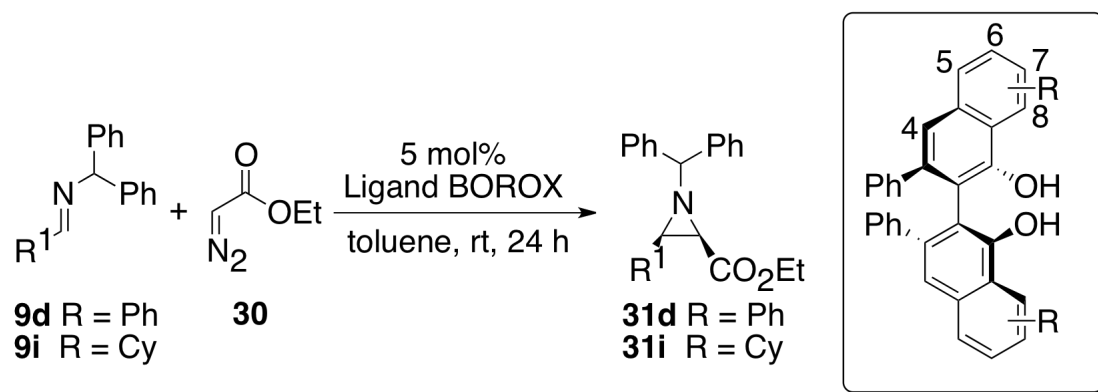
In addition to introducing different groups in various positions of the naphthalene rings of VANOL, It was also of interest to examine H8-VANOL **234** given the proposed important π - π stacking interaction in Complex I (Scheme 4.1). After trials with various reduction conditions, H8-VANOL was successfully prepared via the hydrogenation catalyzed by Adams' catalyst (Scheme 4.16).⁸⁸

Scheme 4.16 Synthesis of H8-VANOL



With the naphthalene skeleton modified VANOL derivatives in hand, phenyl and cyclohexyl imines were treated with boroxinate catalysts derived from these new ligands (Table 4.3).

Table 4.3 Ligand screen in the aziridination of benzhydryl imines^a



entry	Ligand	position of R	R	31d R ¹ =Ph		31i R ¹ =Cy	
				% yield ^b	% ee ^c	% yield ^b	% ee ^c
1	VANOL			84	92	77	81
2	232ah	8,8'	Ph	62	8	26	15
3	232h	8,8'	Me	83	80	72	77
4	174d	7,7'	Br	89	89	78	85
5	174q	7,7'	4- <i>t</i> -BuC ₆ H ₄	85	97	83	93
6	174p	7,7'	4-CF ₃ C ₆ H ₄	92	84	93	78
7	228d	6,6'	Br	83	90	76	79
8	228q	6,6'	4- <i>t</i> -BuC ₆ H ₄	82	89	77	82
9	228p	6,6'	4-CF ₃ C ₆ H ₄	92	87	86	78
10	227d	5,5'	Br	87	92	80	83

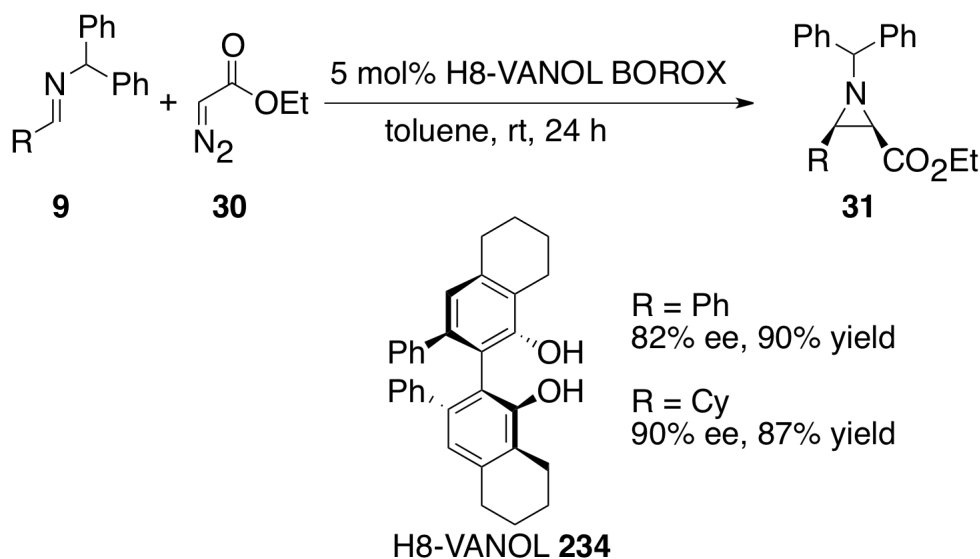
Table 4.3 (cont'd)

11	227q	5,5'	4- <i>t</i> -BuC ₆ H ₄	87	84	79	74
12	227p	5,5'	4-CF ₃ C ₆ H ₄	92	78	84	69
13	229d	4,4'	Br	86	45	81	45
14	229q	4,4'	4- <i>t</i> -BuC ₆ H ₄	75	3	68	1

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst.

The catalyst was prepared as indicated in Table 4.2. ^b yield of isolated *cis*-aziridine by chromatography on silica gel. ^c determined by HPLC on a Chiralcel OD-H column.

Scheme 4.17 Aziridination of benzhydryl imines catalyzed by the H8-VANOL BOROX catalyst



The 8,8'-positions are apparently be too close to the boroxinate core. Introducing methyl groups in the 8,8'-positions gave lower asymmetric induction than VANOL (Table 4.3, entry 3). The even bigger phenyl group led to much lower induction and the reaction was much slower (Table

4.3, entry 2). As the substituents are moved from the 7-, to the 6-, to the 5-position, the groups are moving away from the boroxinate core. Generally, for each position, 4-*t*-BuC₆H₄ is better than Br, followed by 4-CF₃C₆H₄ in terms of asymmetric induction. For each substituent, 7-position is superior to the 6-position, followed by the 5-position with respect to average asymmetric induction. However, each substituent behaves differently. The 4,4'-dibromo VANOL gave phenyl aziridine with 45% ee and cyclohexyl aziridine with 45% ee (Table 4.3, entry 13). Introducing the even bigger *para-tert*-butylphenyl group into the 4-position gave the phenyl aziridine **31d** with 3% ee and cyclohexyl aziridine **31i** with 1% ee (Table 4.3, entry 14). Those observed detrimental effects in the 4,4'-positions might be resulted from the change in the dihedral angle.

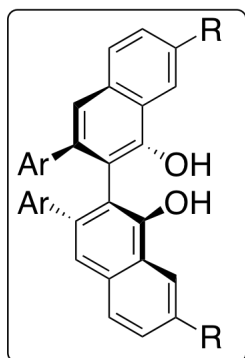
To our surprise, H8-VANOL afforded the phenyl aziridine **31d** with 82% ee and the cyclohexyl aziridine **31i** with 90% ee (Scheme 4.17). The diminished asymmetric induction for the phenyl aziridine might be due to the loss of the π - π stacking interaction. However, neither of the crystal structures in Schemes 4.1 & 4.2. could rationalize all the above observations. The interactions in the solid state might not be the same as those in the solution state or more likely in the transition states with ethyl diazo acetate. And also different imines might adopt different interactions in their individual transition states.

4.3.2 Effect of C3-aryl substituents

After illustrating the effect of perturbations in the substituents at various positions of the naphthalene skeleton on the aziridination reaction, the next set of ligands to be examined involve

varying the electronic and steric properties of the C3 phenyl group and looking for a relationship with the asymmetric induction of the aziridination reaction as well as to identify a superior ligand (Scheme 4.18).

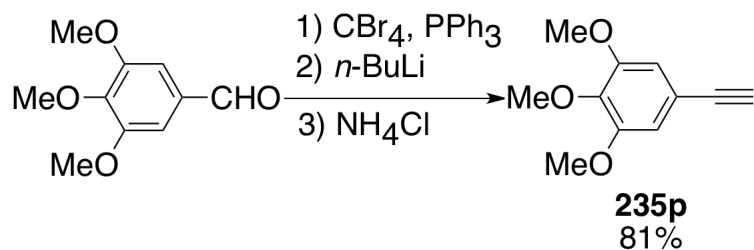
Scheme 4.18 Ligands for C3 aryl effect study



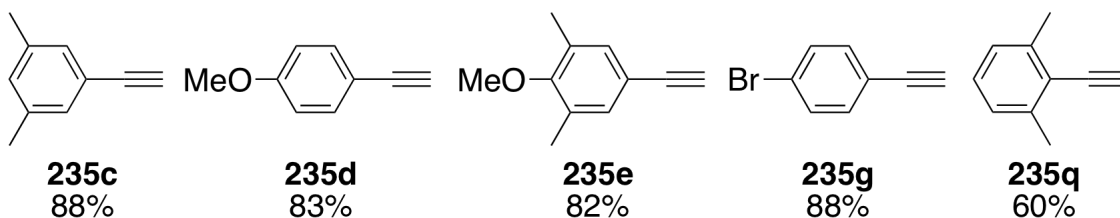
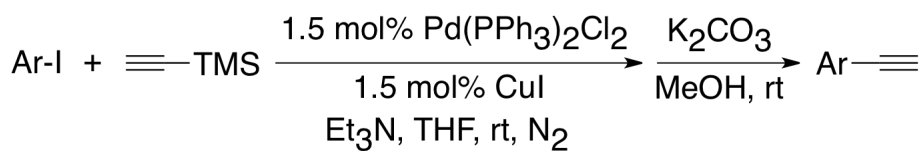
Several aryl alkynes were synthesized via two routes (Scheme 4.19). The first route involves the Corey-Fuchs reaction.⁸⁹ Treatment of the aldehyde with CBr_4 and PPh_3 leads to a dibromoalkene. Treatment with $n\text{-BuLi}$ generates a bromoalkyne intermediate via dehydrohalogenation, which undergoes metal-halogen exchange and yields the terminal alkyne upon acidic work-up. The second route takes advantage of the Sonogashira coupling reaction.⁹⁰⁻⁹³ The palladium and copper catalyzed coupling reactions of aryl iodides with trimethylsilylacetylene, followed by cleavage of the TMS group under basic conditions, gave the desired aryl acetylenes in good isolated yields.

Scheme 4.19 Synthesis of aryl alkynes

Route I

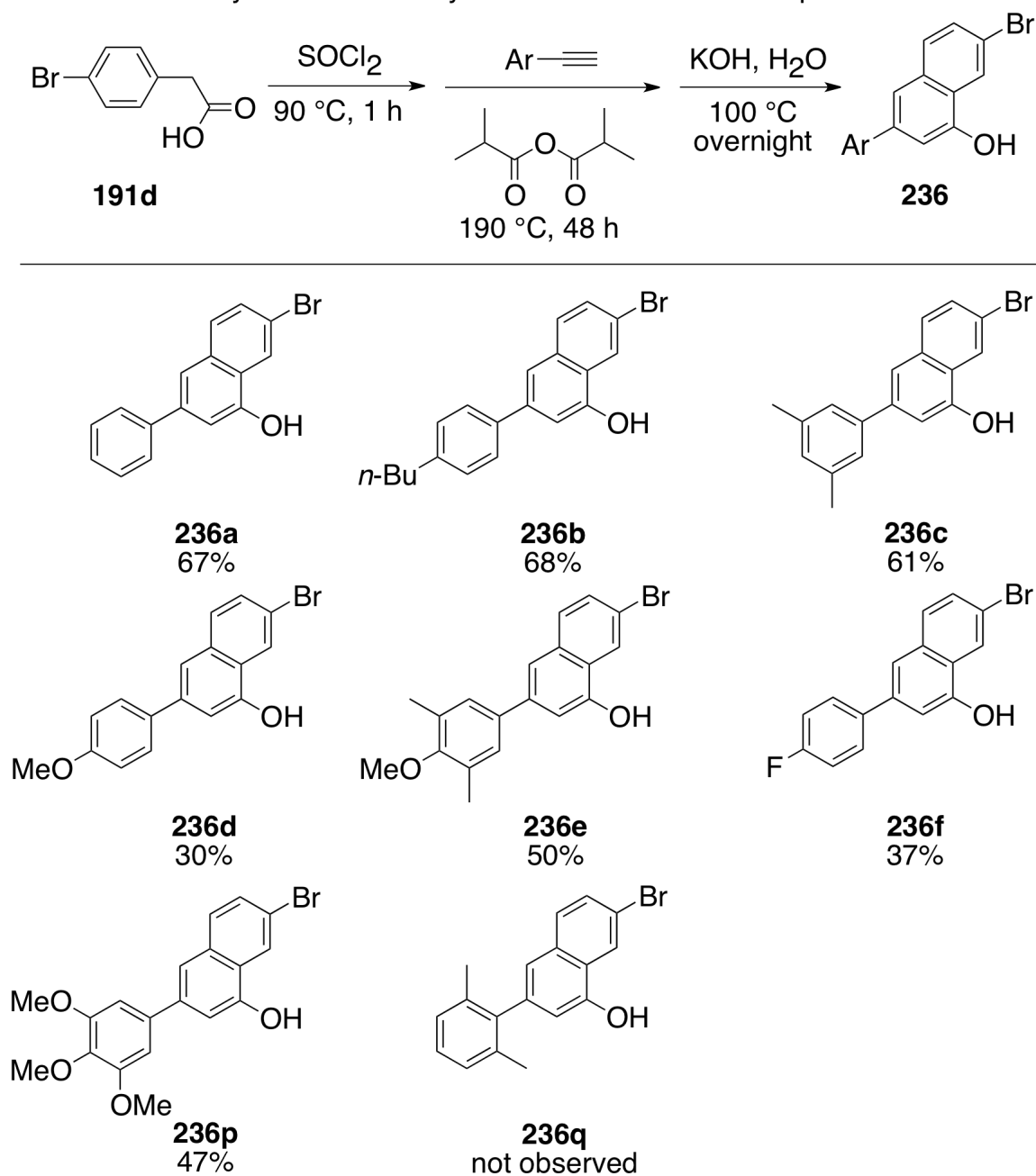


Route II



The CAEC cascade reactions with various aryl acetylenes with 4-bromo phenylacetic acid gave different C3 aryl 7-bromo-1-naphthols as desired monomeric intermediates (Scheme 4.20). The reaction with 1,3-dimethyl-2-ethynyl-benzene gave complicated mixture and no desired product was observed from ¹H NMR of the crude mixture.

Scheme 4.20 Synthesis of C3 aryl substituted 7-bromo-1-naphthols



Those monomers were then applied to the oxidative coupling reaction conditions. All of the monomers except the 3,4,5-(OMe)₃C₆H₂ substituted one gave dimmers that could be brought to purity. Gratefully, all the racemates underwent deracemization smoothly, affording the optically pure dibomo ligands with > 99% ee.

Table 4.4 Synthesis of 7,7'-dibromo VANOL ligands

Entry	Ar	% yield (±)- 237 ^a	% yield (S)- 237 ^a	% ee (S)- 237 ^b
1	Ph	82	70	>99
2	4- <i>n</i> -BuC ₆ H ₄	62	80	>99
3	3,5-Me ₂ C ₆ H ₃	65	75	>99
4	4-MeOC ₆ H ₄	42 ^c	69	>99
5	3,5-Me ₂ -4-MeOC ₆ H ₂	40	74	>99
6	4-FC ₆ H ₄	70	87	>99
7	3,4,5-(OMe) ₃ C ₆ H ₂	nd	-	-

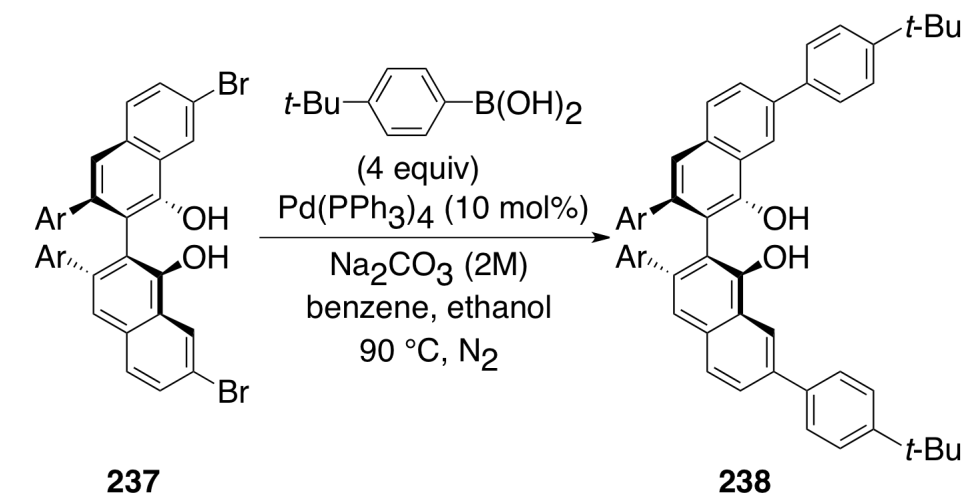
^a isolated yield by chromatography on silica gel. nd = not determined. ^b determined by HPLC. ^c

phenol coupling at 175 °C

Since a 4-*t*-BuC₆H₄ in 7,7'-positions of VANOL was the second best substituent other than *t*-Bu in terms of asymmetric induction of the aziridination reactions (Chapter 3), this group was installed in the 7,7'-positions of all the C3 aryl VANOL derivatives indicated in Table 4.4 was Suzuki coupling. The reactions of two substrates, 4-FC₆H₄ or 4-MeOC₆H₄ substituted ligands,

gave insoluble material and the yields were not determined. The other four ligands yielded the desired diaryl ligands successfully (Table 4.5).

Table 4.5 Synthesis of 7,7-diaryl VANOL ligands



Entry	Ar	% yield 238 ^a
1	Ph	41
2	4- <i>n</i> -BuC ₆ H ₄	50
3	3,5-Me ₂ C ₆ H ₃	48
4	4-MeOC ₆ H ₄	nd
5	3,5-Me ₂ -4-MeOC ₆ H ₂	26
6	4-FC ₆ H ₄	nd

^a isolated yield by chromatography on silica gel. nd = not determined.

Phenyl and anthracenyl group could also be introduced via a protection/Suzuki coupling/deprotection sequence (Table 4.6).

237b $\xrightarrow[\text{MeI, THF}]{\text{NaH}}$ **239b** (88%) $\xrightarrow[\text{Na}_2\text{CO}_3 \text{ (2M), DME, } 90^\circ\text{C, N}_2]{\text{R-B(OH)}_2 \text{ (4 equiv.), Pd(PPh}_3)_4 \text{ (10 mol\%)}}$ $\xrightarrow[\text{DCM}]{\text{BBr}_3}$ **240**

^a isolated yield by chromatography on silica gel.

Table 4.7 Synthesis of C3-aryl-1-naphthol

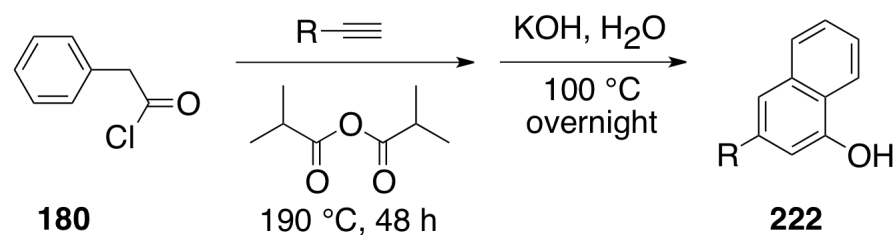
142

Table 4.7 (cont'd)

2	222d	4-MeOC ₆ H ₄	41
3	222e	3,5-Me ₂ -4-MeOC ₆ H ₂	56
4	222f	4-FC ₆ H ₄	53
5	222g	4-BrC ₆ H ₄	45
6	222s	2-C ₄ H ₃ S	37
7	222t	3-C ₄ H ₃ S	57

^a isolated yield by chromatography on silica gel.

To our delight, the oxidative coupling/deracemization sequence was applicable with all the monomers **222** obtained, even the C3 heteroaryl ones (Table 4.8). All the ligands were prepared with > 99% ee.

Table 4.8 Synthesis of C3-aryl VANOL derivatives

222		(±)-223		(S)-223	
entry	compound	R	% yield (±)- 223 ^a	% yield (S)- 223 ^a	% ee (S)- 223 ^b
1	223c	3,5-Me ₂ C ₆ H ₃	76	32	>99

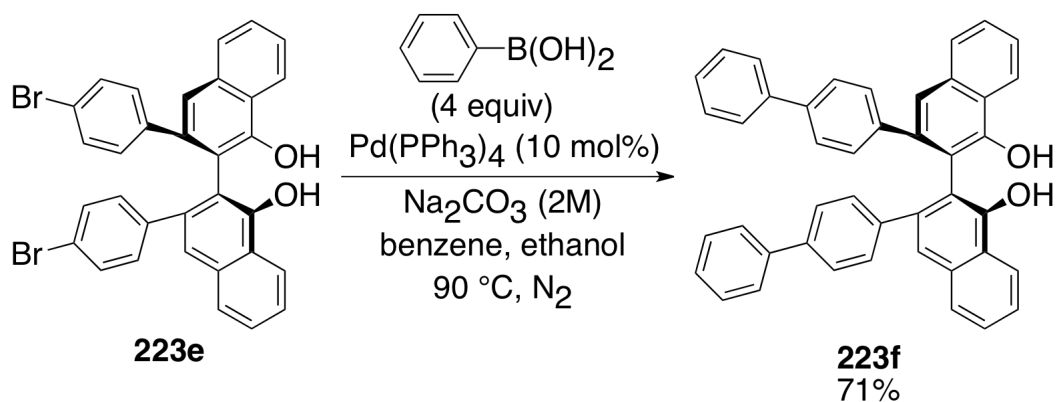
Table 4.8 (cont'd)

2	223d	4-MeOC ₆ H ₄	62	17	>99
3	223e	3,5-Me ₂ -4-MeOC ₆ H ₂	53	47	>99
4	223f	4-FC ₆ H ₄	79	64	>99
5	223g	4-BrC ₆ H ₄	59	74	>99
6	223s	2-C ₄ H ₃ S	45 ^c	73	>99 ^d
7	223t	3-C ₄ H ₃ S	59 ^c	40	>99 ^d

^a isolated yield by chromatography on silica gel. ^b determined by HPLC. ^c phenol coupling at 165 °C. ^d (*R*)-enantiomer obtained upon deracemization with (+)-sparteine.

The *para*-bromo substituted C3 phenyl VANOL derivatives **223e** was then used to prepare an additional C3 aryl VANOL derivative **223f** with a *para*-phenyl group via Suzuki coupling (Scheme 4.21).

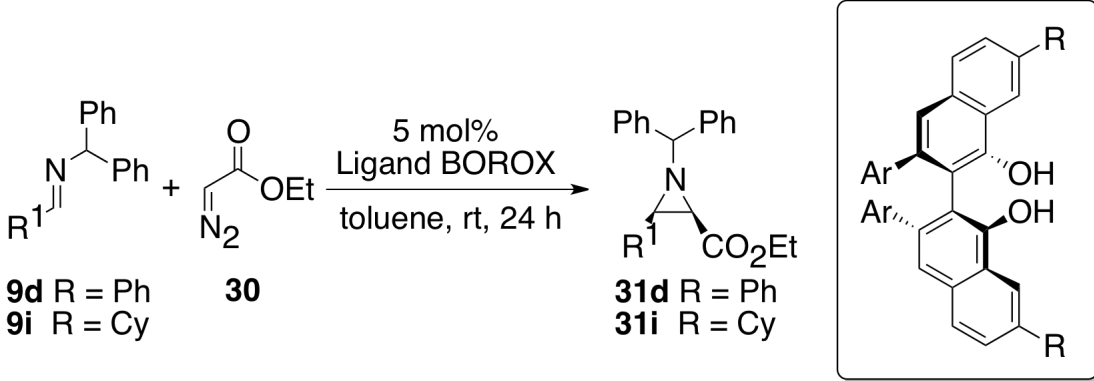
Scheme 4.21 Synthesis of C3-aryl VANOL ligand via Suzuki coupling



All of the C3 aryl modified VANOL ligands were then evaluated in the aziridination reactions of the phenyl and cyclohexyl imines.

The first subset examined was the 7,7'-dibromo ligands (Table 4.9, entries 1 to 6). Introduction of either an electron-withdrawing or an electron-donating substituent on the C3 phenyl group increases the asymmetric induction of the phenyl aziridine **31d**, which does not support the CH- π interaction in complex I (Scheme 4.1) nor the π - π interaction in complex II (Scheme 4.2). However, electron-withdrawing and electron-donating substituent have little effect on the asymmetric induction of the cyclohexyl aziridine **31i**.

Table 4.9 Ligand screen in the aziridination of benzhydryl imines: C3-aryl effect^a



entry	ligand	Ar	R	31d R ¹ =Ph 31i R ¹ =Cy			
				%		%	
				yield ^b	ee ^c	yield ^b	ee ^c
1	237a	Ph	Br	89	89	78	85
2	237b	4- <i>n</i> -BuC ₆ H ₄	Br	87	93	78	85
3	237c	3,5-Me ₂ C ₆ H ₃	Br	82	97	63	86
4	237d	4-MeOC ₆ H ₄	Br	82	95	75	85
5	237e	3,5-Me ₂ -4-MeOC ₆ H ₂	Br	81	98	74	87

Table 4.9 (cont'd)

6	237f	4-FC ₆ H ₄	Br	81	94	77	84
7	238a	Ph	4- <i>t</i> -BuC ₆ H ₄	85	97	83	93
8	238b	4- <i>n</i> -BuC ₆ H ₄	4- <i>t</i> -BuC ₆ H ₄	87	97	80	90
9	238c	3,5-Me ₂ C ₆ H ₃	4- <i>t</i> -BuC ₆ H ₄	87	98	83	93
10	238e	3,5-Me ₂ -4-MeOC ₆ H ₂	4- <i>t</i> -BuC ₆ H ₄	86	96	83	92
11	240ah	4- <i>n</i> -BuC ₆ H ₄	Ph	82	95	84	91
12	240x	4- <i>n</i> -BuC ₆ H ₄	9-anthracenyl	57	90	25 ^d	64
13	223c	Ph	H	84	92	77	81
14	223d	3,5-Me ₂ C ₆ H ₃	H	87	95	84	88
15	223e	4-MeOC ₆ H ₄	H	81	95	80	80
16	223f	3,5-Me ₂ -4-MeOC ₆ H ₂	H	85	96	79	87
17	223g	4-FC ₆ H ₄	H	82	94	84	78
18	223s	4-BrC ₆ H ₄	H	82	94	80	82
19	223t	4-PhC ₆ H ₄	H	82	95	82	82
20	223c	2-C ₄ H ₃ S	H	92	89	83	77
21	223d	3-C ₄ H ₃ S	H	91	89	83	79

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst.

The catalyst was prepared as indicated in Table 4.2. ^b yield of isolated *cis*-aziridine by

Table 4.9 (cont'd)

chromatography on silica gel. ^c determined by HPLC on a Chiralcel OD-H column. ^d the reaction time was 48 h.

The second subset evaluated was the 7,7'-diaryl ligands (Table 4.9, entries 7 to 12). Installation of either an electron-withdrawing or an electron-donating substituent on the C3 phenyl group has little effect on the asymmetric induction in the aziridination reactions of either the phenyl or the cyclohexyl imines. With the same C3 aryl, 4-*t*-BuC₆H₄ in the 7,7'-positions is better than phenyl, followed by 9-anthracenyl in terms of asymmetric induction (Table 4.9, entries 8,11 & 12).

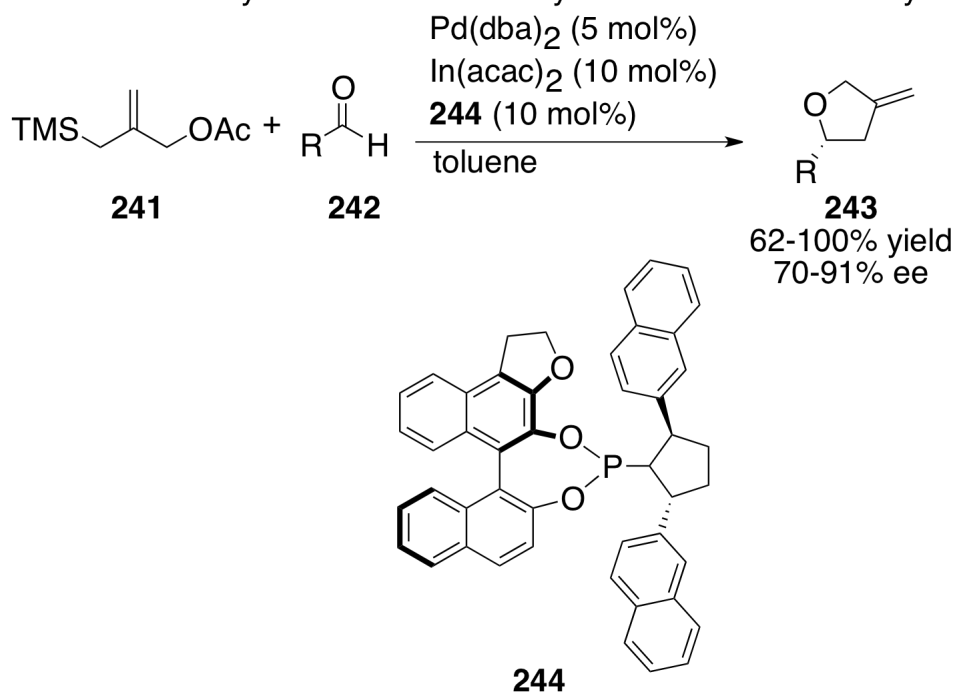
The third subset evaluated was the C3-aryl VANOL derivatives with no substituent in the 7,7'-positions (Table 4.9, entries 13 to 21). As for the phenyl imine, incorporation of either electron-withdrawing or electron-donating substituent on the C3 phenyl group increases the asymmetric induction. A 2- or 3-thienyl substituent leads to lower asymmetric induction, indicating that five-member aryl groups are worse than six-member aryl groups (Table 4.9, entries 20 & 21). Similar trends were observed in the aziridination reactions of the cyclohexyl imine.

4.3.3 *C1*-symmetric VANOL derivatives

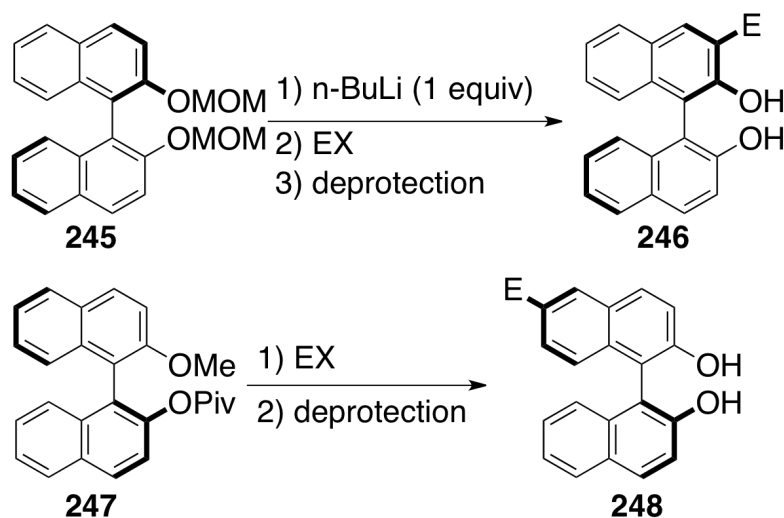
C1-symmetric BINOLs have also proven to be efficient chiral ligands in a variety of reactions and these are summarized in several reviews.^{11a,94} A recent example that is not included in the reviews is the palladium catalyzed [3+2] cycloaddition of trimethylenemethane (TMM) and aldehydes reported by Trost and coworkers.⁹⁵ A novel phosphoramidite **244** derived from *C1*-symmetric BINOL outperformed those derived from *C2*-symmetric BINOLs.

recycled easily for multiple uses.^{11a,94}

Scheme 4.22 Cycloaddition of trimethylenemethane and aldehydes



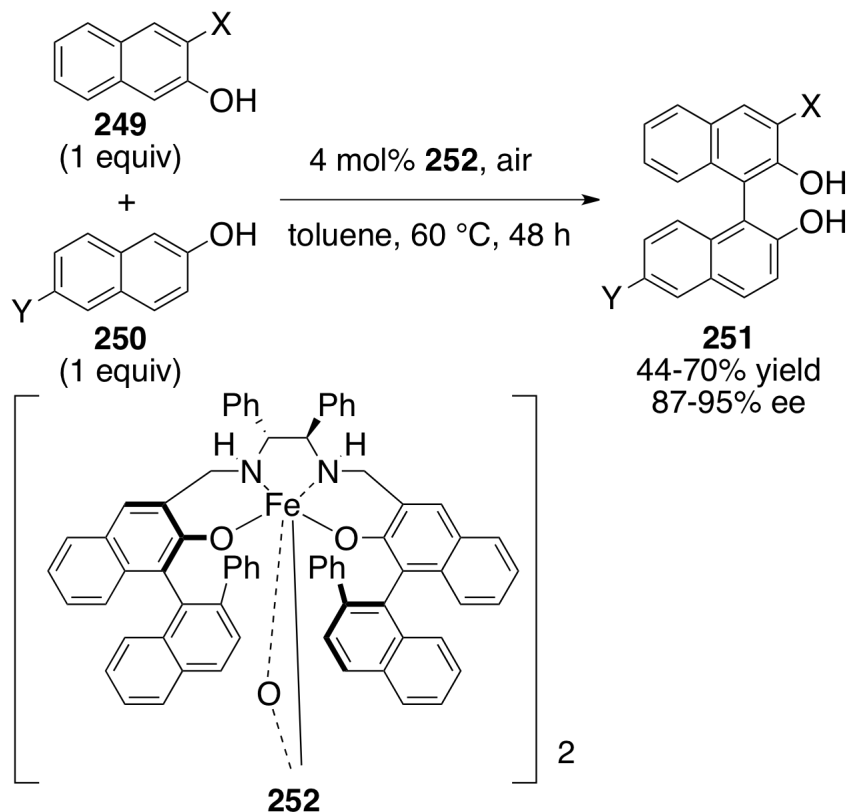
Scheme 4.23 Synthesis of *C*₁-symmetric BINOLs via direct modification of BINOL



The difficulties in the synthesis of *C1*-symmetric BINOLs hamper the study of their potential as useful chiral auxiliaries.

One synthetic route is the direct modification of optically pure BINOL (Scheme 4.23). Directed *ortho* lithiation and subsequent electrophile quench yields 3-substituted BINOLs.⁹⁵ Electrophilic aromatic substitution at the 6-position leads to various 6-substituted BINOLs.⁹⁶ However, one major problem associated with these approaches is the generation of mixtures of both mono- and bis-substituted BINOLs along with unreacted starting material, which requires costly chromatographic separation that is often quite difficult.

Scheme 4.24 Synthesis of *C1*-symmetric BINOLs via asymmetric oxidative cross coupling

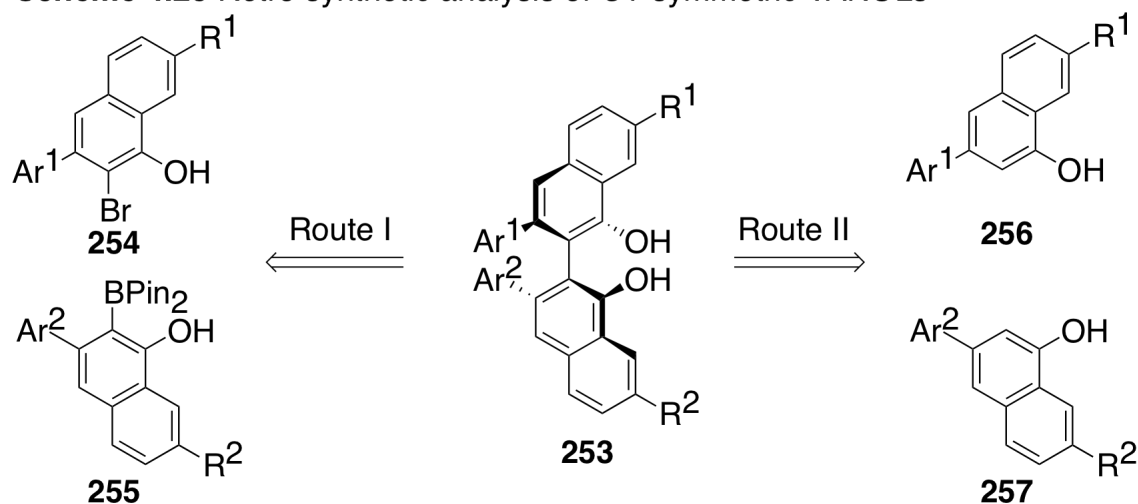


Another attractive route is the Fe(salen) complex catalyzed asymmetric oxidative cross coupling of 2-naphthols with good to excellent enantioselectivities (Scheme 4.24). However, the substrate

scope is narrow and the resulting *C1*-symmetric BINOLs typically will need enhancement of their enantiopurities.

Dr. Ding showed that mono lithiation and subsequent electrophilic quench led to 8-methyl and 8-bromo VANOLs.⁷³ However, there are no methods that will allow 7-mono substituted VANOL to be accessed from direct modification of VANOL.

Scheme 4.25 Retro synthetic analysis of *C1*-symmetric VANOLs

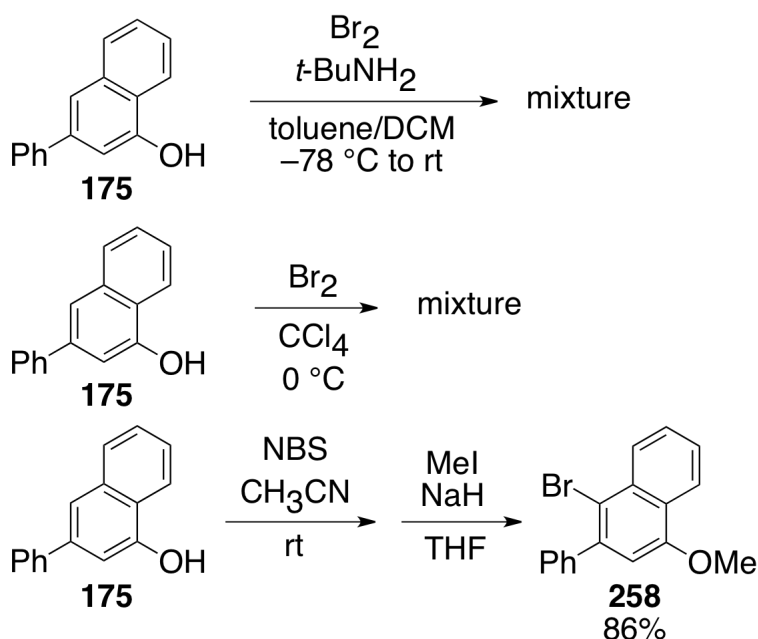


Retrosynthetic analysis discloses two possible routes to mono-substituted VANOL derivatives at the 7-position (Scheme 4.25). One route involves Suzuki cross coupling and the other one is via oxidative cross coupling of two different naphthols.

In order to pursue the first route, bromine needs to be installed at the 2-position of 3-phenyl-1-naphthol **175**. Various bromination conditions were tested and none of them gave required results (Scheme 4.26). Bromination with Br₂ and *t*-BuNH₂ gave a mixture based on the ¹H NMR of the crude reaction mixture. Bromination with Br₂ in CCl₄ also afforded a mixture from the ¹H NMR analysis of the crude reaction mixture. Bromination with NBS in acetonitrile

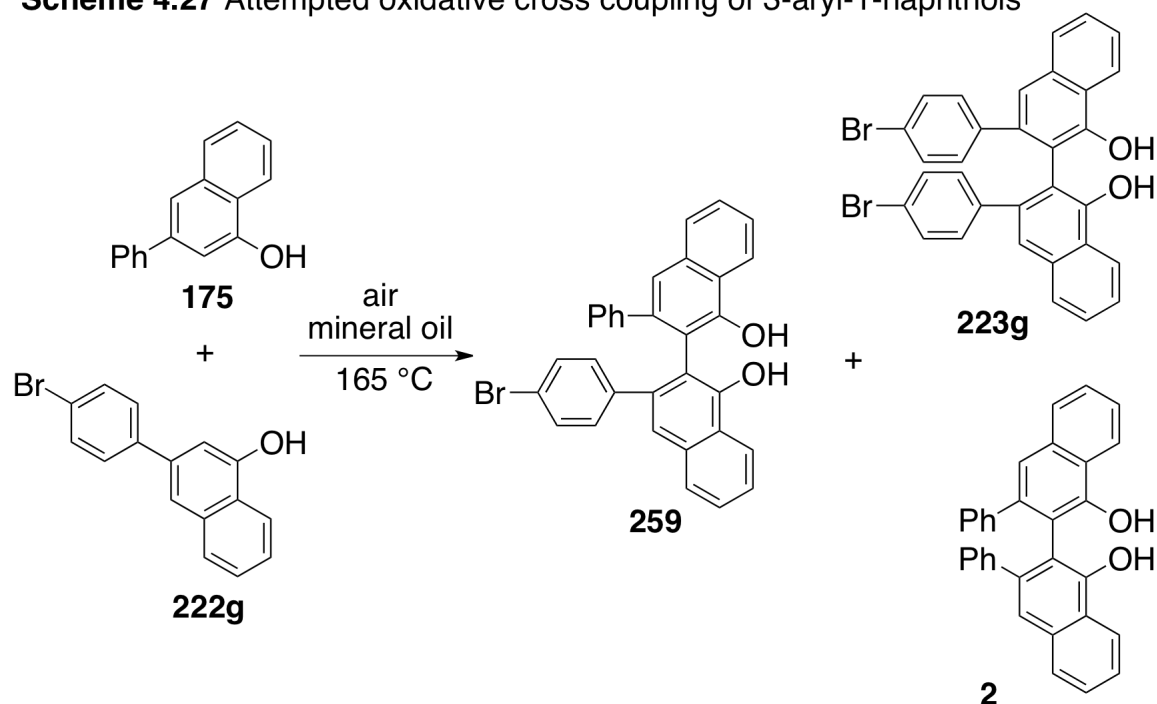
gave a clean reaction based on the ^1H NMR of the crude reaction mixture. The intermediate phenol was not stable for chromatography on silica gel. Therefore it was protected and then purified by column chromatography on silica gel. ^1H NMR analysis revealed that bromine was introduced at the *para*- not *ortho*- position. So far there is no ideal *ortho*-bromination procedure for 3-phenyl-1-naphthol **175**.

Scheme 4.26 Attempted bromination of 3-phenyl-1-naphthol



As for the second route involved a crossed phenol coupling of two different naphthols, Dr. Ding described some preliminary efforts. Exposure of a 2.8:1 mixture of **175** to **222g** to the oxidative coupling conditions led to complete consumption of the starting materials (Scheme 4.27). However, only a single spot was observed on the TLC plate which, however, was a mixture of at least three compounds. Attempts to separate this reaction mixture using crystallization, column chromatography on silica gel and preparative TLC all failed.

Scheme 4.27 Attempted oxidative cross coupling of 3-aryl-1-naphthols



After an extensive study, we found that one of the monomers should bear a MeO group in order to get separation of the products from the oxidative cross-coupling of two different naphthols. With this trick unveiled, several VANOL monomers were examined in the coupling and subsequent deracemization process (Table 4.10). Six *C1*-symmetric VANOL derivatives were obtained with >99% ee.

Table 4.10 Synthesis of *C1*-symmetric VANOL derivatives

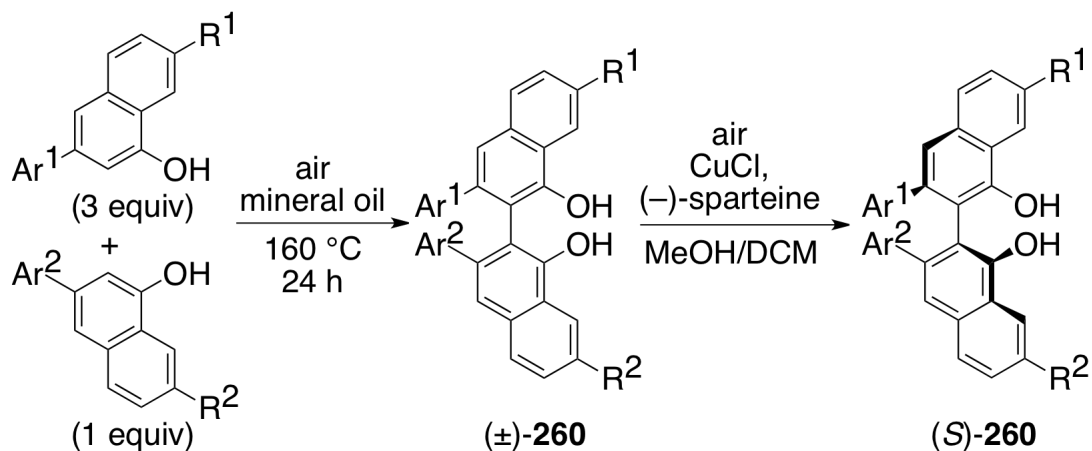


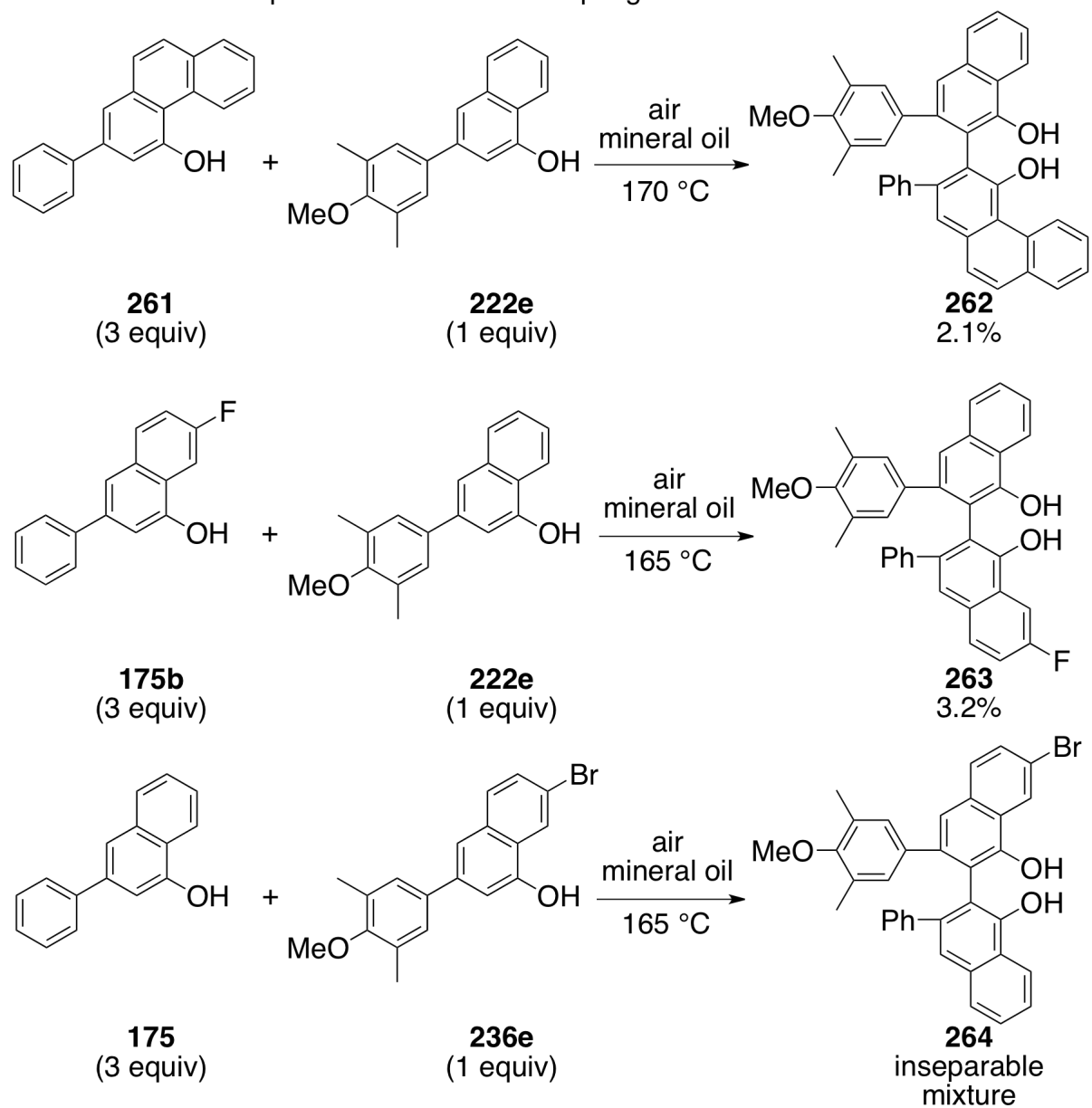
Table 4.10 (cont'd)

entry	series	R ¹	R ²	Ar ¹	Ar ²	% yield (±)- 260 ^a	% yield (S)- 260 ^a	% ee (S)- 260 ^a
1	260a	H	H	Ph	4-MeOC ₆ H ₄	52	18	>99
2	260b	H	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	50	29	>99
3	260c	Br	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	23	59	>99
4	260d	I	Br	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	24	41	>99
5	260e	<i>t</i> -Bu	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	13	63	>99
6	260o	Br	Br	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	51	98 ^c	>99

^a isolated yield by chromatography on silica gel. ^b determined by HPLC. ^c (*R*)-**260o** obtained upon deracemization with (+)-sparteine.

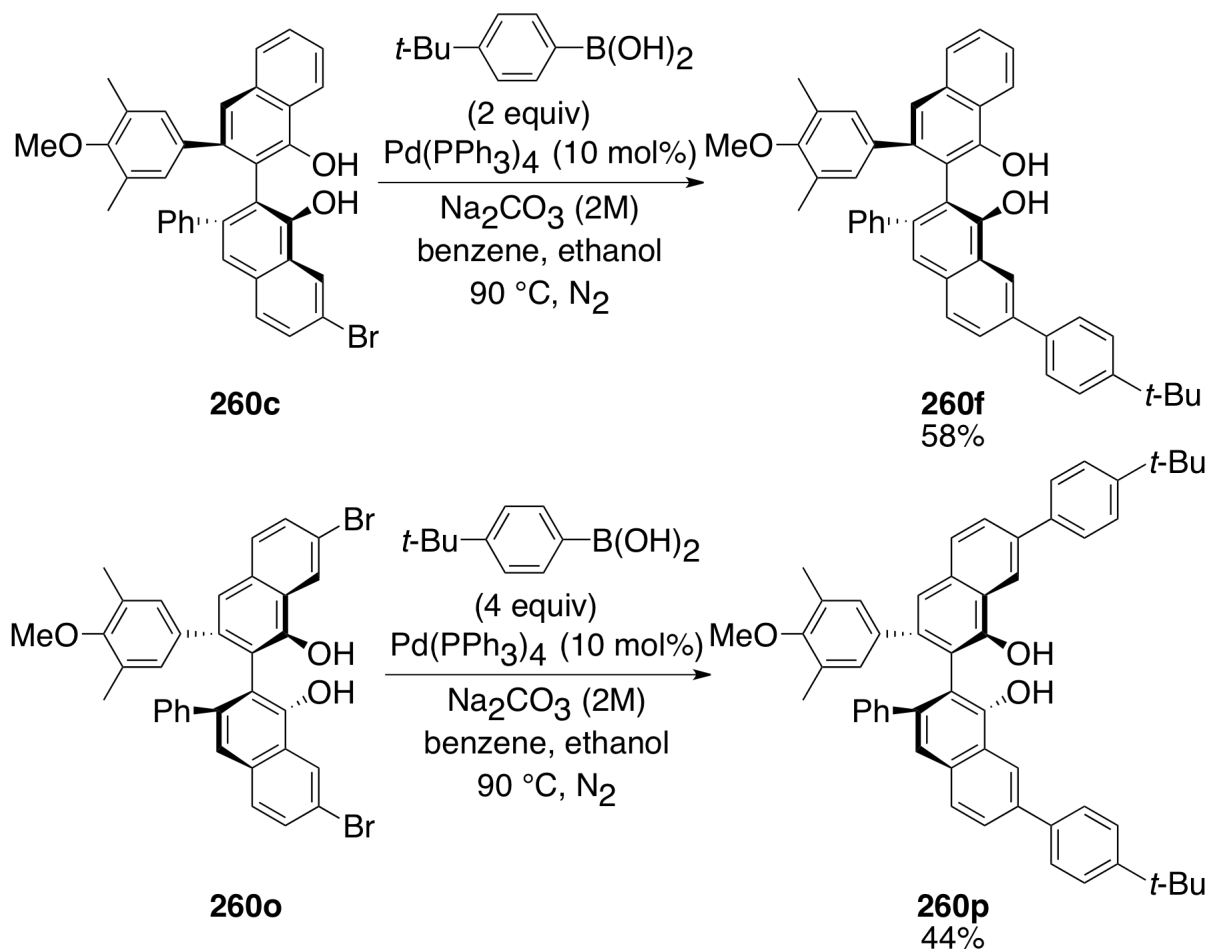
Other unsuccessful coupling reactions are shown in Scheme 4.28. Low yields or inseparable mixture were obtained from the cross coupling reactions.

Scheme 4.28 Attempted oxidative cross coupling

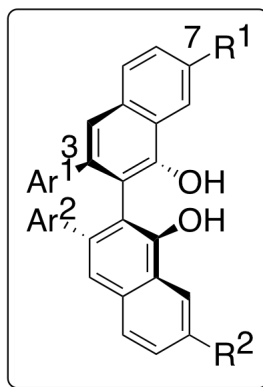
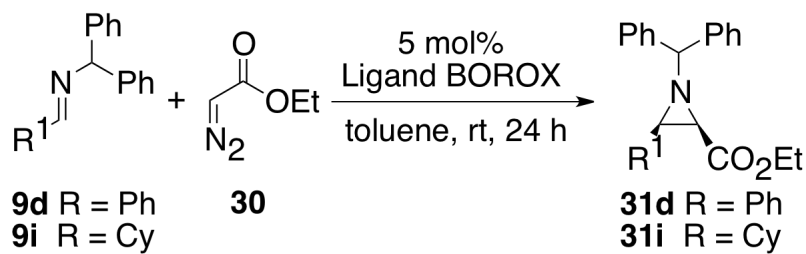


The bromo substituted *CI*-symmetric VANOL derivatives could be further functionalized via the Suzuki coupling reactions with 4-*tert*-butylphenylboronic acid (Scheme 4.29).

Scheme 4.29 Synthesis of *C1*-symmetric VANOL derivatives via Suzuki coupling



With the establishment of the library of *C1*-symmetric VANOL derivatives, the phenyl and cyclohexyl imines were treated with BOROX catalysts prepared from those ligands (Table 4.11). With the same C3 aryl substituent at the 3'-position, 4-*t*-BuC₆H₄, Br and I substituents at the 7-position showed little effect in the aziridination reactions (Table 4.11, entries 3 to 5). Two 4-*t*-BuC₆H₄ substituents showed no beneficial effect compared to one 4-*t*-BuC₆H₄ substituent (Table 4.11, entry 8 vs 5). Two bromo groups gave lower induction than one bromo group (Table 4.11, entry 7 vs 3).

Table 4.11 Ligand screen on the aziridination of benzhydryl imines:*C1*-symmetric VANOL ligands^a

entry	ligand	R ¹	R ²	Ar ¹	Ar ²	R=Ph		R=Cy	
						%	%	%	%
						yield ^b	ee ^c	yield ^b	ee ^c
1	260a	H	H	Ph	<i>p</i> MeOC ₆ H ₂	83	88	85	78
2	260b	H	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	84	94	85	79
3	260c	Br	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	89	97	85	88
4	260d	I	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	87	97	89	87
5	260f	4- <i>t</i> BuC ₆ H ₄	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	90	97	91	89
6	260e	<i>t</i> Bu	H	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	81	98	84	90

Table 4.11 (cont'd)

7	260o	Br	Br	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	96	93	80	75
8	260p	4- <i>t</i> BuC ₆ H ₄	4- <i>t</i> BuC ₆ H ₄	Ph	3,5-Me ₂ -4-MeOC ₆ H ₂	97	94	90	87

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The catalyst was prepared indicated in Table 4.2. ^b yield of isolated *cis*-aziridine by chromatography on silica gel. ^c determined by HPLC on a Chiralcel OD-H column.

The comparison of *C1*- and *C2*-symmetric VANOL ligands is summarized in Table 4.12. Though none of the new ligands could surpass 7,7'-di-*t*-butylVANOL in asymmetric induction, they provide complicated yet valuable mechanistic information in the aziridination reactions. It seems that both 7-substituents and C3-aryl groups influence the transition states.

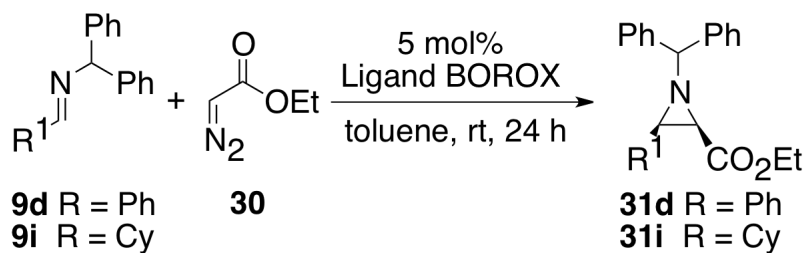
Table 4.12 Ligand screen in the aziridination of benzhydryl imines:*C1*- vs *C2*-symmetric VANOL ligands^a

Table 4.12 (cont'd)

entry	Ligand	R ¹	R ²	Ar ¹	Ar ²	R=Ph		R=Cy	
						%	%	%	%
						yield ^b	ee ^c	yield ^b	ee ^c
1	VANOL	H	H	Ph	Ph	84	92	77	81
2	260b	H	H	Ph	Ar	84	94	85	79
3	223e	H	H	Ar	Ar	85	96	79	87
4	260c	Br	H	Ph	Ar	89	97	85	88
5	260o	Br	Br	Ph	Ar	96	93	80	75
6	237a	Br	Br	Ph	Ph	89	89	78	85
7	260f	4- <i>t</i> -Bu- C ₆ H ₄	H	Ph	Ar	90	97	91	89
8	260p	4- <i>t</i> -Bu- C ₆ H ₄	4- <i>t</i> -Bu- C ₆ H ₄	Ph	Ar	97	94	90	87
9	238a	4- <i>t</i> -Bu- C ₆ H ₄	4- <i>t</i> -Bu- C ₆ H ₄	Ph	Ph	85	97	83	93
10	260e	<i>t</i> -Bu	H	Ph	Ar	81	98	84	90
11	174m	<i>t</i> -Bu	<i>t</i> -Bu	Ph	Ph	82	98	88	94

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst.

Table 4.12 (cont'd)

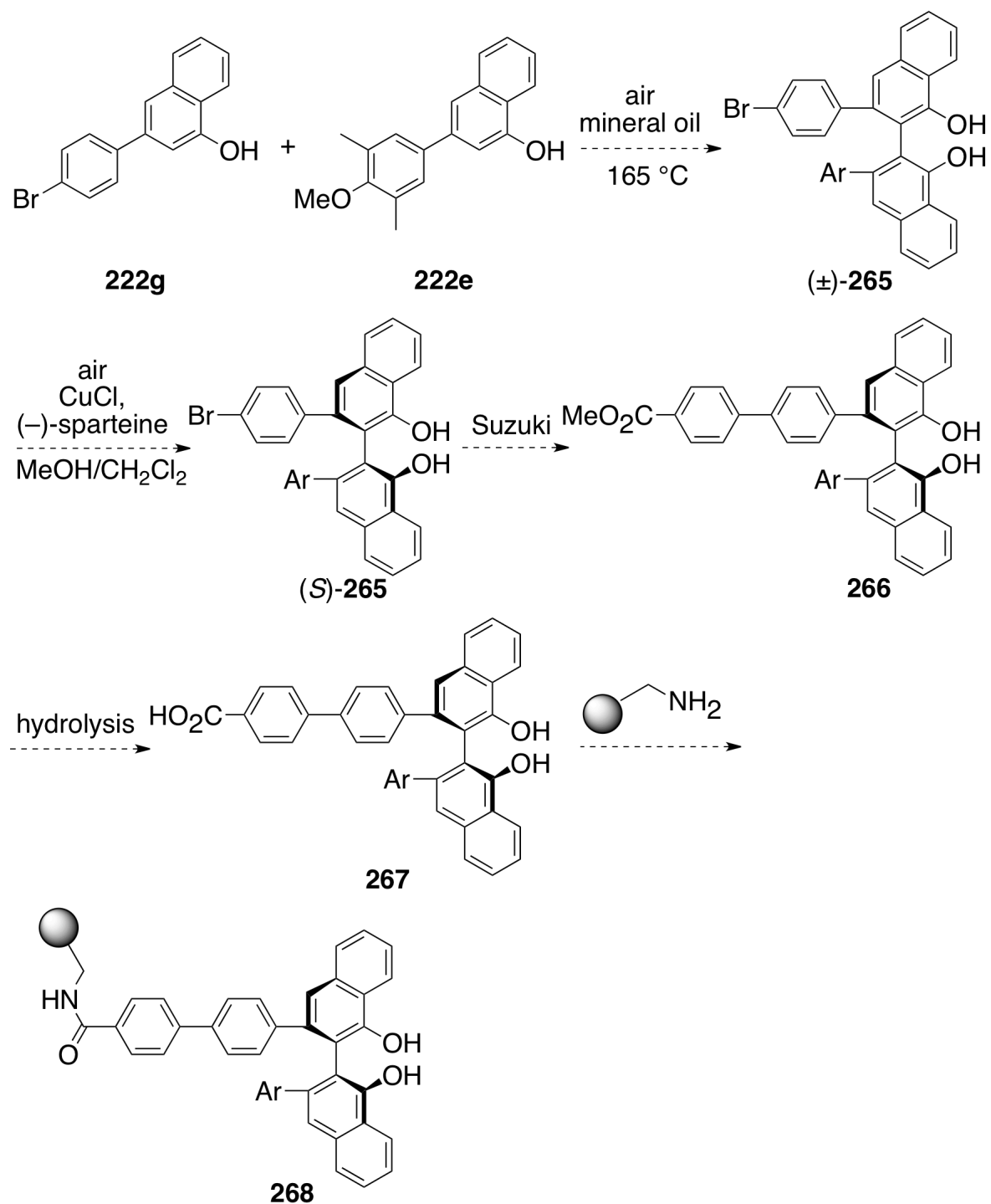
The catalyst was prepared as indicated in Table 4.2. Ar = 3,5-Me₂-4-OMeC₆H₂. ^b yield of isolated *cis*-aziridine by chromatography on silica gel. ^c determined by HPLC on a Chiralcel OD-H column.

4.4 Future plan

One potential use of *CI*-symmetric VANOL ligand is to prepare a polymer-supported VANOL derivative. The proposed synthetic route is outlined in Scheme 4.30.

Suzuki coupling of the *CI*-symmetric VANOL ligand with arylboronic acid, followed by hydrolysis, should give the COOH-functionalized VANOL derivative **267**. Then subsequent amide formation should afford the desired polymer-supported VANOL derivative **268**.

Scheme 4.30 Proposed synthetic route of polymer-supported VANOL derivative



4.5 Conclusion

Three sets of VANOL ligands: 1) naphthalene skeleton modified; 2) C3-aryl group modified; 3) *C1*-symmetric VANOL derivatives were successfully synthesized and evaluated in the aziridination reaction. Several trends were found: 1) Introducing big aryl groups in the 8,8'- or 4,4'-positions lead to dramatic decreased asymmetric inductions; 2) The substituents in the 5,5'- or 6,6'-positions have less effect on the asymmetric induction; 3) C3-aryl groups influences the asymmetric induction to some extent; 4) 7-substituents and C3-aryl groups together effect the asymmetric induction in a complicated manner. The present study not only demonstrates practical routes to those VANOL derivatives but also provides insightful information to guide further computation study on the transition states in the aziridination reaction. From a combination of the outcomes with these ligands in the aziridination reaction and crystal structures of the two catalyst-substrate complexes that have been previously obtained (Scheme 4.1 & 4.20, it could be concluded that The interactions in the solid state might not reflect those in the solution state or in the transition states of the reactions of both aryl or alkyl imines. The *C1*-symmetric ligands described in this work promise to provide access to solid supported VANOL ligands.

CHAPTER FIVE

STUDY OF VAPOL DERIVATIVES AND OTHER ORGANOCATALYSTS

The previous chapters deal with completed major projects. In this chapter, some small projects or unfinished projects will be discussed briefly.

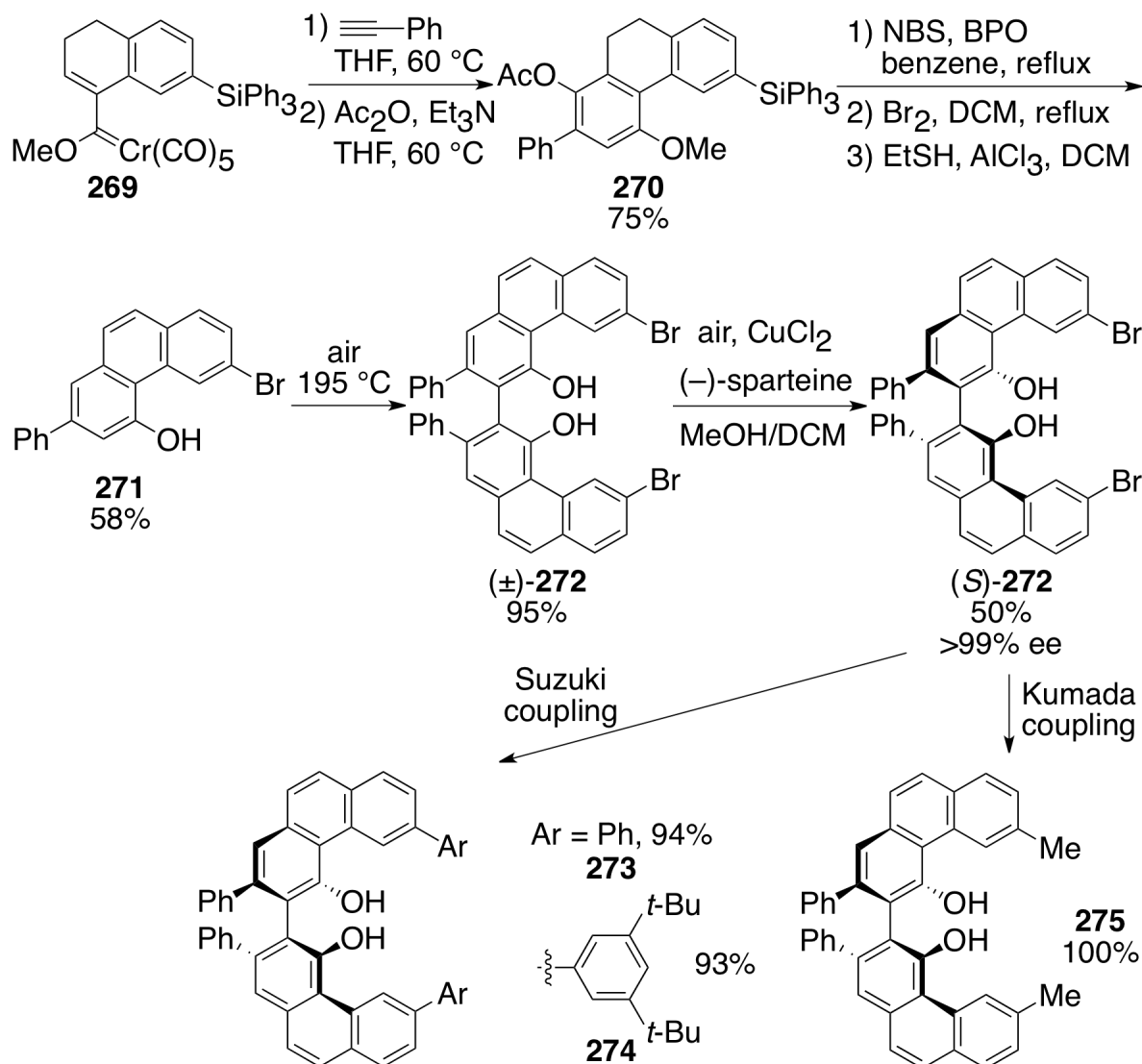
5.1 Synthesis of VAPOL derivatives and their applications in asymmetric catalysis

5.1.1 Background

Previously Dr. Heller from our group reported the synthesis of 6,6'-disubstituted VAPOL ligands (Scheme 5.1).¹⁵ One of the key steps is the benzannulation reaction of Fischer carbene complex **269** and phenylacetylene, leading to the formation of dihydrophenanthrene **270** in 75% yield. Dehydrogenation of **270** gave phenanthrene intermediate **271**, of which the triphenylsilyl group could be converted into the bromide by treatment with bromine. This was followed by simultaneous demethylation and acetate reduction with AlCl₃ and ethanethiol. The oxidative coupling step follows the procedure developed for the synthesis of VAPOL. Heating the neat melted monomer **271** in air afforded racemic 6,6'-dibromo-VAPOL **272** in 95% yield. The racemate was deracemized with (–)-sparteine and copper (II) complex, providing optically pure (>99% ee) (*S*)-6,6'-dibromo-VAPOL **272**. From the 6,6'-dibromo-VAPOL (*S*)-**272**, other derivatives could be accessed divergently. The nickel-catalyzed Kumada coupling of 6,6'-dibromo-VAPOL with methyl magnesium bromide yielded 6,6'-dimethyl VAPOL **275**. The 6,6'-diaryl VAPOL ligands **273** and **274** could be prepared via the Suzuki coupling reactions of 6,6'-dibromo VAPOL with different aryl boronic acids. Those VAPOL derivatives were evaluated in the Diels-Alder

reactions of both methyl acrylate and methacrolein. However, none of these ligands were found to exceed VAPOL in terms of asymmetric induction.

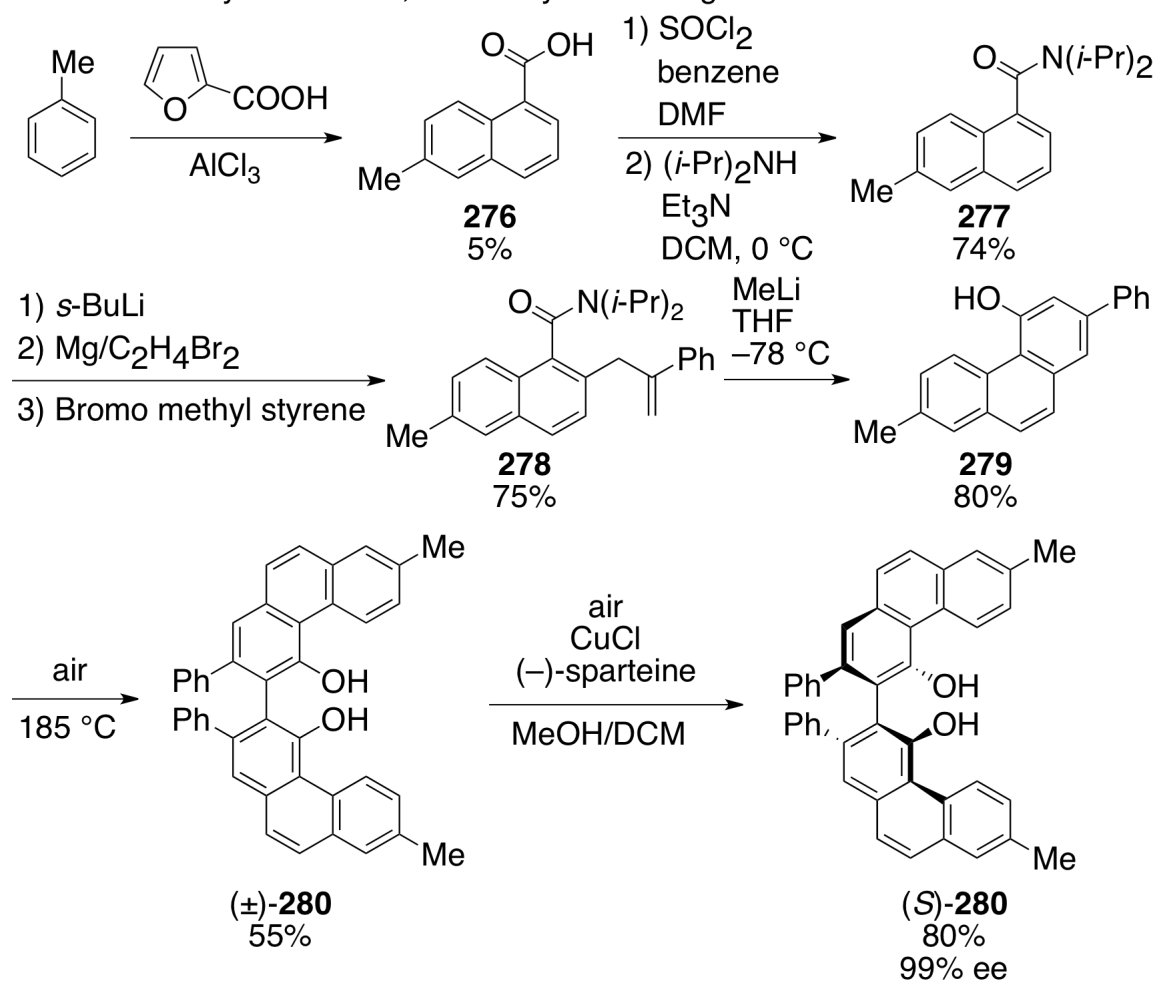
Scheme 5.1 Synthesis of 6,6'-disubstituted VAPOL ligands



Later on, Dr. Rampalakos from our group synthesized 7,7'-dimethyl VAPOL in a different fashion (Scheme 5.2).¹⁹ The first step involves a formal Diels-Alder reaction between toluene and furoic acid, furnishing 6-methylnaphthoic acid **276**. The acyl chloride generated from acid **276** reacted with $(i\text{-Pr})_2\text{NH}$ to afford diisopropyl-6-methyl naphthamide **277** in 74% yield over

two steps. Treatment of the 6-methyl naphthamide **277** with *s*-BuLi, MgBr₂ and α -bromomethyl styrene gave the *o*-allylation product **278** in 75% yield. Upon treatment of the *o*-allyl naphthamide **278** with MeLi at $-78\text{ }^{\circ}\text{C}$, the cyclization went smoothly to give the monomer **279** in 80% yield. The subsequent dimerization and deracemization led to (*S*)-7,7'-dimethyl VAPOL **280**. This ligand was examined in the iminoaldol reaction between imines and silyl ketene acetals.¹⁹

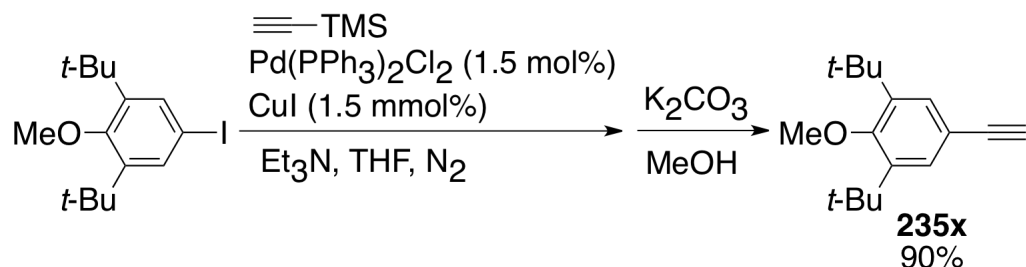
Scheme 5.2 Synthesis of 7,7'-dimethyl VAPOL ligand



5.1.2 Synthesis of novel VAPOL derivatives

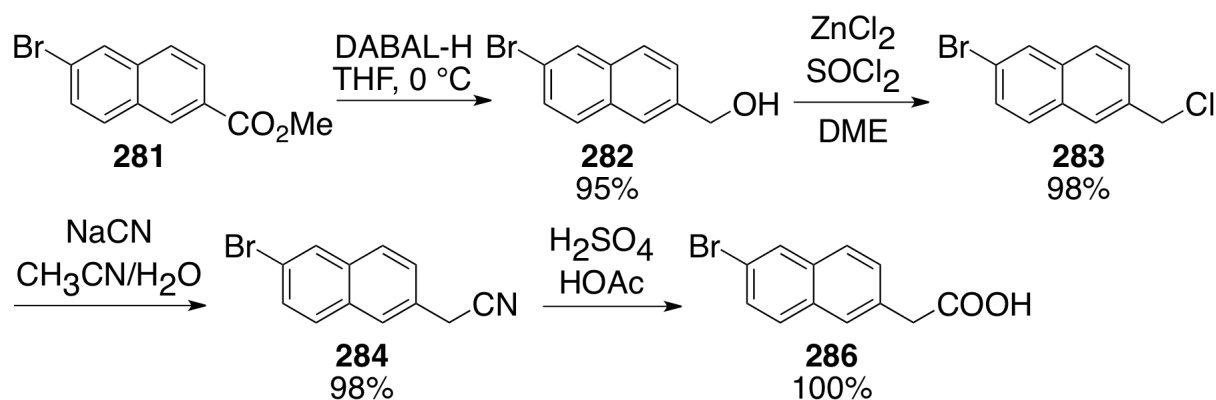
The shortcomings of the above two routes are the narrow substrate scope, the low yields and the numbers of steps, compared to the recent developed cycloaddition/electrocyclic ring-opening/electrocyclic ring closure/tautomerization (CAEC) cascade route.^{13g,73} Therefore, the CAEC cascade was employed in the following study.

Scheme 5.3 Synthesis of aryl alkyne



The desired alkyne was synthesized via a Sonogashira coupling/deprotection sequence (Scheme 5.3). The overall yield was high (90%).

Scheme 5.4 Synthesis of 6-bromo-2-naphthaleneacetic acid



6-Bromo-2-naphthaleneacetic acid **286** was synthesized in a facile, clean and cheap route adapted from the published multikilogram scale synthesis (Scheme 5.4).⁹⁹ Subjection of the commercially available ester **281** to DABAL-H gave the alcohol **282** in 95% yield. Chlorination

of the alcohol **282** was accomplished with SOCl_2 in the presence of ZnCl_2 as a catalyst. The one-carbon homologation of the chloride **283** with NaCN afforded the desired nitrile **284** in 98% yield. The following hydrolysis provided the acid **286** in quantitative yield. The above four steps involve no column chromatography separation.

Table 5.1 Synthesis of 2-aryl-4-phenanthrols

285		287
entry	Ar	% yield
1	3,5-Me ₂ C ₆ H ₃	56
2	3,5-Me ₂ -4-MeOC ₆ H ₂	35
3	3,5- <i>t</i> Bu ₂ -4-MeOC ₆ H ₂	43

The CAEC cascade reactions of 2-naphthaleneacetic acid with various aryl alkynes proceeded smoothly, giving the targeted 2-aryl-4-phenanthrols in decent yields (Table 5.1).

The CAEC cascade reactions of 6-bromo-2-naphthaleneacetic acid with a variety of aryl alkynes also progressed well as expected in moderate yields (Table 5.2).

Table 5.2 Synthesis of 2-aryl-7-bromo-4-phenanthrols

	286		288
entry	compound	Ar	% yield
1	288a	C ₆ H ₅	45
2	288b	4- <i>n</i> -BuC ₆ H ₄	53
3	288c	3,5-Me ₂ C ₆ H ₃	46
4	288x	3,5- <i>t</i> Bu ₂ -4-MeOC ₆ H ₂	25

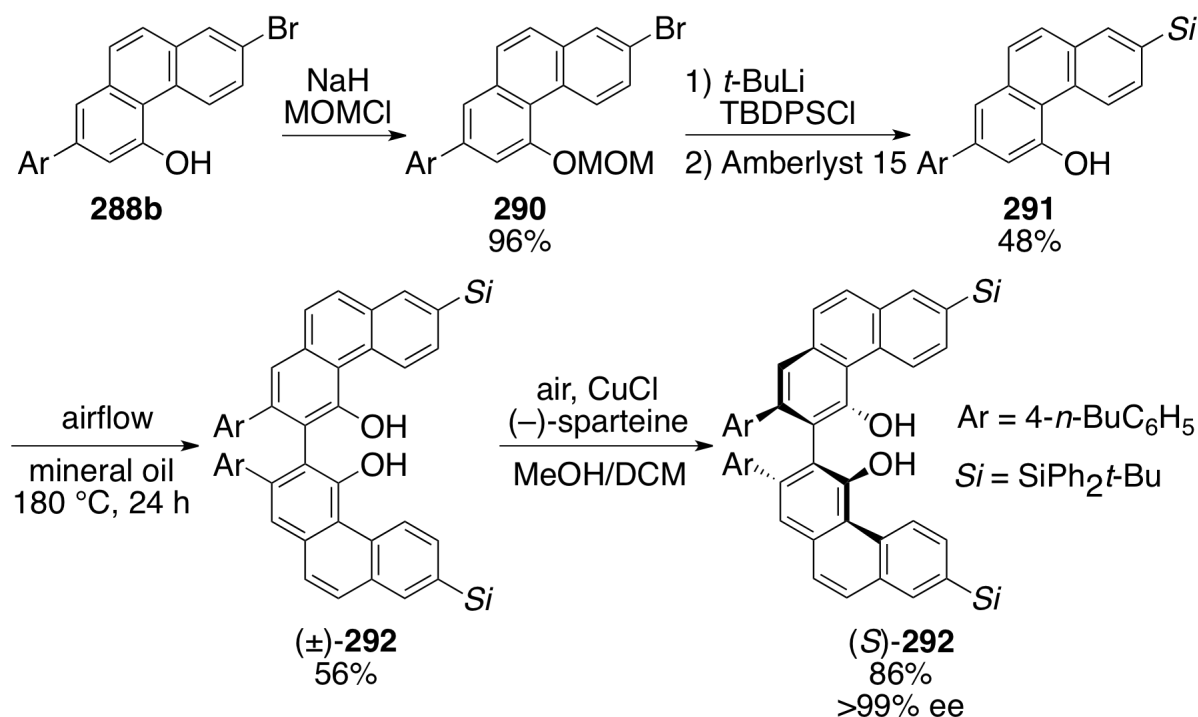
Table 5.3 Synthesis of optically pure C2-aryl VAPOL derivatives

	287		(±)-289		(S)-289
Entry	Ar	series	% yield (±)-289 ^a	% yield (S)-289 ^a	% ee (S)-289 ^b
1	3,5-Me ₂ C ₆ H ₃	289c	80	90	>99
2	3,5-Me ₂ -4-MeOC ₆ H ₂	289d	60	95	>99
3	3,5- <i>t</i> Bu ₂ -4-MeOC ₆ H ₂	289x	82	94	97

The 2-aryl-4-phenanthrols obtained from the CAEC cascade reactions were then subjected to the oxidative thermal coupling conditions (Table 5.3). The reactions proceeded successfully. Deracemization of those racemates progressed smoothly and gave optically pure VAPOL ligands in high yields.

The oxidative couplings of the 2-aryl-7-bromo-4-phenanthrols led to mixtures with very low solubilities in common solvents. The purification and low solubilities made deracemization difficult to pursue.

Scheme 5.5 Synthesis of 7,7'-di-silyl VAPOL derivative



To make utility of the 2-aryl-7-bromo-4-phenanthrols, the MOM protected 7-bromo-4-phenanthrol **290** was treated with *t*-BuLi and *t*-BuPh₂SiCl, and the silyl group was installed successfully (Scheme 5.5). The deprotection with Amberlyst 15 led to 7-silyl-4-phenanthrol **291**. The thermal coupling and deracemization progressed successfully.

5.1.3 VAPOL derivatives in asymmetric catalysis

The four new VAPOL ligands were evaluated in the aziridination reactions with phenyl and cyclohexyl imines, respectively (Table 5.4). If the C3 aryl group is 3,5-Me₂C₆H₃ or 3,5-Me₂-4-MeOC₆H₂, higher asymmetric inductions were observed, though the increases were low (2-4%). However, if the C3 aryl group is 3,5-*t*Bu₂-4-MeOC₆H₂, slightly lower asymmetric inductions were obtained. The increased sterics (SiPh₂*t*-Bu) in the 7,7'-positions in VAPOL appear to have a limited effect on the enantioselectivities.

Table 5.4 VAPOL Ligand screen on the aziridination of benzhydryl imines^a

9d R = Ph
9i R = Cy

30

5 mol%
Ligand BOROX
toluene, rt, 24 h

31d R = Ph
31i R = Cy

entry	ligand	Ar	R	R ¹ =Ph		R ¹ =Cy	
				% yield ^b	% ee ^c	% yield ^b	% ee ^c
1	VAPOL	Ph	H	76	93	78	82
2	289c	3,5-Me ₂ C ₆ H ₃	H	77	95	78	86
3	289e	3,5-Me ₂ -4-MeOC ₆ H ₂	H	76	95	76	86
4	289x	3,5- <i>t</i> Bu ₂ -4-MeOC ₆ H ₂	H	85	89	75	81
5	292	4- <i>n</i> -BuC ₆ H ₄	SiPh ₂ <i>t</i> -Bu	80	95	77	84

Table 5.4 (cont'd)

^a unless otherwise specified, all reactions were run at 0.5 M in imine in toluene on a 0.5 mmol scale with 1.2 equiv EDA at 25 °C for 24 h and went to 100% completion with 5 mol% catalyst. The catalyst was prepared from 1 equiv ligand, 4 equiv B(OPh)₃ and 1 equiv H₂O at 80 °C in toluene for 1 h, followed by removal of volatiles under vacuum (0.5 mm Hg) at 80 °C for 0.5 h. ^b yield of isolated *cis*-aziridine by chromatography on silica gel. ^c determined by HPLC on a Chiralcel OD-H column.

Another important reaction mediated by VAPOL ligands is the enantioselective Ugi-type reaction.²⁵ This project was initiated by Li Huang and taken over by Wenjun Zhao. An examination of the new VAPOL ligands revealed that VAPOL derivative **289x** is much better than VAPOL in terms of asymmetric induction (Table 5.5).

Table 5.5 Ugi-type reaction mediated with VAPOL derivatives^a

entry	ligand	% yield ^b	% ee ^c
1	VAPOL	87	40
2	289x	91	72

^a Unless otherwise specified, the catalyst was prepared by heating a mixture of 1 equiv of the ligand, 3 equiv BH₃•SMe₂, 2 equiv 2,4,6-trimethylphenol, 3 equiv H₂O in toluene at 100 °C for

Table 5.5 (cont'd)

1 h. The volatiles were then removed under vacuum (0.1 mm Hg) at 100 °C for 1 h. ^b yield of isolated *trans*-aziridine by chromatography on silica gel. ^c determined by HPLC.

5.2 The CAEC cascade: scope and limitations

In the previous chapters, we have employed the CAEC cascade in the synthesis of many new ligands. It would be instructive to even further explore the substrate scope of this cascade, leading to valuable polyaromatic compounds. Those results are summarized as below

For a given phenylacetic acid, various alkynes could be successfully employed (Table 5.6). There is no general trend in the relationship of the aryl group and the yield. Heterocycles, such as 2- or 3-thienyl group, are also applicable. More interestingly, but-3-yn-1-ylbenzene gave 3-phenethyl-1-naphthol, making the synthesis of 3-alkyl-1-naphthols feasible (Table 5.6, entry 12).

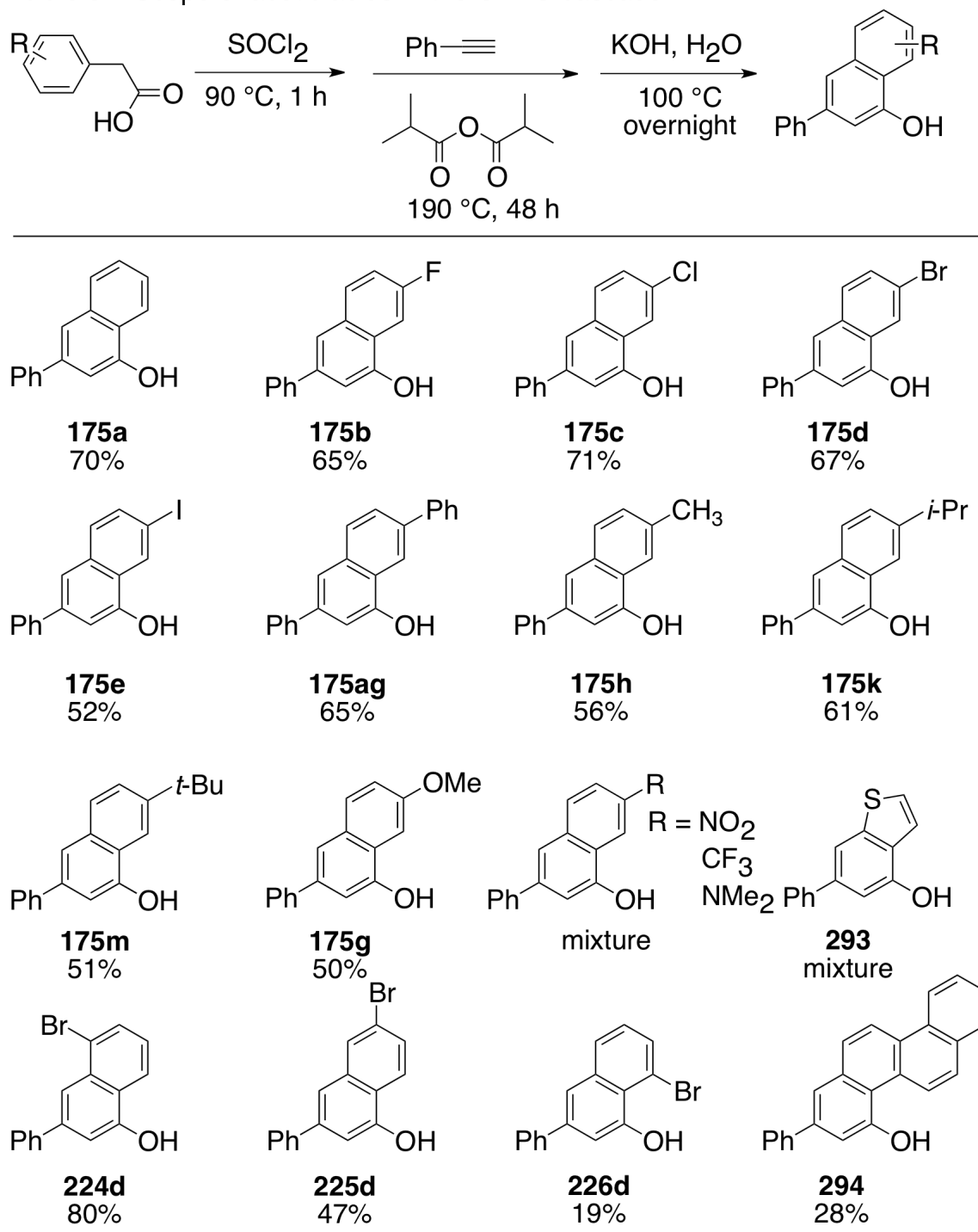
Table 5.6 Scope of acetylenes in the CAEC cascade

entry	compound	R	R ¹	% yield
1	175a	C ₆ H ₅	H	70%
2	222c	3,5-Me ₂ C ₆ H ₃	H	66%
3	222e	3,5-Me ₂ -4-MeOC ₆ H ₂	H	56%
4	222d	4-MeOC ₆ H ₄	H	41%
5	222h	4-EtOC ₆ H ₄	H	61%
6	222i	4-PhC ₆ H ₄	H	61%
7	222f	4-FC ₆ H ₄	H	53%

Table 5.6 (cont'd)

8	222g	4-BrC ₆ H ₄	H	45%
9	222j	3,5-(CF ₃) ₂ C ₆ H ₃	H	51%
10	222s	2-C ₄ H ₃ S	H	37%
11	222t	3-C ₄ H ₃ S	H	57%
12	333	PhCH ₂ CH ₂	H	36%
13	236a	C ₆ H ₅	Br	67%
14	236b	4- <i>n</i> -BuC ₆ H ₄	Br	68%
15	236c	3,5-Me ₂ C ₆ H ₃	Br	61%
16	236f	4-FC ₆ H ₄	Br	37%
17	236p	3,4,5-(MeO) ₃ C ₆ H ₂	Br	47%
18	236d	4-MeOC ₆ H ₄	Br	30%
19	236q	2,6-Me ₂ C ₆ H ₃	Br	nd
20	236e	3,5-Me ₂ -4-MeOC ₆ H ₂	Br	50%
21	175g	C ₆ H ₅	OMe	50%
22	334b	4- <i>n</i> -BuC ₆ H ₄	OMe	43%
23	334c	3,5-Me ₂ C ₆ H ₃	OMe	52%

Table 5.7 Scope of acetic acids in the CAEC cascade



For a given alkyne, such as phenylacetylene, different types of phenylacetic acids are applicable in the CAEC cascade, with some exceptions (Table 5.7). The reactions of *p*-CF₃, *p*-NO₂, or

p-NMe₂ phenylacetic acid led to inseparable mixtures. So did that of 2-thiopheneacetic acid. Interestingly, 2-phenanthreneacetic acid could afford 2-phenylchrysen-4-ol **294**, demonstrating that the CAEC cascade is a good way of making conjugated polycyclic compounds.

Table 5.8 Synthesis of 2-aryl-4-phenanthrols via the CAEC cascade

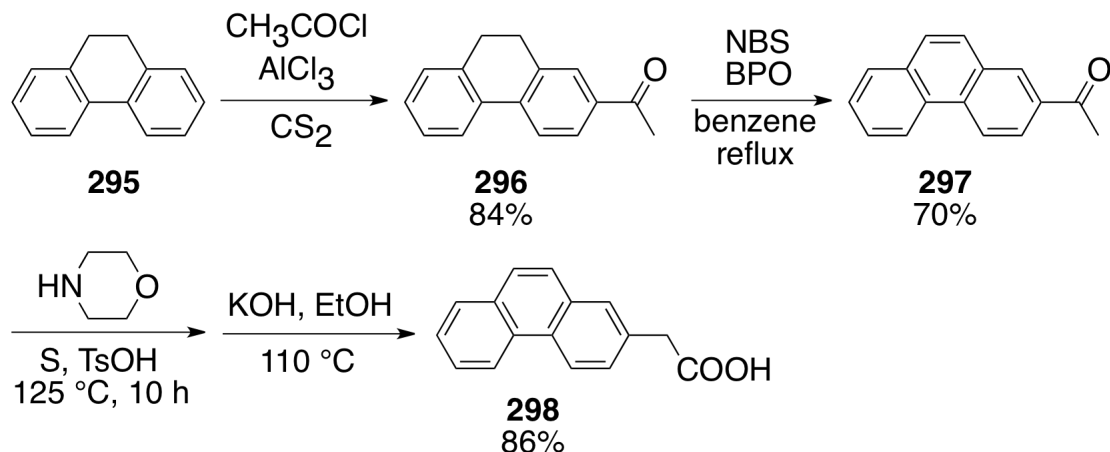
entry	Ar	R	% yield
1	3,5-Me ₂ C ₆ H ₃	H	56
2	3,5-Me ₂ -4-MeOC ₆ H ₂	H	35
3	3,5- <i>t</i> Bu ₂ -4-MeOC ₆ H ₂	H	43
4	C ₆ H ₅	Br	45
5	4- <i>n</i> -BuC ₆ H ₄	Br	53
6	3,5-Me ₂ C ₆ H ₃	Br	46
7	3,5- <i>t</i> Bu ₂ -4-MeOC ₆ H ₂	Br	25

2-Naphthaleneacetic acid and 6-bromo-2-naphthaleneacetic acid were treated with various alkynes as well (Table 5.8). And all the reactions proceeded as expected.

The synthesis of 2-phenanthreneacetic acid is outlined in Scheme 5.6. The Friedel-Crafts acylation of commercially available 9,10-dihydrophenanthrene **295** gave the acyl intermediate **296** in 84% yield.^{74,100} Dehydrogenation led to 1-(phenanthren-2-yl)ethanone **297** in 70%

yield.^{15,101} The subsequent Willgerodt-Kindler reaction afforded 2-phenanthreneacetic acid **298** in 86% yield.^{77,102}

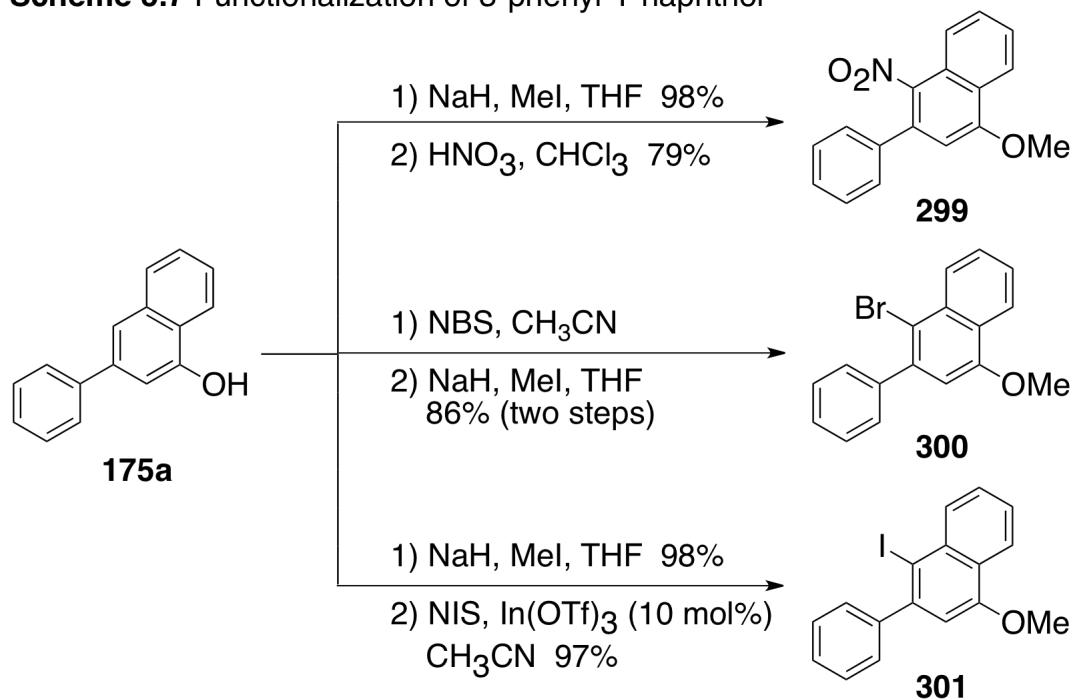
Scheme 5.6 Synthesis of 2-phenanthreneacetic acid



The monomer from the CAEC cascade could be functionalized in a variety of ways (Scheme 5.7).

Nitration, bromination and iodination proceeded smoothly and afforded 1-substituted 4-methoxy-2-phenylnaphthalene in good yields.^{72,73,103}

Scheme 5.7 Functionalization of 3-phenyl-1-naphthol



5.3 Reduction of 2-quinoline

The reduction reaction of 2-quinolines is a useful method to generate 1,2,3,4-tetrahydroquinolines, a common structural motifs in numerous alkaloid natural products. There are a number of successful systems for the asymmetric reduction of quinolines using organometallic catalysts.¹⁰⁴ Later on, BINOL derived phosphoric acids were employed in the asymmetric transfer hydrogenation of quinolines with the Hantzsch ester as the hydrogen source.¹⁰⁵

Dr. Desai in our group initiated a collaborative project with Prof. Odom. He worked on the development of a catalytic asymmetric transfer hydrogenation of 2-quinolines, which were provided by the Odom group, into the corresponding 1,2,3,4-tetrahydroquinolines. The investigation involved the optimization of the solvents, the phenols, the Hantzsch esters, and additional additives.¹⁰⁶

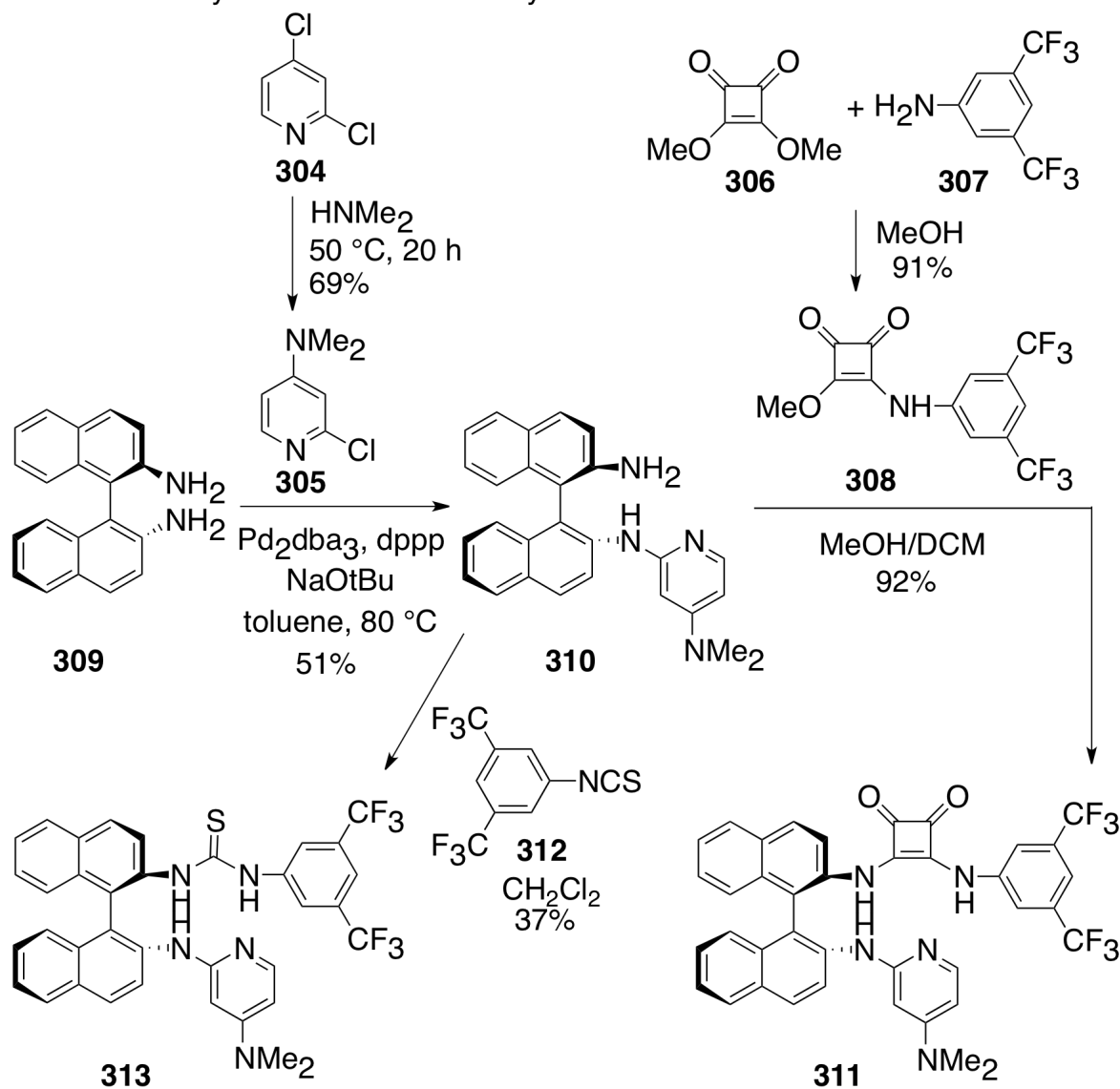
As a continuation of this project, I carried out a ligand screen on this transformation. The results of various ligands tested are summarized in Scheme 5.8. All the ligands gave complete conversion with variable amount of asymmetric induction in a range of 9-78% ee, and VAPOL turned out to be the best ligand of all those examined.

Ar =	R = H	78% ee, >99% yield
Ar =	R = SiPh ₂ t-Bu	7% ee, >99% yield
Ar =	R = H	64% ee, >99% yield
Ar =	R = H	57% ee, >99% yield
	R = SiPh ₂ t-Bu	9% ee, >99% yield
	R = OMe	67% ee, >99% yield
	R = Br	15% ee, >99% yield
	R =	27% ee, >99% yield
	R = Me	25% ee, >99% yield
	R = $\equiv$ -TMS	44% ee, >99% yield
	R = I	17% ee, >99% yield

5.4 Synthesis of a novel DMAP-squaramide catalyst and its applications in catalysis

This work is a continuation of Dr. Rampalakos' research. In 2008, Dr. Rampalakos from our group reported that a bifunctional DMAP-thiourea derived from BINAM could promote a highly enantioselective Michael addition of nitroalkanes to nitroalkenes.¹⁰⁷

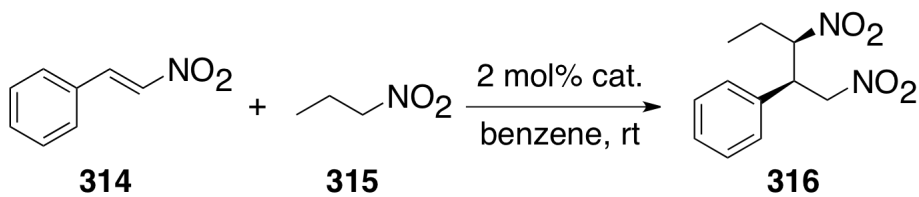
Scheme 5.9 Synthesis of DMAP catalysts derived from BINAM



Though the reaction gives high asymmetric induction, the diastereoselectivity is not good. In order to achieve high diastereoselectivity, the existing ligand should further optimized. Thus, the

thiourea motif was replaced with the squaramide motif and the synthesis of new catalyst **311** is outlined in Scheme 5.9. 2-Chloro DMAP **305** could be obtained through the nucleophilic aromatic substitution of 2,4-dichloropyridine **304**. Buchwald amination of BINAM and 2-chloro DMAP **305** gave the desired monosubstituted product **310** in 51% yield. The reaction of **310** and mono substituted squaramide **308** afforded the desired disubstituted squaramide **311** in 92% yield.¹⁰⁸ The original bifunctional DMAP-thiourea **313** was synthesized as well.

Table 5.9 Michael addition of nitroalkane to nitroalkene with DMAP catalysts^a

				
entry	catalyst	% yield ^b	syn:anti ^c	% ee ^d
1	313	80	84:16	95
2	311	79	88:12	97

^a unless otherwise specified, all reactions were run at 0.2 M in nitroalkene **314** with 30 equiv of **315** and 2 mol% of catalyst. ^b combined isolated yields of syn and anti isomers after chromatography on silica gel. ^c determined by ¹H NMR spectrum of the crude reaction mixture. ^d determined by HPLC.

The two catalysts were examined in the reaction of **314** and **315** with the same reaction conditions indicated in the original report and both gave similar results (Table 5.9).

5.5 One-pot imine formation-AZ reaction

Based on the results and observations accumulated in our studies on the aziridination reaction, it was clear that the quality of the imine was crucial for obtaining good yields and excellent enantioselectivities. These imines tend to decompose via hydrolysis in the presence of a catalytic amount of acid, which can lead to significantly diminished asymmetric inductions. Although the quality of the purified imines can remain high for several months if stored in a well-sealed desiccator, there are some imines that cannot be purified by either crystallization or distillation, especially primary alkyl substituted imines, which are more prone to decomposition.

It was envisioned that a one-pot imine formation-AZ reaction starting directly from amines and aldehydes might be possible. The major concerns for this one-pot protocol are the possible adverse effects on the yield and asymmetric induction that may be due to the presence of an excess of the amine, the aldehyde or the presence of the dehydrating reagent required in the imine formation step. The advantages of such a one-pot procedure would include: (a) simplification of the overall process and (b) prevention of the possible decomposition of imines during the purification step in the synthesis of these imines.

Previous results from Zhenjie's thesis showed that an excess amount of the amine in the reaction would likely have a major detrimental effect due to the strong coordination of the amine nitrogen to the catalyst, which leads to a very low conversion ($< 5\%$).⁶⁴ An excess of the aldehyde would slightly diminish the yield but would not affect the enantioselectivity. We also screened different dehydrating reagents (molecular sieves and MgSO_4) and found that the use of activated 4Å MS

afforded better enantioselectivity than that of MgSO_4 , which might be due to the stronger Lewis acid character of MgSO_4 compared to 4Å MS. Based on these findings, a one-pot imine generation-aziridination procedure was developed.

Table 5.10 Optimization on the one-pot imine generation-aziridination reaction

entry	procedure	mol%	mole%	g	% conv ^c	% yield ^d	% ee ^e
		VAPOL	B(OPh) ₃	MS			
1	I ^a	10	40	1	100	71	96
2	II ^b	10	40	1	100	70	94
3	II ^b	5	15	1	67	42	95
4	II ^b	5	15	0.5	39	31	94
5	II ^b	5	15	0.2	100	63	93

^a reactions were run by using procedure I described in the experimental part. The catalyst was prepared as indicated in Table 5.4. After adding 1.2 equiv. EDA, the reaction mixtures were stirred at room temperature for 40 h. ^b reactions were run by using procedure II described in the experimental part. The solution of (*S*)-VAPOL and B(OPh)₃ in 2 mL distilled toluene was transferred via syringe to the round bottom flask containing imine generated *in situ*. After adding

Table 5.10 (cont'd)

1.2 equiv. EDA, the mixtures were stirred at room temperature for 40 h. ^c determined by ¹H NMR spectrum of the crude reaction mixture. ^d isolated yield of *cis*-aziridine after chromatography on silica gel. ^e determined by HPLC on a CHIRALCEL OD-H column.

Inspired by Gang's one-pot procedure (procedure III), in which the solution of imine, VAPOL/VANOL ligand (5 mol %) and triphenyl borate (15 mol %) could react with EDA in an open vessel, a new simplified one-pot procedure was proposed and tested. The new procedure (procedure II in the experimental part) worked well for the following reaction (Table 5.10, entry 2), in which the toluene solution of VAPOL/VANOL ligand and triphenyl borate was transferred into the vessel where the imine generation step was completed in 2 h. It gave comparable result as Zhenjie's one-pot imine generation-aziridination procedure (Table 5.10, entry 2 vs entry 1).

Encouraged by procedure II, efforts have been made to optimize it. Reducing the catalyst loading from 10 mol% to 5 mol% resulted in lower conversion and lower yield albeit the same enantioselectivity (Table 5.10, entry 3). The assumption that 4Å MS attributed to the lower yield led us to reduce the amount of 4Å MS. It was found that 0.2 g seems to be the best amount and the last entry in table 1 is the optimal condition by far (Table 5.10, entry 5).

However, Gang's procedure, in which 5 mol% of VAPOL, 15 mol% of B(OPh)₃, and the imine were mixed in toluene and stirred for 10 min opened to air before the addition of EDA (procedure III), turned out to be not that generally applicable from some results by other group members. Therefore, we decided to revisit Gang's procedure (Table 5.11).

Table 5.11 Procedure III of the aziridination of benzhydryl imines^a

	9	30				
	9	30				
entry	R	% conv ^b	% yield ^c	% ee ^d	% yield (ref 26j)	% ee (ref 26j)
1	H	100	80	90	82	94
2	NO ₂	81	76	87	79	79
3	Br	56	43	88	78	90
4	OMe	43	34	86	51	86

^a Unless otherwise specified, all the reactions were run in toluene containing 0.5 M imine, 5 mol% (*S*)-VAPOL, 15 mol% B(OPh)₃ at room temperature for 24 h with 1.2 equiv of EDA opened to air. ^b determined by ¹H NMR spectrum of the crude reaction mixture. ^c isolated yield of *cis*-aziridine after chromatography on silica gel. ^d determined by HPLC on a CHIRALCEL OD-H column.

From the results in Table 5.11, some conclusion could be made: 1) only the imine from benzaldehyde works well with Gang's procedure and 2) the ee will be low if the conversion is low.

At this point, the improvement on Gang's procedure became a priority. We assumed that the moisture in the air might affect the catalyst and carried out experiments in Table 5.12. Therefore,

procedure IV, a variation of procedure III, in which the AZ reaction was performed under argon, was investigated.

Table 5.12 Procedure IV of the aziridination of benzhydryl imines^a

entry	R	mol% VAPOL	mol% B(OPh) ₃	% conv ^b	% yield ^c	% ee ^d
1	H	5	15	94	83	89
2	NO ₂	5	15	44	nd	nd
3	NO ₂	5	20	48	nd	nd
4	NO ₂	10	40	87	nd	nd

^a Unless otherwise specified, all the reactions were run in toluene containing 0.5 M imine, 5 mol% (*S*)-VAPOL, 15 mol% B(OPh)₃ at room temperature for 24 h with 1.2 equiv of EDA under Ar. nd = not determined.

^b determined by ¹H NMR spectrum of the crude reaction mixture.

^c isolated yield of *cis*-aziridine after chromatography on silica gel. ^d determined by HPLC on a CHIRALCEL OD-H column.

However, the results in Table 5.12 showed that the attempted improvement on Gang's procedure was not successful even by increasing the catalyst loading up to 10 mol % (Table 5.12, entry 4).

Therefore, we resumed the investigation of Zhenjie's one-pot procedure. Several trials on further optimization in Table 5.13 revealed that the first entry was the optimal condition.

Table 5.13 Optimization of the one-pot imine generation-aziridination reaction^a

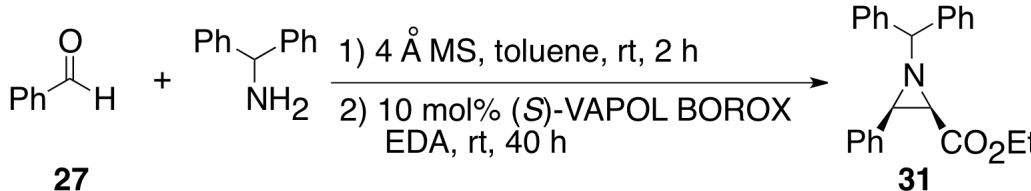
entry	mol% VAPOL	mol% B(OPh) ₃	g MS	% conv ^b	% yield ^c	% ee ^d
1	10	40	1	100	66	93
2	10	40	0.25	98	63	92
3	5	20	0.25	97	58	91

^a Unless otherwise specified, all the reactions were run by using procedure I described in the experimental part. The catalyst was prepared as indicated in Table 5.4. After adding 1.2 equiv. EDA, the mixtures were stirred at room temperature for 40 h. ^b determined by ¹H NMR spectrum of the crude reaction mixture. ^c isolated yield of *cis*-aziridine after chromatography on silica gel. ^d determined by HPLC on a CHIRALCEL OD-H column.

The optimal conditions were then applied to different aldehydes with benzhydryl amine. From the results in Table 5.14, this one-pot protocol gave better yields and enantioselectivities compared with the published results. This improvement may be attributed to the existence of 4Å MS that might slow down the reactions. Both electron rich and electron poor aromatic aldehydes

gave excellent yields and enantioselectivities. However, sterically hindered aldehydes, such as 2-methyl-benzaldehyde, would not go to complete conversion in 40 h. 1-Naphthaldehyde would not undergo condensation with benzaldehyde in 4 h even in the presence of 2 g 4Å MS.

Table 5.14 One-pot imine generation-aziridination reactions with aldehydes^a

						
entry	R	% conv ^b	% yield ^c	% ee ^d	% yield (ref 26j)	% ee (ref 26j)
1	C ₆ H ₅	100	66	93	63	94
2	4-BrC ₆ H ₄	100	61	94	55	90
3	4-NO ₂ C ₆ H ₄ ^e	96	64	89	63	79
4	4-NO ₂ C ₆ H ₄ ^f	93	60	89	63	79
5	4-MeC ₆ H ₄	100	64	95	63	92
6	4-MeOC ₆ H ₄ ^g	100	55	91	43	86

^a Unless otherwise specified, all the reactions were run by using procedure A described in the experimental part. The catalysts were prepared as indicated in Table 5.4. After adding 1.2 equiv. EDA, the mixtures were stirred at room temperature for 40 h. ^b determined by ¹H NMR spectrum of the crude reaction mixture. ^c isolated yield of *cis*-aziridine after chromatography on silica gel. ^d determined by HPLC on a CHIRALCEL OD-H column. ^e used as purchased without purification. ^f used with purification. ^g 1.5 g MS and 2 equiv EDA were used.

CHAPTER SIX

EXPERIMENTAL PART

General information

Material: Dichloromethane, acetonitrile and triethylamine were distilled from calcium hydride under nitrogen. Toluene, THF, benzene and diethyl ether were distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased. Other reagents were used as purchased from Aldrich or other commercial sources. Commercially available benzhydrylamine and propynals were distilled prior to use. Both VAPOL and VANOL ligands are commercially available from Aldrich as well as Strem Chemicals, Inc. If desired, they could be purified using column chromatography on regular silica gel using an eluent mixture of 2:1 dichloromethane:hexanes. Phenol was sublimed and stored under Argon in a dry desiccator. Diazoacetamides **31**, **36**,^{27a} bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (MEDAM amine),^{26j} bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (BUDAM amine),^{26h} imines **9a-j**^{26g} were prepared according to the published procedures.

Instrumentation: The silica gel for column chromatography was purchased from Sorbent Technologies with the following specifications: standard grade, 60 Å porosity, 230 X 400 mesh particle size, 500 – 600 m²/g surface area and 0.4 g/mL bulk density. Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were taken on a Galaxy series FTIR-3000 spectrometer. ¹H NMR and ¹³C NMR were recorded on a Varian Inova-300 MHz, Varian UnityPlus-500 MHz or Varian Inova-600 MHz

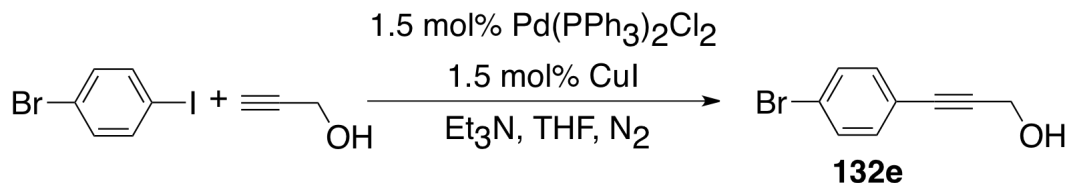
instrument in CDCl₃ unless otherwise noted. CDCl₃ was used as the internal standard for both ¹H NMR (δ = 7.24) and ¹³C NMR (δ = 77.0). Low-resolution mass spectra and elemental analysis were performed in the Department of Chemistry at Michigan State University. HR-MS was performed in the Department of Biochemistry at Michigan State University. Analytical thin-layer chromatography (TLC) was performed on 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 phosphomolybdic acid in ethanol. Column chromatography was performed with silica gel 60 (230 – 450 mesh). HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1.0 mL.

6.1 Experimental for chapter two

6.1.1 Preparation of propynols

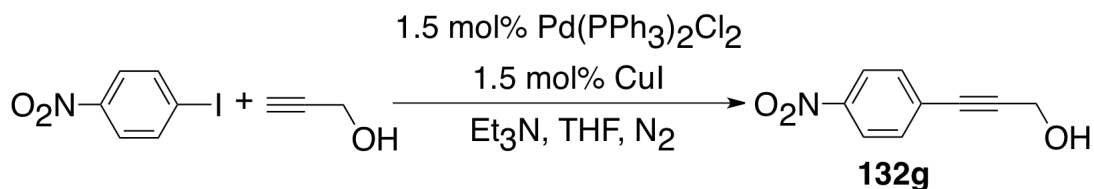
General procedure for the preparation of propynols – illustrated for the synthesis of

***3-(4-bromophenyl)prop-2-yn-1-ol 132e* (Procedure A)^{63a}**



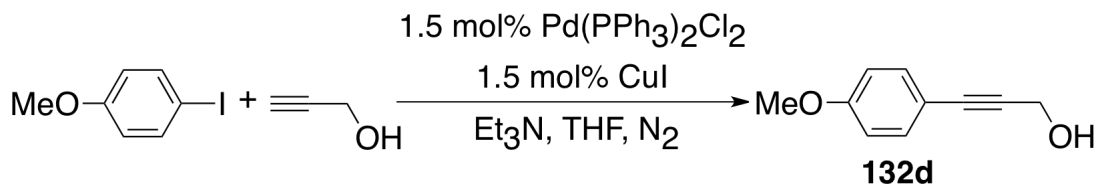
To a 250 mL flame dried flask filled with argon was added 1-bromo-4-iodobenzene (11.32 g, 40.0 mmol), Pd(PPh₃)₂Cl₂ (421 mg, 0.60 mmol), CuI (114 mg, 0.60 mmol) and dry THF (40

mL). After the addition of Et₃N (16.2 g, 22.3 mL, 160 mmol), the reaction mixture was stirred at room temperature for 5 minutes and then prop-2-yn-1-ol (2.60 mL, 44.0 mmol) was added. After stirring at the room temperature over night under an argon balloon, hexanes were added to the mixture. After removal of the solvent, the crude mixture was purified by column chromatography on silica gel (50 mm x 200 mm, CH₂Cl₂/hexanes 1:1 to 1:0, then ethyl acetate/hexanes 1:3) to afford **132e** as an off-white solid (6.90 g, 32.7 mmol, 82%). mp 80-81 °C (lit.^{63a} mp 68-69 °C); R_f = 0.17 (CH₂Cl₂). Spectral data for **132e**: ¹H NMR (CDCl₃, 500 MHz) δ 1.67 (t, 1H, OH, *J* = 6.0 Hz), 4.46 (d, 2H, *J* = 6.0 Hz), 7.25-7.29 (m, 2H), 7.41-7.45 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 51.60, 84.66, 88.29, 121.45, 122.79, 131.59, 133.10; IR (thin film) 3223br s, 1483s, 1393s, 1013s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 212 M⁺ (⁸¹Br, 84), 210 M⁺ (⁷⁹Br, 88), 131 (100), 102 (100), 77 (100), 74 (100).

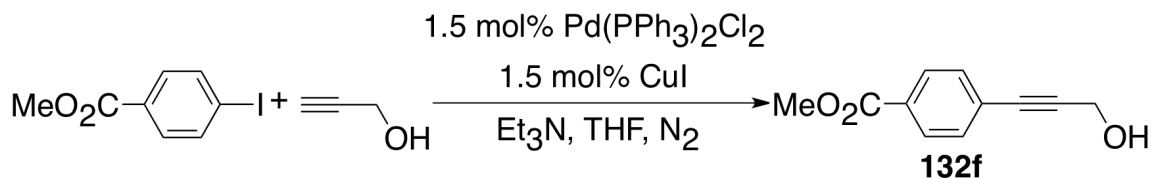


3-(4-Nitrophenyl)prop-2-yn-1-ol 132g: The reaction of 1-iodo-4-nitrobenzene (14.94 g, 60.0 mmol) and prop-2-yn-1-ol (3.90 mL, 66.0 mmol) was performed according to the general procedure (Procedure A). Purification of the crude mixture by column chromatography on silica gel (50 mm x 200 mm, CH₂Cl₂/hexanes 1:1 to 1:0, then ethyl acetate/hexanes 1:3) gave **132g** as a yellow solid (9.91 g, 56.0 mmol, 93%). mp 95-96 °C (lit.^{63a} mp 95-96 °C); R_f = 0.13 (CH₂Cl₂). Spectral data for **132g**: ¹H NMR (CDCl₃, 500 MHz) δ 1.89 (t, 1H, OH, *J* = 6.5 Hz), 4.52 (d, 2H, *J* = 6.5 Hz), 7.53-7.57 (m, 2H), 8.14-8.17 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 51.48, 83.78,

92.48, 123.56, 129.41, 132.38, 147.20; IR (thin film) 3318br s, 1595s, 1516s, 1348s, 1024s cm^{-1} ; mass spectrum, m/z (% rel intensity) 177 M^+ (12), 160 (22), 130 (74), 102 (62), 77 (100).

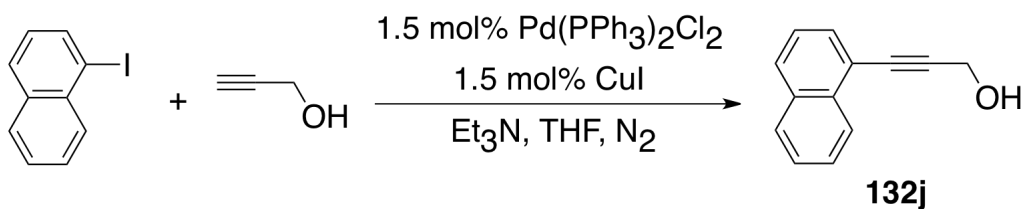


3-(4-Methoxyphenyl)prop-2-yn-1-ol 132d: The reaction of 1-iodo-4-methoxybenzene (9.36 g, 40.0 mmol) and prop-2-yn-1-ol (2.60 mL, 44.0 mmol) was performed according to the general procedure (Procedure A). Purification of the crude mixture by column chromatography on silica gel (50 mm x 200 mm, CH_2Cl_2 /hexanes 1:1 to 1:0, then ethyl acetate/hexanes 1:3) gave **132d** as an off-white solid (3.80 g, 23.5 mmol, 59%). mp 65-66 °C (lit.^{63d} mp 62.5-64.5 °C); R_f = 0.12 (1:3 EtOAc / hexane). Spectral data for **132d**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.67 (t, 1H, OH, J = 6.0 Hz), 4.46 (d, 2H, J = 6.0 Hz), 6.80-6.84 (m, 2H), 7.34-7.37 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 51.70, 55.26, 85.64, 85.82, 113.92, 114.57, 133.16, 159.72; IR (thin film) 3250 br s, 1507s, 1252s, 1028s cm^{-1} ; mass spectrum, m/z (% rel intensity) 162 M^+ (100), 145 (37), 131 (32), 119 (26), 91 (27), 77 (15).



Methyl 4-(3-hydroxyprop-1-yn-1-yl)benzoate 132f: The reaction of methyl 4-iodobenzoate (20.96 g, 80.0 mmol) and prop-2-yn-1-ol (5.20 mL, 88.0 mmol) was performed according to the general procedure (Procedure A). Purification of the crude mixture by column chromatography

on silica gel (50 mm x 200 mm, CH₂Cl₂/hexanes 1:1 to 1:0, then ethyl acetate/hexanes 1:3) gave **132f** as a white solid (13.26 g, 69.8 mmol, 87%). mp 82-83 °C; R_f = 0.18 (1:2 EtOAc/hexanes). Spectral data for **132f**: ¹H NMR (CDCl₃, 500 MHz) δ 1.93 (t, 1H, OH, *J* = 6.0 Hz), 3.89 (s, 3H), 4.50 (s, 2H, *J* = 6.0 Hz), 7.44-7.47 (m, 2H), 7.94-7.97 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 51.55, 52.26, 84.87, 90.18, 127.22, 129.46, 129.74, 131.56, 166.51; IR (thin film) 3320br s, 1725s, 1431s, 1281s, 1117s, 1032s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 190 M⁺ (41), 159 (33), 131 (100), 103 (33), 77 (30). Anal calcd for C₁₁H₁₀O₃: C, 69.46; H, 5.30. Found: C, 69.10; H, 5.73.

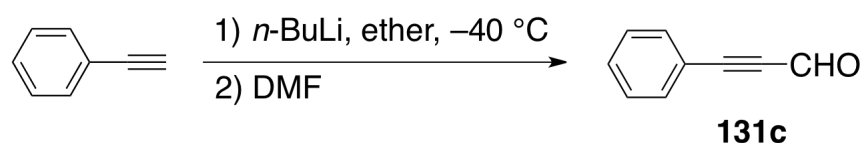


3-(naphthalen-1-yl)prop-2-yn-1-ol **132j**:^{63e} The reaction of 1-iodonaphthalene (20.32 g, 80.0 mmol) and prop-2-yn-1-ol (5.20 mL, 88.0 mmol) was performed according to the general procedure (Procedure A). Purification of the crude mixture by column chromatography on silica gel (50 mm x 300 mm, CH₂Cl₂/hexanes 1:1 to 1:0) gave **132j** as an off-white solid (8.04 g, 44.2 mmol, 55%). mp 46-48 °C; R_f = 0.20 (CH₂Cl₂). Spectral data for **132j**: ¹H NMR (CDCl₃, 500 MHz) δ 1.83 (t, 1H, OH, *J* = 6.0 Hz), 4.64 (d, 2H, *J* = 6.0 Hz), 7.38-7.42 (m, 1H), 7.48-7.52 (m, 1H), 7.54-7.58 (m, 1H), 7.65-7.67 (m, 1H), 7.83 (t, 2H, *J* = 8.0 Hz), 8.31 (d, 1H, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 51.88, 83.79, 92.02, 120.12, 125.14, 126.02, 126.43, 126.80,

128.26, 128.98, 130.62, 133.09, 133.23; IR (thin film) 3331br s, 3059s, 2226w, 1586s, 1509s, 1397s cm^{-1} .

6.1.2 Preparation of propynals

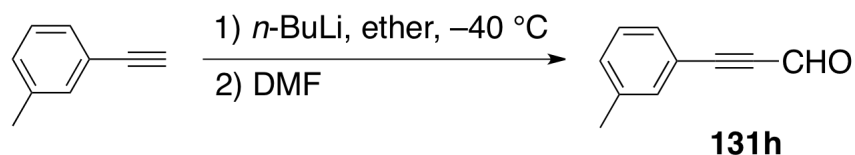
General procedure for the preparation of propynal – illustrated for the synthesis of phenyl-2-propynal **131c**



Procedure B:^{62a} *n*-Butyllithium (2.5 M in hexanes, 20.0 mL, 50.0 mmol) was added dropwise to a solution of phenylacetylene (5.49 mL, 50.0 mmol) in dry Et_2O (40 mL) at $-40\text{ }^{\circ}\text{C}$ under nitrogen. After 30 min, dry DMF (5.81 mL, 75.0 mmol) was added, and then the mixture was allowed to warm up to room temperature, and stirring was continued for 30 min. The mixture was poured into ice water and acidified slightly with concentrated hydrochloric acid. The mixture was then neutralized with sodium hydrogen carbonate until a pH between 6 and 7 was reached. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified by vacuum distillation ($65\text{ }^{\circ}\text{C}$ at 0.5 mmHg) to afford **131c** as a colorless oil (3.37 g, 25.2 mmol, 50%).

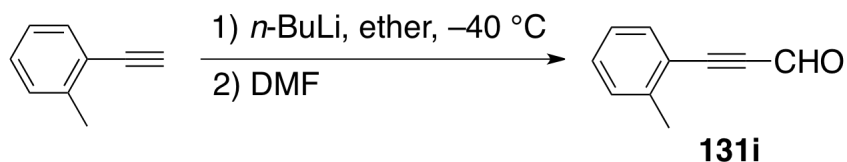
Procedure C:^{62b,62c} *n*-Butyllithium (2.5 M in hexanes, 24.0 mL, 60.0 mmol) was added dropwise to a solution of phenylacetylene (6.12 g, 60.0 mmol) in dry THF (150 mL) at $-40\text{ }^{\circ}\text{C}$ under nitrogen. After 30 min, dry DMF (9.28 mL, 120.0 mmol) was added, and then the mixture

was allowed to warm up to room temperature, and stirring was continued for 30 min. The reaction mixture was then poured into a vigorously stirred biphasic solution prepared from a 10% aqueous solution of KH_2PO_4 (325 mL) and Et_2O (300 mL) at 0 °C. Layers were separated and the organic layer was washed with water (2 x 200 mL). The combined aqueous layers were then extracted with Et_2O (200 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel (30 mm x 200 mm, CH_2Cl_2 /hexanes 1:1) and then vacuum distillation (65 °C at 0.5 mmHg) to afford phenyl-2-propynal **131c** as a colorless oil (6.62 g, 50.9 mmol, 85%). $R_f = 0.21$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **41c**: ^1H NMR (CDCl_3 , 500 MHz) δ 7.37-7.41 (m, 2H), 7.45-7.50 (m, 1H), 7.57-7.61 (m, 2H), 9.41 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 88.41, 95.11, 119.42, 128.72, 131.28, 133.27, 176.76; IR (thin film) 3061w, 2857m, 2242m, 2189s, 1661s, 1445m, 1389m, 1262m cm^{-1} ; mass spectrum, m/z (% rel intensity) 130 M^+ (100), 103 (81), 75 (32).

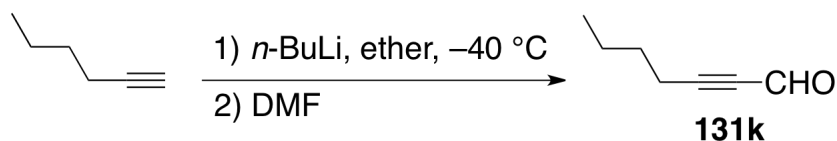


3-(m-tolyl)propionaldehyde 131h:^{62c} The reaction of 3-ethynyltoluene (2.32 g, 20.0 mmol) with *n*-Butyllithium (2.5 M in hexanes, 8 mL, 20.0 mmol) and dry DMF (2.32 mL, 30.0 mmol) was performed according to the general procedure (Procedure B). The residue was purified by column chromatography on silica gel (35 mm x 300 mm, CH_2Cl_2 /hexanes 1:2) to afford **131h** as a light yellow oil (2.17 g, 15.0 mmol, 75%). $R_f = 0.26$ (1:1 CH_2Cl_2 /hexanes). Spectral data for

131h: ^1H NMR (CDCl_3 , 500 MHz) δ 2.38 (s, 3H), 7.25-7.30 (m, 2H), 7.37-7.41 (m, 2H), 9.40 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.15, 88.24, 95.56, 119.22, 128.61, 130.43, 132.24, 133.74, 138.60, 176.80; IR (thin film) 2857m, 2188s, 1658s, 1559m, 1456m cm^{-1} .

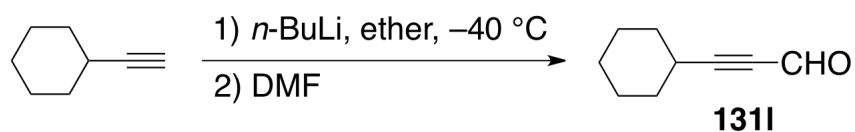


3-(o-tolyl)propionaldehyde 131i:^{62e} The reaction of 2-ethynyltoluene (1.16 g, 10.0 mmol) with *n*-butyllithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) and dry DMF (1.16 mL, 15.0 mmol) was performed according to the general procedure (Procedure B). The residue was purified by column chromatography on silica gel (30 mm x 280 mm, CH_2Cl_2 /hexanes 1:3) to afford **131i** as a light yellow oil (0.99 g, 6.9 mmol, 69%). R_f = 0.30 (1:1 CH_2Cl_2 /hexanes). Spectral data for **131i**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.49 (s, 3H), 7.18-7.22 (m, 1H), 7.24-7.27 (m, 1H), 7.36 (td, 1H, J = 7.5, 1.5 Hz), 7.55 (dd, 1H, J = 7.5, 1.0 Hz), 9.45 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 20.58, 92.22, 94.24, 119.24, 125.96, 129.91, 131.32, 133.81, 142.61, 176.73; IR (thin film) 2857m, 2234m, 2186s, 1661s, 1456m, 1387m, 1256m cm^{-1} .

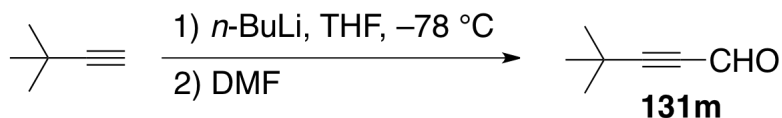


*hept-2-ynal 131k:*⁶² The reaction of 1-hexyne (2.46 g, 30.0 mmol) with *n*-Butyllithium (1.6 M in hexanes, 18.75 mL, 30.0 mmol) and dry DMF (3.50 mL, 45.2 mmol) was performed according to the general procedure (Procedure B). The residue was purified by column chromatography on silica gel (30 mm x 200 mm, CH_2Cl_2 /hexanes 1:1) and then by vacuum

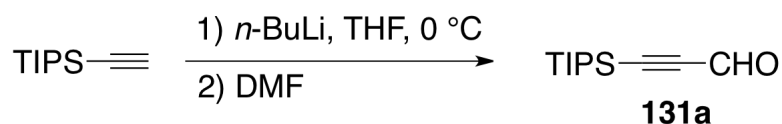
distillation (52 °C at 0.5 mm Hg with a slow bleed of air through a needle) to afford **131k** as a colorless oil (1.85 g, 16.8 mmol, 56%). $R_f = 0.39$ (1:1 CH₂Cl₂/hexanes). Spectral data for **131k**: ¹H NMR (CDCl₃, 500 MHz) δ 0.89 (t, 3H, $J = 7.0$ Hz), 1.37-1.45 (m, 2H), 1.51-1.58 (m, 2H), 2.38 (td, 2H, $J = 7.0, 1.0$ Hz), 9.14 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.39, 18.76, 21.87, 29.49, 81.63, 99.29, 177.22; IR (thin film) 2963s, 2238s, 1686s cm⁻¹; mass spectrum, m/z (% rel intensity) 110 M⁺ (3), 109 (48), 95 (94), 81 (79), 68 (84), 41 (100).



3-cyclohexylpropionaldehyde 131l:^{62d} The reaction of cyclohexylacetylene (3.24 g, 30.0 mmol) with *n*-butyllithium (2.5 M in hexanes, 12.0 mL, 30.0 mmol) and dry DMF (3.50 mL, 45.2 mmol) was performed according to the general procedure (Procedure B). The residue was purified by vacuum distillation (86 °C at 0.5 mm Hg with a slow bleed of air through a needle) to afford **131l** as a colorless oil (3.03 g, 22.2 mmol, 74%). $R_f = 0.32$ (1:1 CH₂Cl₂/hexanes). Spectral data for **131l**: ¹H NMR (CDCl₃, 500 MHz) δ 1.30-1.37 (m, 3H), 1.46-1.54 (m, 3H), 1.66-1.73 (m, 2H), 1.81-1.85 (m, 2H), 2.54-2.60 (m, 1H), 9.18 (d, 1H, $J = 1.0$ Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 24.58, 25.52, 29.25, 31.40, 81.60, 102.77, 177.39; IR (thin film) 2934s, 2857s, 2234m, 2201s, 1669s cm⁻¹; mass spectrum, m/z (% rel intensity) 136 M⁺ (4), 135 (29), 107 (59), 91 (37), 79 (100).



4,4-dimethylpent-2-ynal **131m**:^{62f} The reaction of 3,3-dimethylbutyne (4.41 g, 53.8 mmol) with *n*-butyllithium (1.5 M in hexanes, 35.9 mL, 53.8 mmol) and dry DMF (3.50 mL, 45.2 mmol) was performed according to the general procedure (Procedure C). The residue was purified by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂/hexanes 1:2) and then by distillation (bp 132 °C at 760 mmHg) to afford **131m** as a colorless oil (2.98 g, 27.1 mmol, 50%). *R*_f = 0.30 (1:1 CH₂Cl₂/hexanes). Spectral data for **131m**: ¹H NMR (CDCl₃, 500 MHz) δ 1.28 (s, 9H), 9.17 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 27.92, 29.88, 80.22, 106.32, 177.44; IR (thin film) 2975s, 2220s, 1686s cm⁻¹.

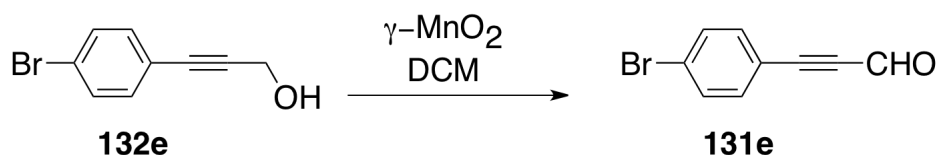


3-(triisopropylsilyl)propionaldehyde **131a**:^{62f} *n*-Butyllithium (2.5 M in hexanes, 10.7 mL, 50.0 mmol) was added dropwise to a solution of (triisopropylsilyl)acetylene (4.87 mL, 26.7 mmol) in dry THF (35 mL) at 0 °C under nitrogen. After stirring 2 h at room temperature, dry DMF (5.81 mL, 75.0 mmol) was added to the mixture at 0 °C, and then the mixture was allowed to warm up to room temperature, and stirring was continued for 12 h. The mixture was poured into ice cold HCl solution (aq. 10%, 30 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (35 mm x 300 mm, EtOAc/hexanes 1:10) to afford **131a** as a light yellow oil (4.40 g, 21.0 mmol, 78%). *R*_f = 0.15 (1:10 EtOAc/hexanes). Spectral data for **131a**:

^1H NMR (CDCl_3 , 500 MHz) δ 1.07-1.14 (m, 21H), 9.19 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 10.92, 18.41, 100.81, 104.45, 176.61; IR (thin film) 2947s, 2869s, 2151m, 1671s cm^{-1} .

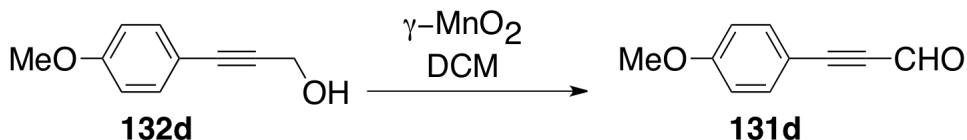
General procedure for the MnO_2 oxidation reaction in the preparation of propynals – illustrated for the preparation of (4-Bromophenyl)-propynal **131e (Procedure D)**

*Preparation of $\gamma\text{-MnO}_2$:*¹⁰⁹ To a solution of $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ (30.2 g, 0.178 mol) in H_2O (574 mL) at 60 °C was added, with stirring, a solution of KMnO_4 (21.0 g, 0.133 mol) in H_2O (400 mL), and the suspension was stirred at 60 °C for 1 h, filtered, and the precipitate washed with water until free of sulfate ions. The precipitate was dried to constant weight at 60 °C; yield 32.2 g (dark-brown, amorphous powder).

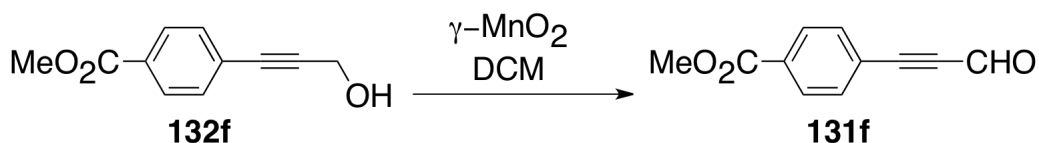


$\gamma\text{-MnO}_2$ (4.17 g, 47.9 mmol) was added to a solution of 3-(4-bromophenyl)-prop-2-yn-1-ol **132e** (2.02 g, 9.58 mmol) in dry CH_2Cl_2 (20 mL). The resulting mixture was stirred at room temperature over night and then filtered through a pad of silica gel with CH_2Cl_2 as eluent. After removal of the solvent **131e** was obtained as an off-white solid (1.33 g, 6.36 mmol, 66%). mp 104-106 °C (lit.^{63a} mp 54-55 °C); R_f = 0.20 (1:1 CH_2Cl_2 /hexanes). Spectral data for **131e**: ^1H NMR (CDCl_3 , 500 MHz) δ 7.43-7.46 (m, 2H), 7.52-7.56 (m, 2H), 9.39 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 89.03, 93.57, 118.30, 126.22, 132.17, 134.49, 176.52; IR (thin film) 2193s, 1653s, 1584s, 1476s, 1393s, 1263s cm^{-1} ; mass

spectrum, m/z (% rel intensity) 210 M^+ (^{81}Br , 39), 208 M^+ (^{79}Br , 46), 182 (47), 180 (55), 101 (94), 74 (100).

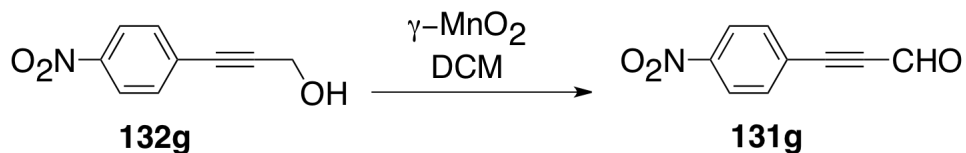


3-(4-methoxyphenyl)prop-2-yn-1-ol **132d**: The reaction of 3-(4-methoxyphenyl)prop-2-yn-1-ol **132d** (2.43 g, 15.0 mmol) with $\gamma\text{-MnO}_2$ (6.52 g, 75.0 mmol) was performed according to the general procedure (Procedure D). Ynal **131d** was obtained as an off-white solid (1.60 g, 10.0 mmol, 67%). mp 47-48 °C (lit.^{63d} mp 47-48.5 °C); R_f = 0.14 (1:1 CH_2Cl_2 /hexanes). Spectral data for **131d**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.83 (s, 3H), 6.88-6.90 (m, 2H), 7.53-7.55 (m, 2H), 9.37 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.44, 88.72, 96.54, 111.13, 114.48, 135.42, 162.12, 176.71; IR (thin film) 2180s, 1643s, 1599s, 1510s, 1451s, 1389s, 1256s cm^{-1} ; mass spectrum, m/z (% rel intensity) 160 M^+ (100), 132 (39), 117 (31), 89 (35).

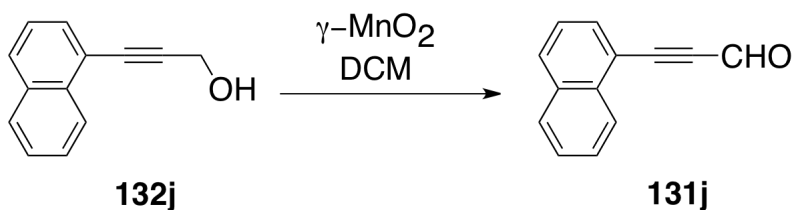


methyl 4-(3-oxoprop-1-yn-1-yl)benzoate **131f**: The reaction of methyl 4-(3-hydroxyprop-1-yn-1-yl)benzoate **132f** (3.80 g, 20.0 mmol) with $\gamma\text{-MnO}_2$ (8.69 g, 100.0 mmol) was performed according to the general procedure (Procedure D). Ynal **131f** was obtained as a white solid (2.53 g, 13.4 mmol, 67%). mp 85-86 °C; R_f = 0.39 (CH_2Cl_2). Spectral data for **131f**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.92 (s, 3H), 7.63-7.65 (m, 2H), 8.03-8.06 (m, 2H), 9.42 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 52.48, 89.63, 93.02, 123.80, 129.70, 132.18,

133.00, 165.93, 176.45; IR (thin film) 2188s, 1717s, 1645s, 1433s, 1277s cm^{-1} ; mass spectrum, m/z (% rel intensity) 188 M^+ (77), 157 (100), 129 (50), 101 (46), 75 (28). Anal calcd for $\text{C}_{11}\text{H}_8\text{O}_3$: C, 70.21; H, 4.29. Found: C, 70.34; H, 4.48.



3-(4-nitrophenyl)propiolaldehyde 131g: The reaction of 3-(4-nitrophenyl)-prop-2-yn-1-ol **132g** (1.77 g, 10.0 mmol) with $\gamma\text{-MnO}_2$ (4.35 g, 50.0 mmol) was performed according to the general procedure (Procedure D). Ynal **131g** was obtained as a yellow solid (1.22 g, 7.0 mmol, 70%). mp 120-122 $^\circ\text{C}$ (lit.^{63a} mp 122-123 $^\circ\text{C}$); R_f = 0.14 (1:1 CH_2Cl_2 /hexanes). Spectral data for **131g**: ^1H NMR (CDCl_3 , 500 MHz) δ 7.73-7.77 (m, 2H), 8.24-8.28 (m, 2H), 9.44 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 90.59, 90.76, 123.85, 125.97, 133.87, 148.80, 176.10; IR (thin film) 2197s, 1657s, 1593, 1516s, 1345s, 1290s cm^{-1} ; mass spectrum, m/z (% rel intensity) 175 M^+ (100), 147 (20), 128 (29), 101 (63), 89 (25), 75 (55).



3-(naphthalen-1-yl)propiolaldehyde 131j:^{63e} The reaction of 3-(naphthalen-1-yl)prop-2-yn-1-ol **132j** (3.64 g, 20.0 mmol) with $\gamma\text{-MnO}_2$ (8.69 g, 100.0 mmol) was performed according to the general procedure (Procedure D). The crude mixture was purified by column chromatography on silica gel (50 mm x 200 mm, CH_2Cl_2 /hexanes 1:1) to

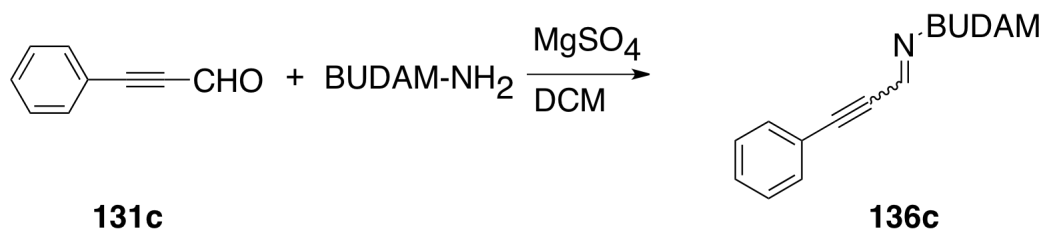
afford **131j** as an orange oil (2.60 g, 14.4 mmol, 72%). $R_f = 0.25$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **131j**: ^1H NMR (CDCl_3 , 500 MHz) δ 7.46-7.50 (m, 1H), 7.54-7.59 (m, 1H), 7.61-7.65 (m, 1H), 7.86-7.90 (m, 2H), 7.98 (d, 1H, $J = 8.0$ Hz), 8.32 (dd, 1H, $J = 8.5, 0.5$ Hz), 9.56 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 93.09, 93.44, 116.93, 125.17, 125.62, 127.06, 127.86, 128.59, 132.13, 133.01, 133.58, 133.73, 176.62; IR (thin film) 3059m, 2857m, 2203s, 2184s, 1653s, 1508, 1397s, 1283s cm^{-1} .

6.1.3 Preparation of alkynyl imines

General procedure for the preparation of the aldimines – illustrated for the synthesis of

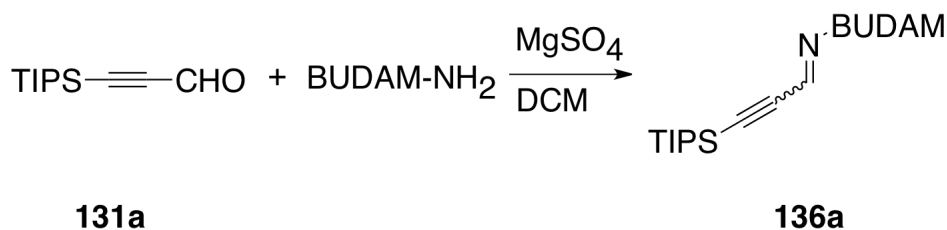
1,1-bis(3,5-di-tert-butyl-4-methoxyphenyl)-N-(3-phenylprop-2-yn-1-ylidene)methanamine

136c (Procedure E)^{27a,26h,26j}



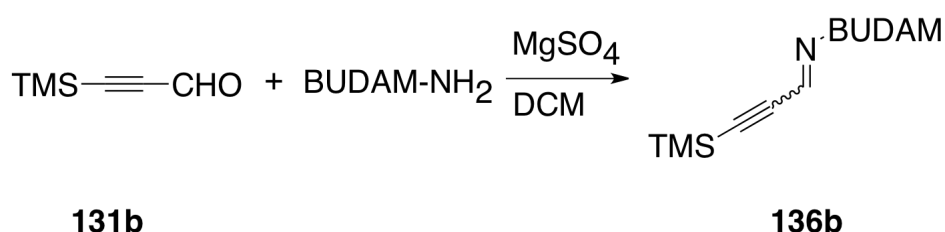
To a flame dried 100 mL round bottom flask filled with argon was added MgSO_4 (4.0 g, 33.3 mmol) and dried DCM (40 mL). This was followed by the addition of bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (4.77 g, 10.2 mmol). After stirring for 5 minutes, phenyl-2-propynal **131c** (1.33 g, 10.2 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. Thereafter, the reaction mixture was filtered through a pad of Celite, concentrated and placed under high vacuum (0.5 mm Hg) for 5 minutes to afford the crude imine as a white solid. Crystallization (1:30 EtOAc/hexanes) afforded **136c** as an off-white

solid (4.79 g, 8.27 mmol, 83%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.63:1 (from ^1H NMR). Spectral data for **136c**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.37 (s, 36H), 3.65 (s, 6H), 6.17 (s, 1H), 7.20 (s, 4H), 7.30-7.41 (m, 3H), 7.51-7.55 (m, 2H), 7.87 (d, 1H, J = 1.0 Hz); *trans* isomer: δ 1.38 (s, 36H), 3.65 (s, 6H), 5.40 (s, 1H), 7.11 (s, 4H), 7.30-7.41 (m, 3H), 7.51-7.55 (m, 2H), 7.92 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.08, 35.79, 35.80, 64.15, 64.19, 72.67, 79.17, 82.72, 87.00, 91.98, 97.20, 121.41, 121.73, 126.22, 128.39, 128.55, 129.43, 129.74, 132.15, 132.29, 136.17, 136.87, 141.58, 143.19, 143.31, 144.50, 158.42, 158.58; IR (thin film) 2961s, 2870s, 2207m, 1412s, 1221s cm^{-1} ; mass spectrum, m/z (% rel intensity) 580 $\text{M}^+ + 1$ (10), 451 (23), 183 (10), 114 (37), 57 (100). Anal calcd for $\text{C}_{40}\text{H}_{53}\text{NO}_2$: C, 82.85; H, 9.21; N, 2.42. Found: C, 82.70; H, 9.51; N, 2.35.



1,1-Bis(3,5-di-tert-butyl-4-methoxyphenyl)-N-(3-(triisopropylsilyl)prop-2-yn-1-ylidene)methanamine **19a**: The reaction of **131a** (2.31 g, 11.0 mmol) with bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (5.14 g, 11.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:30 EtOAc/hexanes) afforded **136a** as a white solid (6.14 g, 9.30 mmol, 85%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 2.68:1 (from ^1H NMR). Spectral data for **136a**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.08-1.13 (m, 21H), 1.37 (s, 18H), 3.65 (s, 6H), 6.24 (s, 1H), 7.18 (s, 4H), 7.64 (s, 1H); *trans* isomer: δ 1.07-1.12 (m, 21H), 1.36 (s, 18H), 3.65 (s, 6H), 5.33 (s,

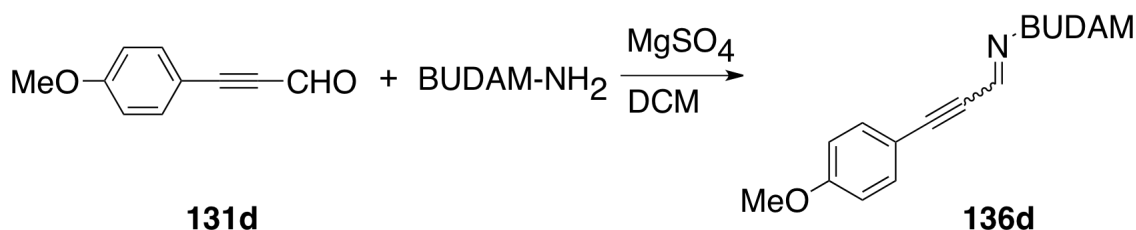
1H), 7.06 (s, 4H), 7.73 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 11.13, 11.15, 18.53, 18.65, 32.05, 35.76, 35.79, 64.12, 64.18, 73.19, 78.78, 95.76, 98.93, 100.70, 103.87, 126.09, 126.27, 136.10, 136.64, 140.95, 143.23, 143.25, 144.61, 158.46, 158.55; IR (thin film): 2961s, 2869s, 1593s, 1414s, 1221s cm^{-1} ; mass spectrum m/z (% rel intensity): 660 M^+ (<1), 451 (9), 183 (10), 155 (100), 108 (30). Anal calcd for $\text{C}_{43}\text{H}_{69}\text{NO}_2\text{Si}$: C, 78.24; H, 10.54; N, 2.12. Found: C, 78.62; H, 10.97; N, 2.15.



(*E*)-1,1-Bis(3,5-di-*tert*-butyl-4-methoxyphenyl)-*N*-(3-(trimethylsilyl)prop-2-yn-1-ylidene)methanamine

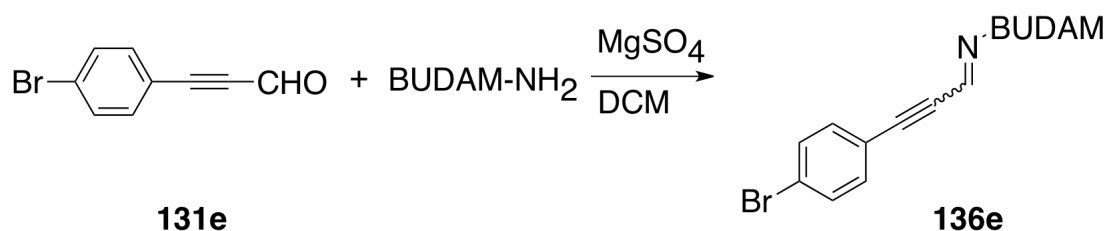
136b: The reaction of **131b** (2.07 g, 16.5 mmol) with bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (7.01 g, 15.0 mmol) was performed according to the general procedure for imine formation (Procedure E). The crude product was a mixture of *cis:trans* imines in a ratio of 1.5 : 1, and was purified by crystallization (1: 30 EtOAc/hexanes) to afford **136b** as a white solid as a mixture of *cis:trans* isomers in a ratio of 19 : 1 (6.46 g, 11.2 mmol, 75%); mp 142-143 °C. The major isomer was assigned as *cis* based on NOE studies. Irradiation of the methine proton in the minor isomer (δ = 7.66 ppm) gave an enhancement in the imine proton at δ = 5.32, but irradiation of the methine proton in the major isomer (δ = 7.62) gave no enhancement at the imine proton at δ = 6.15. The *cis* isomer (19:1) was observed to isomerize to a mixture of *cis* and *trans* isomers slowly in solution over a few

hours. Spectral data for *cis*-**136b**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.26 (s, 9H), 1.37 (s, 36H), 3.65 (s, 6H), 6.15 (s, 1H), 7.15 (s, 4H), 7.62 (d, 1H, $J = 1.5$ Hz); *trans*-**136b**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.20 (s, 9H), 1.36 (s, 36H), 3.64 (s, 6H), 5.32 (s, 1H), 7.06 (s, 4H), 7.66 (s, 1H). The following data were collected on the 19:1 mixture of *cis:trans* isomers: ^{13}C (CDCl_3 , 125 MHz) δ -0.42, 32.06, 35.75, 64.15, 72.55, 76.57, 97.12, 126.22, 136.62, 141.25, 143.16, 158.44; IR (thin film) 2961s, 1412s, 1221s, 849s cm^{-1} ; mass spectrum, m/z (% rel intensity) 575 M^+ (10), 451 (100), 421 (9), 379 (7), 218 (15), 197 (11), 182 (30), 168 (11), 128 (10), 110 (10), 83 (19), 73 (64), 57 (97), 41 (45). HRMS (EI+) m/z calcd for $\text{C}_{37}\text{H}_{57}\text{NO}_2\text{Si}$ (M^+) 575.4159, meas 575.4136.



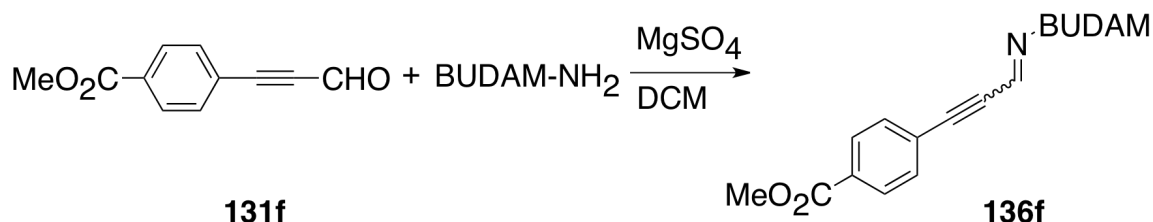
1,1-Bis(3,5-di-tert-butyl-4-methoxyphenyl)-N-(3-(4-methoxyphenyl)prop-2-yn-1-ylidene)methanamine 136d: The reaction of **131d** (1.60 g, 10.0 mmol) with bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (4.67 g, 10.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:30 EtOAc/hexanes) afforded **136d** as a white solid (3.97 g, 6.52 mmol, 65%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 1.30:1 (from ^1H NMR). Spectral data for **136d**: ^1H NMR (CDCl_3 , 300 MHz): *cis* isomer: δ 1.37 (s, 36H), 3.65 (s, 6H), 3.83 (s, 3H), 6.16 (s, 1H), 6.87-6.91 (m, 2H), 7.20 (s, 4H), 7.45-7.47 (m, 2H), 7.84 (d, 1H, $J = 2.5$ Hz); *trans* isomer: δ 1.37 (s, 36H), 3.65 (s, 6H), 3.80 (s, 3H), 5.38 (s, 1H), 6.83-6.87 (m, 2H), 7.10 (s, 4H), 7.47-7.50 (m,

2H), 7.90 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.08, 35.78, 35.79, 55.30, 55.36, 64.15, 64.18, 72.46, 79.09, 82.16, 86.26, 92.49, 97.75, 113.38, 113.71, 114.10, 114.26, 126.24, 133.87, 133.96, 136.28, 136.98, 141.84, 143.13, 143.25, 144.65, 158.38, 158.54, 160.57, 160.82; IR (thin film) 2961s, 2870s, 2188s, 1597s, 1510s, 1412s, 1254s, 1223s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{41}\text{H}_{56}\text{NO}_3$ ($\text{M}+\text{H}^+$) 610.4260, meas 610.4269.



N-(3-(4-Bromophenyl)prop-2-yn-1-ylidene)-1,1-bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine **136e**: The reaction of **131e** (2.09 g, 10.0 mmol) with bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (4.67 g, 10.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:30 EtOAc/hexanes) afforded **136e** as a white solid (4.76 g, 7.23 mmol, 72%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.56:1 (from ^1H NMR). Spectral data for **136e**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.36 (s, 36H), 3.65 (s, 6H), 6.13 (s, 1H), 7.18 (s, 4H), 7.36-7.38 (m, 2H), 7.50-7.53 (m, 2H), 7.85 (d, 1H, J = 1.5 Hz); *trans* isomer: δ 1.37 (s, 36H), 3.65 (s, 6H), 5.40 (s, 1H), 7.10 (s, 4H), 7.38-7.40 (m, 2H), 7.45-7.48 (m, 2H), 7.89 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.08, 35.80, 35.81, 64.16, 64.20, 72.81, 79.24, 83.59, 87.95, 90.66, 95.90, 120.30, 120.66, 123.98, 124.35, 126.17, 126.19, 131.75, 131.94, 133.46, 133.63, 136.05, 136.73, 141.28, 143.25, 143.36, 144.23, 158.47, 158.62; IR (thin film) 2961s, 2209m, 1607s,

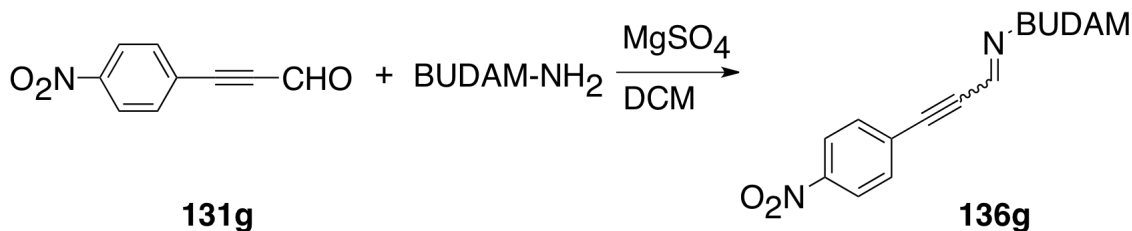
1485s, 1412s, 1221s cm^{-1} ; mass spectrum, m/z (% rel intensity) 660 $\text{M}^+ + 1$ (^{81}Br , 16), 658 $\text{M}^+ + 1$ (^{79}Br , 16), 452 (35), 451 (100). Anal calcd for $\text{C}_{40}\text{H}_{52}\text{BrNO}_2$: C, 72.93; H, 7.96; N, 2.13. Found: C, 72.80; H, 8.20; N, 2.05.



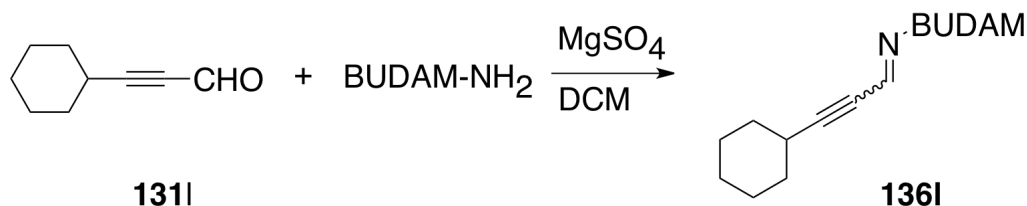
*Methyl 4-(3-((bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl)imino)prop-1-yn-1-yl)benzoate* **136f**:

The reaction of **131f** (1.88 g, 10.0 mmol) with bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (4.67 g, 10.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:30 EtOAc/hexanes) afforded **136f** as a white solid (5.10 g, 8.00 mmol, 80%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.64:1 (from ^1H NMR). Spectral data for **136f**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.36 (s, 36H), 3.65 (s, 6H), 3.93 (s, 3H), 6.15 (s, 1H), 7.19 (s, 4H), 7.57-7.59 (m, 2H), 7.89 (d, 1H, J = 1.5 Hz), 8.03-8.05 (m, 2H); *trans* isomer: δ 1.37 (s, 36H), 3.65 (s, 6H), 3.91 (s, 3H), 5.14 (s, 1H), 7.11 (s, 4H), 7.58-7.60 (m, 2H), 7.92 (s, 1H), 7.98-8.01 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.07, 35.79, 35.80, 52.27, 52.35, 64.16, 64.19, 72.94, 79.30, 84.77, 89.26, 90.60, 95.85, 125.87, 126.16, 126.17, 126.28, 129.50, 129.65, 130.61, 130.94, 132.02, 132.16, 136.01, 136.68, 141.12, 143.28, 143.38, 144.10, 158.49, 158.63, 166.18, 166.28; IR (thin film) 2961s, 2870s, 2209m, 1728s, 1609s, 1412s, 1277s, 1223s cm^{-1} ;

mass spectrum, m/z (% rel intensity) 638 $M^+ + 1$ (23), 550 (9), 452 (35), 451 (100). Anal calcd for $C_{42}H_{55}NO_4$: C, 79.08; H, 8.69; N, 2.20. Found: C, 78.71; H, 8.68; N, 2.20.

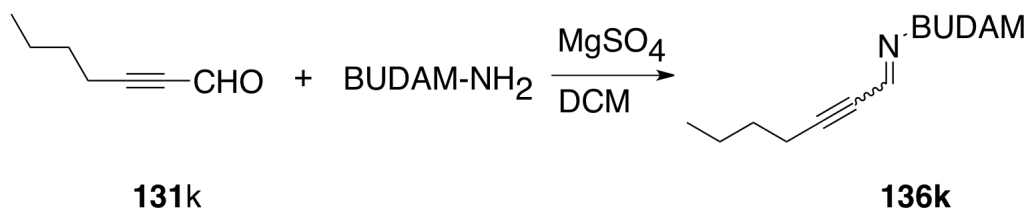


1,1-Bis(3,5-di-tert-butyl-4-methoxyphenyl)-N-(3-(4-nitrophenyl)prop-2-yn-1-ylidene)methanamine **136g**: The reaction of **131g** (1.75 g, 10.0 mmol) with bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (4.67 g, 10.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:25 EtOAc/hexanes) afforded **136g** as a white solid (5.70 g, 9.13 mmol, 91%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.77:1 (from ^1H NMR). Spectral data for **136g**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.36 (s, 36H), 3.65 (s, 6H), 6.11 (s, 1H), 7.17 (s, 4H), 7.65-7.67 (m, 2H), 7.91 (d, 1H, $J = 1.0$ Hz), 8.23-8.26 (m, 2H); *trans* isomer: δ 1.37 (s, 36H), 3.65 (s, 6H), 5.43 (s, 1H), 7.10 (s, 4H), 7.67-7.69 (m, 2H), 7.92 (s, 1H), 8.18-8.21 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.06, 35.82, 64.18, 64.20, 73.24, 79.41, 86.33, 88.93, 91.03, 94.16, 123.62, 123.79, 126.09, 126.15, 128.00, 128.47, 132.87, 133.01, 135.82, 136.49, 140.59, 143.38, 143.48, 143.71, 147.80, 148.01, 158.58, 158.71; IR (thin film) 2963s, 2870s, 2209w, 1597s, 1524s, 1414s, 1346s, 1223s cm^{-1} ; HRMS (ESI+) m/z calcd for $C_{40}H_{53}N_2O_4$ ($M+H^+$) 625.4005, meas 625.3979.



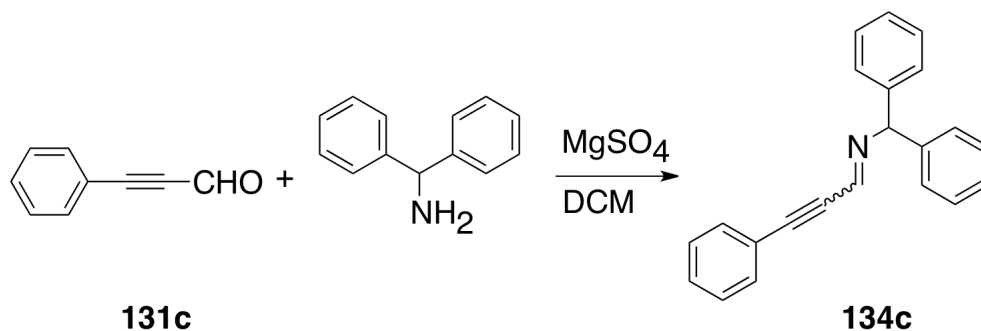
N-(3-Cyclohexylprop-2-yn-1-ylidene)-1,1-bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine

136I: The reaction of **131I** (1.42 g, 10.0 mmol) with bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (4.67 g, 10.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:40 EtOAc/hexanes) afforded **136I** as a white solid (4.89 g, 8.36 mmol, 84%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 3.47:1 (from ^1H NMR). Spectral data for **136I**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.28-1.37 (m, 3H), 1.36 (s, 36H), 1.49-1.55 (m, 3H), 1.72-1.77 (m, 2H), 1.80-1.86 (m, 2H), 2.61-2.67 (m, 1H), 3.65 (s, 6H), 6.11 (s, 1H), 7.15 (s, 4H), 7.61 (s, 1H); *trans* isomer: δ 1.28-1.37 (m, 3H), 1.37 (s, 36H), 1.49-1.55 (m, 3H), 1.72-1.77 (m, 2H), 1.80-1.86 (m, 2H), 2.48-2.54 (m, 1H), 3.64 (s, 6H), 5.29 (s, 1H), 7.07 (s, 4H), 7.70 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 24.55, 24.86, 25.72, 25.77, 29.50, 29.63, 32.02, 32.07, 35.75, 35.77, 64.14, 64.17, 72.13, 75.21, 78.82, 78.98, 98.40, 103.44, 126.20, 136.37, 136.93, 141.99, 143.08, 143.16, 144.96, 158.34, 158.46; IR (thin film) 2959s, 2863s, 2207m, 1609s, 1449s, 1412s, 1221s cm^{-1} ; mass spectrum, m/z (% rel intensity) 586 $\text{M}^+ + 1$ (46), 452 (40), 451 (100). Anal calcd for $\text{C}_{40}\text{H}_{59}\text{NO}_2$: C, 82.00; H, 10.15; N, 2.39. Found: C, 81.68; H, 10.52; N, 2.33.

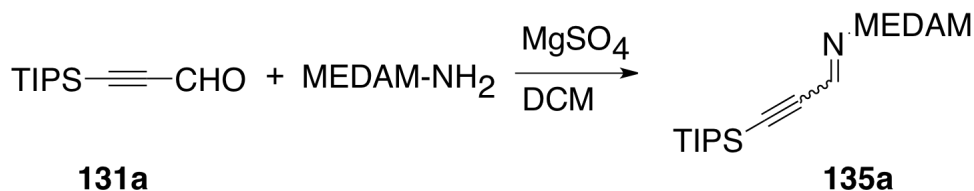


1,1-Bis(3,5-di-tert-butyl-4-methoxyphenyl)-N-(hept-2-yn-1-ylidene)methanamine **136k**:

The reaction of **131k** (1.28 g, 11.6 mmol) with bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (5.43 g, 11.6 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:40 EtOAc/hexanes) afforded **136k** as a white solid (3.81 g, 6.82 mmol, 59%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 10.6:1 (from ^1H NMR). Spectral data for **136k**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 0.94 (t, 3H, $J = 7.0$ Hz), 1.37 (s, 36H), 1.45-1.51 (m, 2H), 1.55-1.62 (m, 2H), 2.43 (td, 2H, $J = 7.0, 1.0$ Hz), 3.65 (s, 6H), 6.09 (s, 1H), 7.15 (s, 4H), 7.60 (d, 1H, $J = 1.0$ Hz); *trans* isomer: δ 0.89 (t, 3H, $J = 7$ Hz), 1.35 (s, 36H), 1.41-1.47 (m, 2H), 1.53-1.60 (m, 2H), 2.35 (t, 2H, $J = 7.0$ Hz), 3.64 (s, 6H), 5.29 (s, 1H), 7.07 (s, 4H), 7.68 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.52, 13.55, 19.78, 21.98, 22.01, 30.10, 30.27, 32.07, 35.76, 64.14, 64.17, 72.16, 75.24, 78.98, 94.56, 99.80, 126.16, 126.19, 136.40, 136.92, 141.93, 143.07, 143.16, 144.76, 158.34, 158.46; IR (thin film) 2961s, 2870s, 2207w, 1559m, 1456s, 1412s, 1221s cm^{-1} ; mass spectrum, m/z (% rel intensity) 560 $\text{M}^+ + 1$ (32), 466 (9), 452 (70), 451 (100). Anal calcd for $\text{C}_{38}\text{H}_{57}\text{NO}_2$: C, 81.52; H, 10.26; N, 2.50. Found: C, 81.55; H, 10.52; N, 2.52.

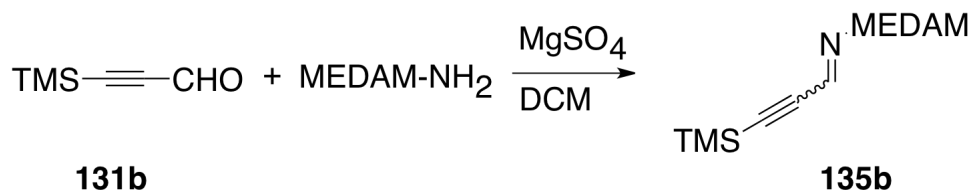


1,1-Diphenyl-N-(3-phenylprop-2-yn-1-ylidene)methanamine 134c: The reaction of **131c** (1.30 g, 10.0 mmol) with benzhydramine (1.83 g, 10.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:30 EtOAc/hexanes) afforded **134c** as an off-white solid (2.72 g, 9.22 mmol, 92%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.22:1 (from ^1H NMR). Spectral data for **134c**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 6.28 (s, 1H), 7.21-7.26 (m, 2H), 7.29-7.42 (m, 11H), 7.50-7.54 (m, 2H), 7.90 (d, 1H, $J = 1.5$ Hz); *trans* isomer: δ 5.54 (s, 1H), 7.21-7.26 (m, 2H), 7.29-7.42 (m, 11H), 7.50-7.54 (m, 2H), 7.88 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 72.64, 78.83, 82.26, 86.66, 92.61, 97.83, 121.13, 121.46, 127.07, 127.24, 127.71, 128.40, 128.46, 128.53, 128.58, 129.54, 129.89, 132.16, 132.25, 142.61, 142.65, 143.30, 145.45; IR (thin film) 3061s, 3027s, 2209s, 1609s, 1491s, 1453s, 1364m cm^{-1} . Anal calcd for $\text{C}_{22}\text{H}_{17}\text{N}$: C, 89.46; H, 5.80; N, 4.74. Meas: C, 89.21; H, 5.98; N, 4.72.



1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-(triisopropylsilyl)prop-2-yn-1-ylidene)methanamine 135a: The reaction of **131a** (420 mg, 2.00 mmol) with

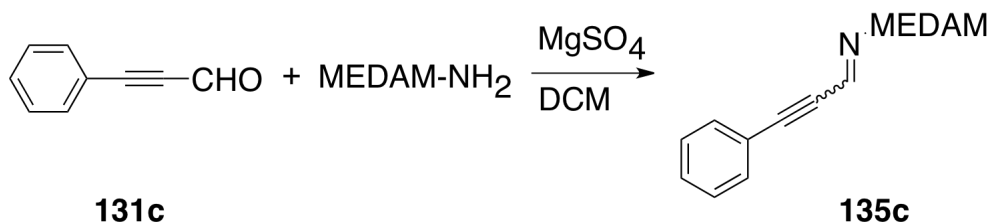
bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). The crude product was obtained as a yellow liquid and was used without purification. Imine **135a** was produced as a mixture of *trans* and *cis* isomers. *Cis:trans* = 2.36 :1 (from ^1H NMR). Spectral data for **135a**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.10-1.14 (m, 21H), 2.24 (s, 12H), 3.68 (s, 6H), 6.09 (s, 1H), 7.00 (d, 4H, $J = 0.5$ Hz), 7.65 (d, 1H, $J = 1.5$ Hz); *trans* isomer: δ 1.07-1.10 (m, 21H), 2.25 (s, 12H), 3.68 (s, 6H), 5.24 (s, 1H), 6.93 (s, 4H), 7.64 (d, 1H, $J = 1.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 11.09, 11.15, 16.14, 16.16, 18.53, 18.56, 59.58, 59.59, 72.00, 78.25, 96.45, 98.74, 101.84, 103.57, 127.82, 127.92, 130.70, 130.77, 137.98, 138.60, 141.92, 144.92, 155.90, 156.00; IR (thin film) 2944s, 2867s, 1609s, 1483s, 1221s, 1144s, 1017s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{31}\text{H}_{46}\text{NO}_2\text{Si}$ ($\text{M}+\text{H}^+$) 492.3298, meas 492.3305.



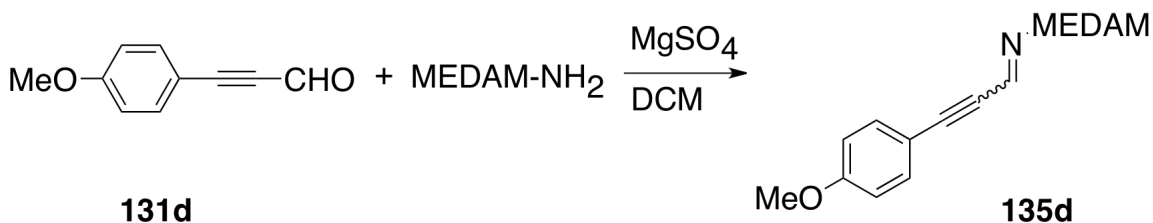
1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-(trimethylsilyl)prop-2-yn-1-ylidene)methanamine

135b: The reaction of **131b** (252 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:60 EtOAc/hexanes) afforded **135b** as a white solid (658 mg, 1.62 mmol, 81%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.34:1 (from ^1H NMR). Spectral data for **135b**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 0.26 (s, 9H), 2.25 (s, 12H), 3.68 (s, 6H), 5.99 (s, 1H), 6.99 (s,

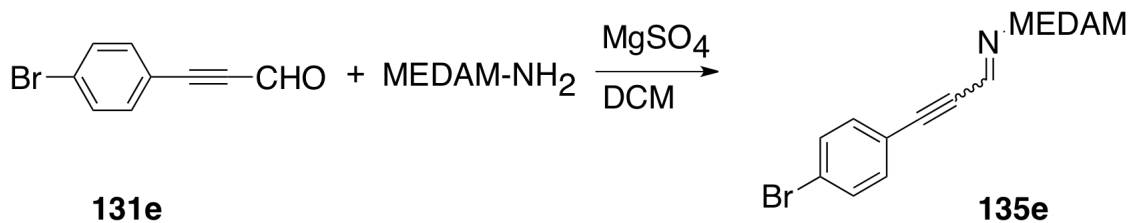
4H), 7.60 (d, 1H, $J = 1.0$ Hz); *trans* isomer: δ 0.21 (s, 9H), 2.24 (s, 12H), 3.68 (s, 6H), 5.22 (s, 1H), 6.92 (s, 4H), 7.58 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ -0.53, -0.52, 16.13, 16.18, 59.58, 71.66, 78.27, 96.86, 99.04, 101.49, 104.92, 127.83, 127.86, 130.66, 130.76, 137.90, 138.65, 141.98, 144.70, 155.88, 156.00; IR (thin film) 2953s, 1609s, 1483s, 1221s, 1144s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{25}\text{H}_{34}\text{NO}_2\text{Si}$ ($\text{M}+\text{H}^+$) 408.2359, meas 408.2372.



1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-phenylprop-2-yn-1-ylidene)methanamine 135c: The reaction of **131c** (1.30 g, 10.0 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (2.99 mg, 10.0 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:30 EtOAc/hexanes) afforded **135c** as an off-white solid (2.72 g, 9.22 mmol, 92%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.48:1 (from ^1H NMR). Spectral data for **135c**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.24 (s, 12H), 3.68 (s, 6H), 6.05 (s, 1H), 7.02 (s, 4H), 7.30-7.42 (m, 3H), 7.50-7.53 (m, 2H), 7.82 (s, 1H); *trans* isomer: δ 2.24 (s, 12H), 3.68 (s, 6H), 5.29 (s, 1H), 6.96 (s, 4H), 7.30-7.42 (m, 3H), 7.50-7.53 (m, 2H), 7.85 (d, 1H, $J = 1.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.16, 16.19, 59.59, 59.60, 71.93, 78.38, 82.32, 86.78, 92.41, 97.71, 121.26, 121.54, 127.83, 127.86, 128.38, 128.56, 129.48, 129.82, 130.72, 130.81, 132.13, 132.22, 138.08, 138.68, 142.01, 144.84, 155.89, 156.01; IR (thin film) 2944s, 2209s, 1609s, 1485s, 1221s, 1144s, 1015s cm^{-1} . Anal calcd for $\text{C}_{28}\text{H}_{29}\text{NO}_2$: C, 81.72; H, 7.10; N, 3.40. Found: C, 81.82; H, 7.02; N, 3.36.

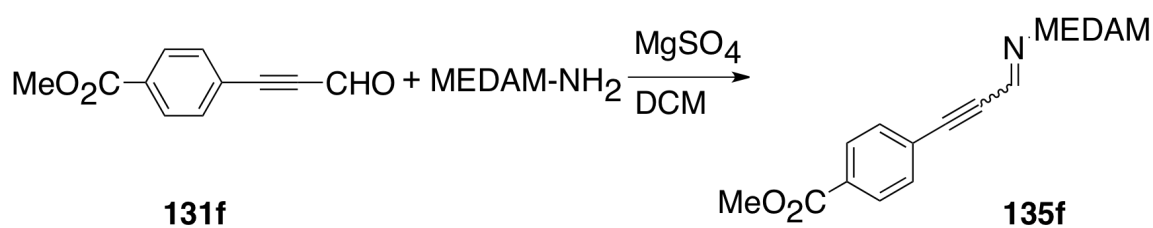


1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-(4-methoxyphenyl)prop-2-yn-1-ylidene)methanamine **135d**: The reaction of **131d** (320 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). The crude product was obtained as a yellow foamy solid and was used without purification. Imine **135d** was produced as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.67:1 (from ^1H NMR). Spectral data for **135d**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.25 (s, 12H), 3.68 (s, 6H), 3.83 (s, 3H), 6.06 (s, 1H), 6.90 (d, 2H, $J = 9.0$ Hz), 7.03 (s, 4H), 7.46 (d, 2H, $J = 9.0$ Hz), 7.84 (d, 1H, $J = 1.5$ Hz); *trans* isomer: δ 2.25 (s, 12H), 3.68 (s, 6H), 3.80 (s, 3H), 5.29 (s, 1H), 6.84 (d, 2H, $J = 9.0$ Hz), 6.97 (s, 4H), 7.47 (d, 2H, $J = 9.0$ Hz), 7.81 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.14, 16.17, 55.26, 55.33, 59.57, 71.73, 78.29, 81.79, 86.04, 92.94, 98.31, 113.20, 113.50, 114.06, 114.24, 127.83, 127.87, 130.66, 130.75, 133.85, 133.89, 138.20, 138.79, 142.25, 144.98, 155.84, 155.96, 160.56, 160.84; IR (thin film) 2938s, 2201s, 1599s, 1510s, 1483s, 1221s, 1144s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_3$ ($\text{M}+\text{H}^+$) 442.2382, meas 442.2380.



N-(3-(4-Bromophenyl)prop-2-yn-1-ylidene)-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine

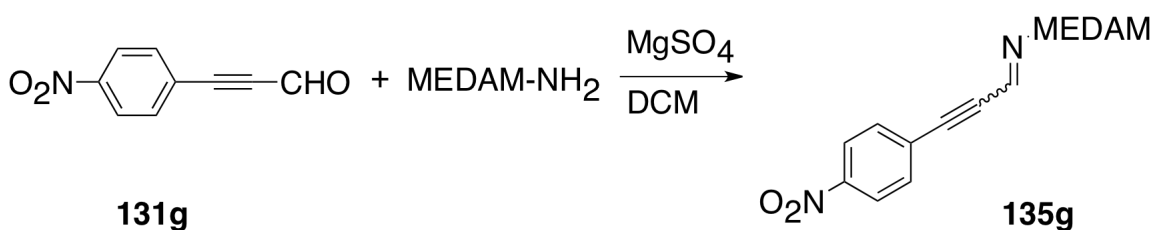
135e: The reaction of **131e** (418 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). The crude product was obtained as a yellow foamy solid and was used without purification. Imine **135e** was produced as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.51:1 (from ^1H NMR). Spectral data for **135e**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.24 (s, 12H), 3.68 (s, 6H), 6.01 (s, 1H), 7.01 (s, 4H), 7.36 (d, 2H, $J = 8.0$ Hz), 7.52 (d, 2H, $J = 8.0$ Hz), 7.83 (s, 1H); *trans* isomer: δ 2.24 (s, 12H), 3.68 (s, 6H), 5.30 (s, 1H), 6.95 (s, 4H), 7.37 (d, 2H, $J = 8.0$ Hz), 7.46 (d, 2H, $J = 8.0$ Hz), 7.79 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.17, 16.21, 59.61, 72.09, 78.44, 83.17, 87.72, 91.07, 96.44, 120.16, 120.49, 124.04, 124.43, 127.81, 127.82, 130.77, 130.87, 131.75, 131.93, 133.46, 133.57, 137.96, 138.56, 141.71, 144.59, 155.94, 156.05; IR (thin film) 2942s, 2209s, 1609s, 1486s, 1221s, 1144s, 1010s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{28}\text{H}_{29}\text{NO}_2$ ^{79}Br ($\text{M}+\text{H}^+$) 490.1382, meas 490.1365.



Methyl 4-(3-((bis(4-methoxy-3,5-dimethylphenyl)methyl)imino)prop-1-yn-1-yl)benzoate **135f**:

The reaction of **131f** (376 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:60

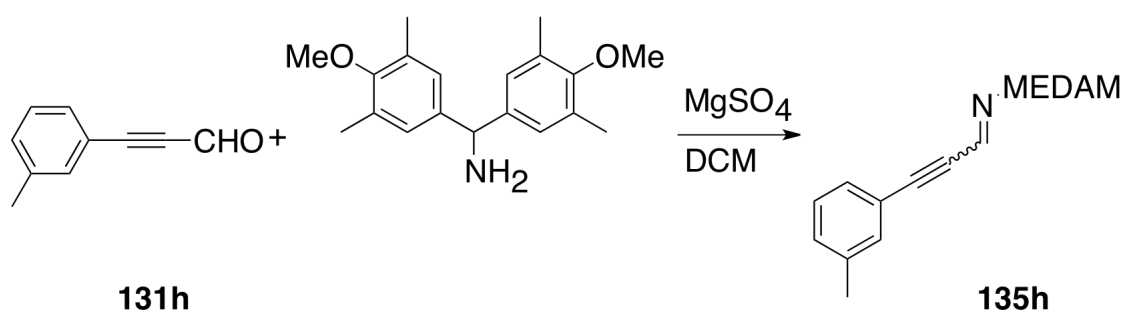
EtOAc/hexanes) afforded **135f** as an off-white solid (910 mg, 1.94 mmol, 97%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.52:1 (from ^1H NMR). Spectral data for **135f**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.25 (s, 12H), 3.68 (s, 6H), 3.93 (s, 3H), 6.04 (s, 1H), 7.02 (s, 4H), 7.55-7.58 (m, 2H), 7.87 (d, 1H, $J = 1.0$ Hz), 8.03-8.06 (m, 2H); *trans* isomer: δ 2.25 (s, 12H), 3.68 (s, 6H), 3.90 (s, 3H), 5.32 (s, 1H), 6.96 (s, 4H), 7.56-7.59 (m, 2H), 7.82 (s, 1H), 7.98-8.01 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.14, 16.18, 52.26, 52.35, 59.58, 72.19, 78.45, 84.32, 89.02, 90.95, 96.34, 125.71, 126.09, 127.79, 127.81, 129.47, 129.62, 130.61, 130.77, 130.86, 130.95, 132.00, 132.08, 137.89, 138.49, 141.54, 144.45, 155.95, 156.06, 166.13, 166.23; IR (thin film) 2951s, 2211s, 1727s, 1609s, 1484s, 1221s, 1142s, 1019s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{30}\text{H}_{32}\text{NO}_4$ ($\text{M}+\text{H}^+$) 470.2331, meas 470.2352.



1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-(4-nitrophenyl)prop-2-yn-1-ylidene)methanamine

135g: The reaction of **131g** (350 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). The crude product was obtained as a yellow foamy solid and was used without purification. Imine **135g** was produced as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.35:1 (from ^1H NMR). Spectral data for **135g**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.25 (s, 12H), 3.68 (s, 6H), 6.00 (s, 1H), 6.99 (s, 4H), 7.65 (d, 2H, $J = 9.0$ Hz), 7.89 (d, 1H, $J = 1.0$ Hz), 8.25 (d, 2H, $J = 9.0$ Hz); *trans* isomer: δ 2.25

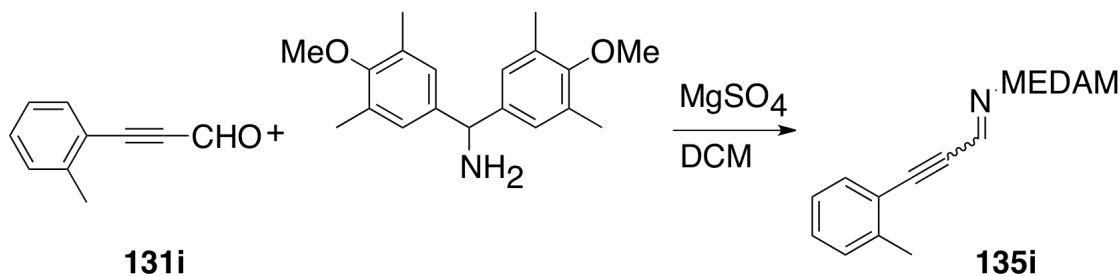
(s, 12H), 3.68 (s, 6H), 5.33 (s, 1H), 6.95 (s, 4H), 7.66 (d, 2H, $J = 9.0$ Hz), 7.82 (s, 1H), 8.20 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.14, 16.18, 59.57, 72.47, 78.52, 85.82, 89.23, 90.75, 94.61, 123.58, 123.73, 127.73, 127.75, 127.80, 128.24, 130.83, 130.92, 132.84, 132.92, 137.68, 138.29, 140.98, 144.06, 147.72, 147.94, 156.01, 156.10; IR (thin film) 2940s, 2211m, 1595s, 1522s, 1484s, 1345s, 1221s, 1142s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$) 457.2127, meas 457.2147.



1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-(m-tolyl)prop-2-yn-1-ylidene)methanamine **135h**:

The reaction of **131h** (288 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). The crude product was obtained as a yellow semi-solid and was used without purification. Imine **135h** was produced as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.59:1 (from ^1H NMR). Spectral data for **135h**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.25 (s, 12H), 2.37 (s, 3H), 3.69 (s, 6H), 6.07 (s, 1H), 7.04 (s, 4H), 7.16-7.29 (m, 2H), 7.32-7.35 (m, 2H), 7.85 (d, 1H, $J = 1.0$ Hz); *trans* isomer: δ 2.25 (s, 12H), 2.32 (s, 3H), 3.69 (s, 6H), 5.30 (s, 1H), 6.98 (s, 4H), 7.16-7.29 (m, 2H), 7.32-7.35 (m, 2H), 7.82 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.15, 16.19, 21.15, 21.19, 59.59, 71.88, 78.37, 82.07, 86.51, 92.58, 98.02, 121.07, 121.34, 127.83, 127.88, 128.27, 128.45, 129.24,

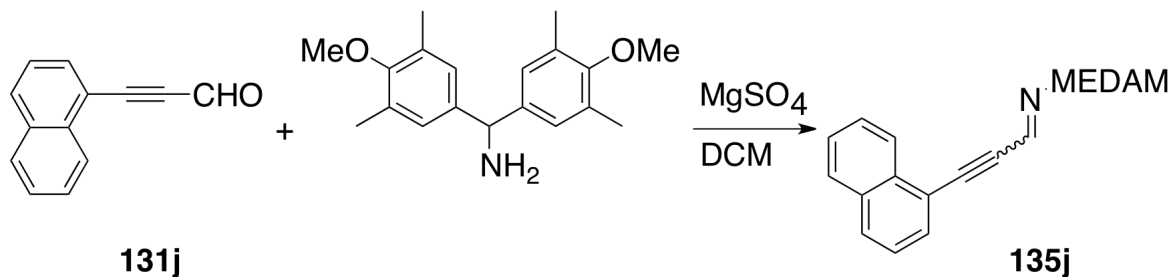
129.33, 130.41, 130.69, 130.73, 130.79, 132.62, 132.74, 138.10, 138.13, 138.34, 138.72, 142.11, 144.87, 155.88, 156.00; IR (thin film) 2942s, 2205s, 1609s, 1484s, 1219s, 1142s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_2$ ($\text{M}+\text{H}^+$) 426.2433, meas 426.2420.



1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-(o-tolyl)prop-2-yn-1-ylidene)methanamine **135i**:

The reaction of **131i** (288 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:60 EtOAc/hexanes) afforded **135i** as a white solid (750 mg, 1.76 mmol, 88%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.88:1 (from ^1H NMR). Spectral data for **135i**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.25 (s, 12H), 2.49 (s, 3H), 3.68 (s, 6H), 6.11 (s, 1H), 7.03 (s, 4H), 7.18-7.21 (m, 2H), 7.31 (t, 1H, $J = 7.5$ Hz), 7.49 (t, 1H, $J = 7.5$ Hz), 7.90 (s, 1H); *trans* isomer: δ 2.26 (s, 12H), 2.46 (s, 3H), 3.69 (s, 6H), 5.31 (s, 1H), 6.98 (s, 4H), 7.14 (t, 1H, $J = 7.5$ Hz), 7.24-7.27 (m, 2H), 7.49 (t, 1H, $J = 7.5$ Hz), 7.88 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.17, 16.19, 20.69, 20.81, 59.59, 59.60, 72.05, 78.39, 86.07, 90.49, 91.54, 96.70, 121.13, 121.35, 125.60, 125.80, 127.82, 127.86, 129.46, 129.52, 129.72, 129.89, 130.73, 130.81, 132.67, 132.68, 138.14, 138.66, 140.92, 141.05, 142.02, 144.94, 155.90, 156.01; IR (thin film) 2940s, 2197s,

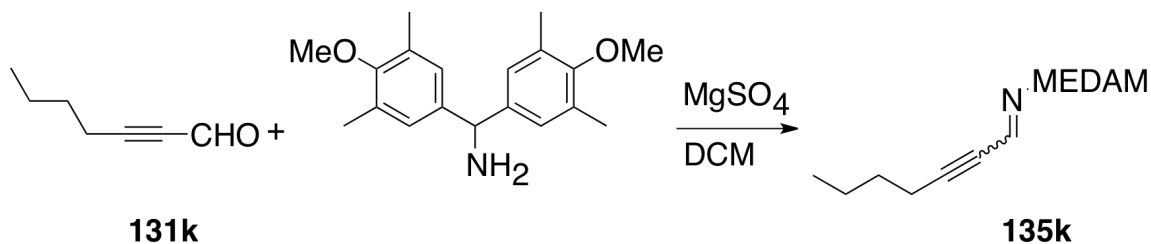
1607s, 1484s, 1221s, 1144s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_2$ ($\text{M}+\text{H}^+$) 426.2433, meas 426.2438.



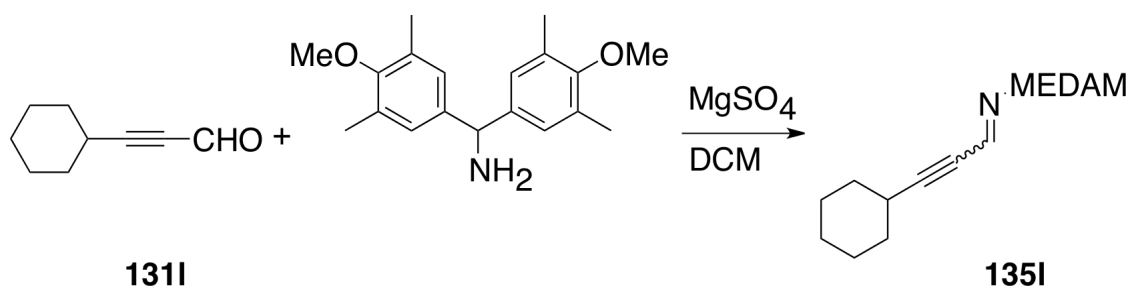
1,1-Bis(4-methoxy-3,5-dimethylphenyl)-N-(3-(naphthalen-1-yl)prop-2-yn-1-ylidene)methanamine

135j: The reaction of **131j** (360 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:60 EtOAc/hexanes) afforded **135j** as an off-white solid (798 mg, 1.73 mmol, 87%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.36 :1 (from ^1H NMR). Spectral data for **135j**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 2.27 (s, 12H), 3.70 (s, 6H), 6.24 (s, 1H), 7.10 (s, 4H), 7.47 (t, 1H, $J = 8.0$ Hz), 7.49-7.59 (m, 2H), 7.76-7.80 (m, 1H), 7.88 (d, 1H, $J = 8.0$ Hz), 7.92 (d, 1H, $J = 8.0$ Hz), 8.03 (d, 1H, $J = 1.0$ Hz), 8.26 (d, 1H, $J = 8.0$ Hz); *trans* isomer: δ 2.28 (s, 12H), 3.70 (s, 6H), 5.38 (s, 1H), 7.02 (s, 4H), 7.43 (t, 1H, $J = 8.0$ Hz), 7.49-7.59 (m, 2H), 7.76-7.80 (m, 1H), 7.85 (d, 1H, $J = 8.0$ Hz), 7.87 (d, 1H, $J = 8.0$ Hz), 7.99 (s, 1H), 8.37 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.18, 16.21, 59.58, 59.59, 72.27, 78.41, 86.90, 90.70, 91.49, 95.94, 118.87, 119.18, 125.13, 125.18, 125.81, 126.08, 126.60, 126.75, 127.08, 127.31, 127.85, 127.91, 128.30, 128.48, 130.06, 130.44, 130.78, 130.84, 131.70, 131.75, 133.02, 133.09, 133.13, 133.27, 138.07, 138.71, 142.03, 144.89, 155.95, 156.05; IR (thin film) 2944s, 2201s, 1605s, 1485s,

1221s, 1144s, 1017s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{32}\text{H}_{32}\text{NO}_2$ ($\text{M}+\text{H}^+$) 462.2433, meas 462.2441.

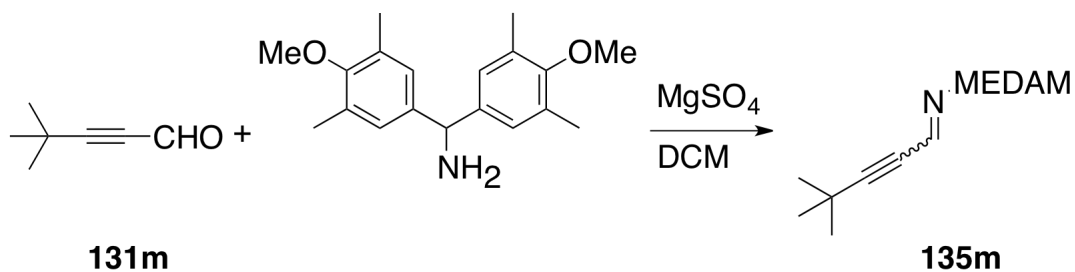


N-(Hept-2-yn-1-ylidene)-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine **135k**: The reaction of **131k** (220 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). The crude product was obtained as an orange liquid was used without purification. Imine **135k** was produced as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.76:1 (from ^1H NMR). Spectral data for **135k**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 0.94 (t, 3H, $J = 7.5$ Hz), 1.37-1.48 (m, 4H), 2.23 (s, 12H), 2.41 (td, 2H, $J = 7.0, 1.5$ Hz), 3.67 (s, 6H), 5.96 (s, 1H), 6.97 (s, 4H), 7.57-7.59 (m, 1H); *trans* isomer: δ 0.89 (t, 3H, $J = 7.5$ Hz), 1.49-1.60 (m, 4H), 2.22 (s, 12H), 2.34 (td, 2H, $J = 7.0, 1.5$ Hz), 3.67 (s, 6H), 5.18 (s, 1H), 6.93 (s, 4H), 7.57-7.59 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.50, 13.52, 16.13, 16.17, 19.05, 19.07, 21.94, 21.98, 30.05, 30.14, 59.57, 71.37, 74.93, 78.18, 78.77, 95.01, 100.55, 127.74, 127.82, 130.60, 130.70, 138.35, 138.81, 142.23, 145.06, 155.81, 155.91; IR (thin film) 2934s, 2865s, 2220s, 1611s, 1484s, 1221s, 1144s, 1017s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{26}\text{H}_{34}\text{NO}_2$ ($\text{M}+\text{H}^+$) 392.2590, meas 392.2608.



N-(3-Cyclohexylprop-2-yn-1-ylidene)-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine **135I**:

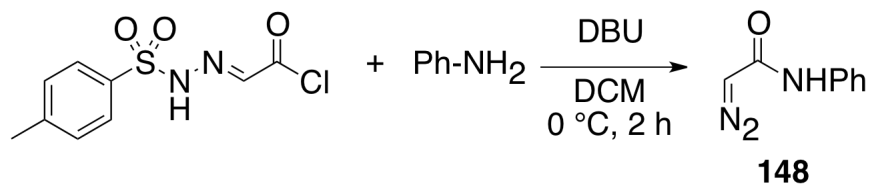
The reaction of **131I** (272 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:60 EtOAc/hexanes) afforded **135I** as an off-white solid (755 mg, 1.81 mmol, 91%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.92:1 (from ^1H NMR). Spectral data for **135I**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.28-1.84 (m, 10H), 2.60-2.65 (m, 1H), 2.25 (s, 12H), 3.68 (s, 6H), 5.97 (s, 1H), 6.99 (s, 4H), 7.62 (s, 1H); *trans* isomer: δ 1.28-1.84 (m, 10H), 2.49-2.54 (m, 1H), 2.24 (s, 12H), 3.67 (s, 6H), 5.20 (s, 1H), 6.94 (s, 4H), 7.62 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.12, 16.16, 24.53, 24.83, 25.66, 25.70, 29.49, 29.61, 31.94, 59.56, 71.26, 74.91, 78.18, 78.63, 98.86, 104.26, 127.77, 127.83, 130.58, 130.67, 138.29, 138.86, 142.61, 145.24, 155.77, 155.88; IR (thin film) 2932s, 2216s, 1611s, 1483s, 1221s, 1144s, 1017s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{28}\text{H}_{36}\text{NO}_2$ ($\text{M}+\text{H}^+$) 418.2746, meas 418.2762.



N-(4,4-Dimethylpent-2-yn-1-ylidene)-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine **135m**:

The reaction of **131m** (220 mg, 2.00 mmol) with bis-(3,5-dimethyl-4-methoxyphenyl)methanamine (598 mg, 2.00 mmol) was performed according to the general procedure for imine formation (Procedure E). Crystallization (1:60 EtOAc/hexanes) afforded **135m** as a white solid (678 mg, 1.73 mmol, 87%) and as a mixture of *trans* and *cis* isomers. *Cis:trans* = 0.86:1 (from ^1H NMR). Spectral data for **135m**: ^1H NMR (CDCl_3 , 500 MHz): *cis* isomer: δ 1.30 (s, 9H), 2.24 (s, 12H), 3.68 (s, 6H), 5.93 (s, 1H), 6.99 (s, 4H), 7.59 (d, 1H, $J = 1.0$ Hz); *trans* isomer: δ 1.26 (s, 9H), 2.23 (s, 12H), 3.67 (s, 6H), 5.20 (s, 1H), 6.93 (s, 4H), 7.61 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.14, 16.18, 27.93, 28.18, 30.41, 30.43, 59.58, 71.14, 73.56, 77.39, 78.18, 102.76, 108.12, 127.85, 127.87, 130.60, 130.69, 138.22, 138.91, 142.67, 145.35, 155.79, 155.91; IR (thin film) 2971s, 2865s, 2211s, 1610s, 1484s, 1221s, 1144s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{26}\text{H}_{34}\text{NO}_2$ ($\text{M}+\text{H}^+$) 392.2590, meas 392.2599.

6.1.4 Preparation of diazoacetamide **148**^{27a}

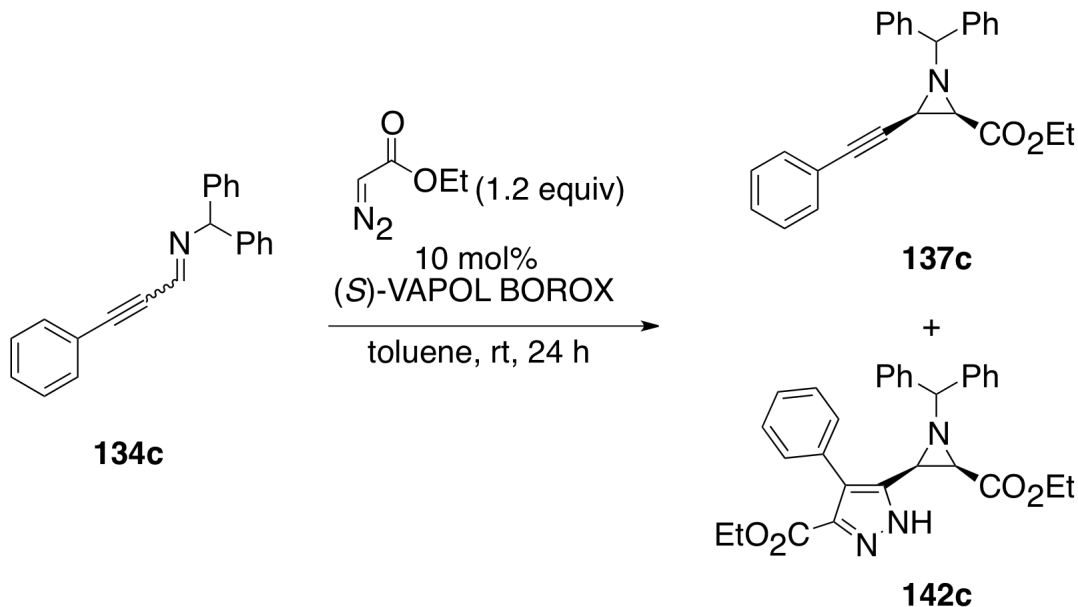


A 100 mL round bottom flask fitted with a magnetic stir bar was flame dried and cooled under Argon. The *p*-toluenesulfonylhydrazide of glyoxylic acid chloride (3.60 g, 13.8 mmol) was added to this flask followed by the addition of dry CH_2Cl_2 (30 mL). The flask was then

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 °C for 15 min. Aniline (1.40 mL, 15.2 mmol) and DBU (4.20 mL, 28.1 mmol) were then added sequentially to the reaction flask at 0 °C via plastic syringes. The reaction mixture was stirred at 0 °C for 2 h, and then warmed up to room temperature. It was then added to NH₄Cl (sat. aq. 30 mL), and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (30 mL). The organic layers were combined, washed with brine (30 mL), dried over MgSO₄ and filtered. Purification of the major product by silica gel chromatography (30 mm × 270 mm, 1:50 MeOH/CH₂Cl₂) afforded the impure product **148** as a yellow solid. The impure product was then washed with ether (15 mL x 3) until a single spot was observed on TLC, which afforded pure **148** as a bright yellow solid (1.17 g, 7.27 mmol, 52% yield). R_f = 0.18 (1:50 MeOH/CH₂Cl₂). Spectral data for **31**: ¹H NMR (DMSO-*d*₆, 500 MHz) δ 5.48 (s, 1H), 6.97-7.01 (m, 1H), 7.24-7.28 (m, 2H), 7.50-7.52 (m, 2H), 9.69 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 47.97, 118.57, 122.64, 128.72, 139.50, 163.50.

6.1.5 Catalytic asymmetric aziridination of alkynyl imines with ethyl diazoacetate

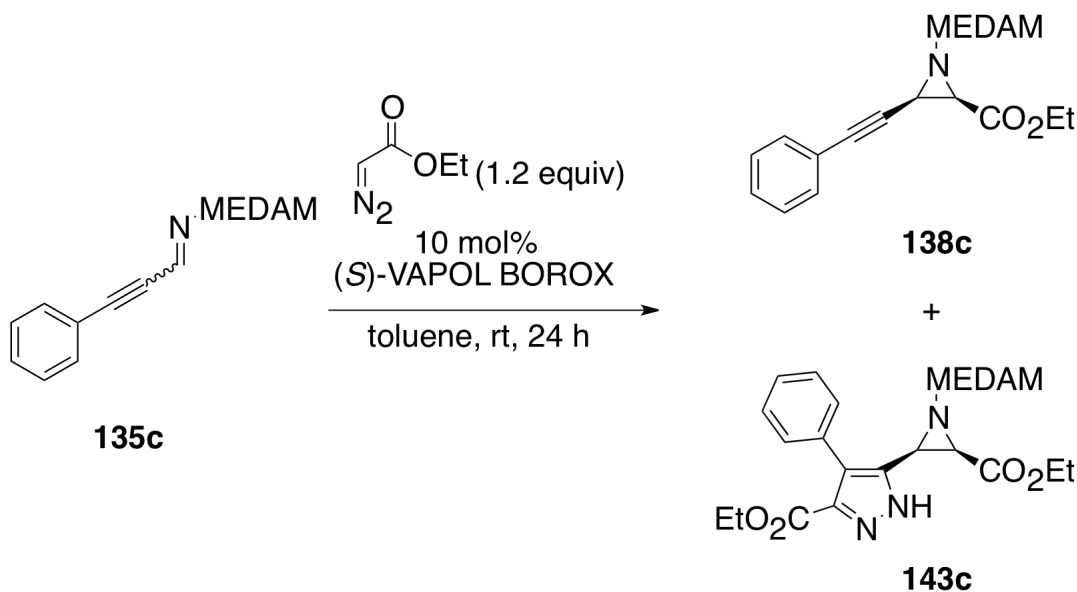
General procedure for catalytic asymmetric aziridination of alkynyl imines with ethyl diazoacetate – illustrated for the synthesis of *(2R,3R)*-Ethyl 1-benzhydryl-3-(phenylethynyl)aziridine-2-carboxylate **137c** (Procedure F)^{26h}



A 25 mL pear-shaped single necked Schlenk flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it) and cooled to room temperature under N₂ and charged with (*S*)-VAPOL (54 mg, 0.10 mmol) and triphenyl borate (116 mg, 0.40 mmol). The mixture was dissolved in 2 mL distilled toluene. After the addition of H₂O (1.8 μL, 0.10 mmol), the Teflon valve was closed and the flask was heated at 80 °C for 1 h. Toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After removal of the volatiles, the Teflon valve was completely opened and the flask was heated to 80 °C under high vacuum (0.5 mm Hg) for 30 min. After cooling down to room temperature, **134c** (295 mg, 1.00 mmol) and dry toluene (2 mL) were added to the Schlenk flask containing the catalyst. The mixture was stirred at room temperature for 5 minutes and then ethyl diazoacetate (124 μL, 1.2 mmol) was added via syringe and the Teflon valve was closed and the reaction mixture was stirred at room temperature for 24 h. The mixture was then diluted with 5 mL of hexanes and transferred to a 25 mL round bottom flask. The reaction flask was

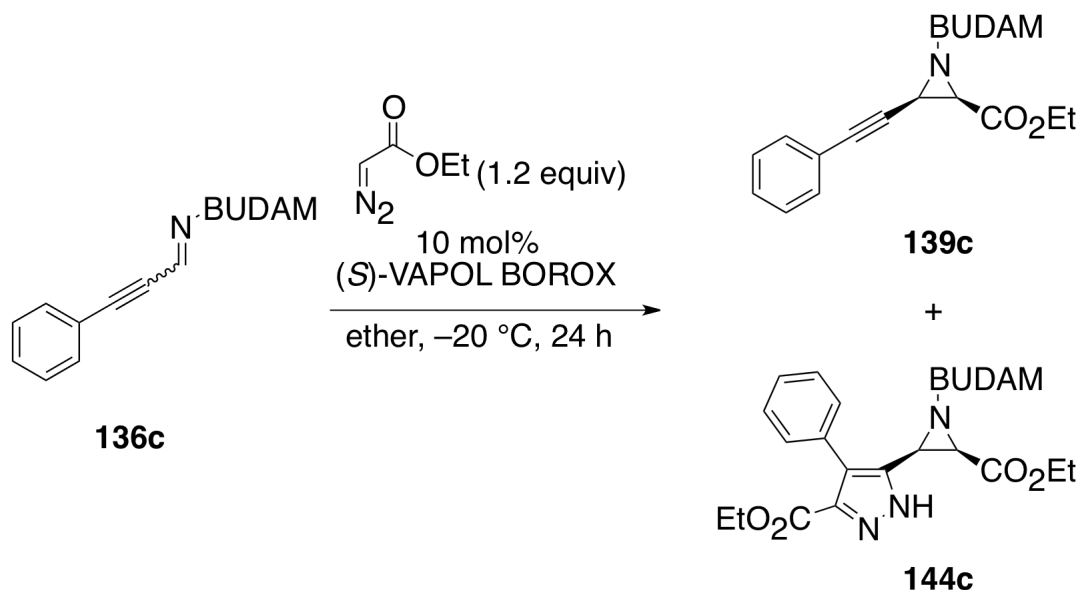
rinsed twice with 5 mL of dichloromethane and the rinse was added to the round bottom flask. Rotary evaporation of the solvent followed by exposure to high vacuum (0.5 mm Hg) for 30 minutes gave the crude aziridine as a yellow amorphous solid. The conversion was determined from the ^1H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the H on the imine carbon. The *cis/trans* ratio was determined on the crude reaction mixture by ^1H NMR integration of the ring methine protons for each aziridine. The *cis* ($J = 6\text{--}8$ Hz) and the *trans* ($J = 1\text{--}3$ Hz) coupling constants were used to differentiate the two isomers. The presence of **142c** in the crude reaction mixture was assigned on the basis of the following absorptions: ^1H NMR (CDCl_3 , 500 MHz) δ 2.73 (d, 1H, $J = 6.5$ Hz), 3.03 (d, 1H, $J = 6.5$ Hz). These data are consistent with the corresponding product **144g** isolated and characterized from the reaction of imine **136g**. The yield of **142c** was determined to be 2% by integration against the aziridine **137c** in the ^1H NMR spectrum of the crude reaction mixture and based on the isolated yield of **137c**. The *trans* isomer of **137c** could not be detected. The major product was purified by column chromatography on silica gel (40 mm x 400 mm, EtOAc/hexanes 1:15) to afford **137c** as a white solid (80 mg, 0.21 mmol, 21%). The optical purity of **137c** was determined to be 17% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 98:2 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: $R_t = 6.54$ min for (2*S*,3*S*)-**137c** (minor) and $R_t = 13.25$ min for (2*R*,3*R*)-**137c** (major). mp 153-154 °C; $R_f = 0.13$ (1:9 EtOAc/hexanes). Spectral data for **137c**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.24 (t, 3H, $J = 7.0$ Hz), 2.61 (d, 1H, $J = 6.5$ Hz), 2.75 (d, 1H, $J = 6.5$ Hz), 3.82 (s, 1H), 4.18-4.28 (m, 2H), 7.20-7.33

(m, 9H), 7.38-7.41 (m, 2H), 7.45-7.50 (m, 4H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.36, 34.81, 45.03, 61.24, 77.34, 82.54, 84.10, 122.59, 127.46, 127.50, 127.54, 128.13, 128.35, 128.51, 128.54, 132.00, 141.66, 167.44 (2 sp^2 C not located); IR (thin film) 2923m, 1738s, 1491s, 1455s, 1373s, 1190s cm^{-1} ; mass spectrum: m/z (% rel intensity) 381 M^+ (2), 308 (3), 214 (77), 186 (35), 167 (100), 152 (56), 114 (52); Anal calcd for $\text{C}_{26}\text{H}_{23}\text{NO}_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.86; H, 6.11; N, 3.47. $[\alpha]_{\text{D}}^{20} -5.2$ ($c = 1.0$, CH_2Cl_2) on 17% *ee* (2*R*,3*R*)-**137c** from (*S*)-VAPOL.



(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(phenylethynyl)aziridine-2-carboxylate **138c**: The reaction of **135c** (411 mg, 1.00 mmol) and ethyl diazoacetate (124 μL , 1.2 mmol) was performed according to the general procedure (Procedure F). An analysis of the ^1H NMR spectrum of the crude reaction mixture revealed that the reaction went to 22% completion and there was <1% formation of the pyrazole aziridine **143c**. The trans isomer of **138c** could not be detected. The product was purified by column chromatography on silica gel (40 mm x 450

mm, EtOAc/hexanes 1:8) to afford **138c** as an off-white solid (70 mg, 0.14 mmol, 14%). The optical purity of **138c** was determined to be 49% *ee* by HPLC (Chiralcel OD-H column, 225 nm, 99:1 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: R_t = 8.37 min for (2*R*,3*R*)-**138c** (major) and R_t = 10.59 min for (2*S*,3*S*)-**138c** (minor); mp 50-55 °C; R_f = 0.20 (1:5 EtOAc/Hexane). Spectral data for **138c**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.25 (t, 3H, J = 7.5 Hz), 2.22 (s, 6H), 2.24 (s, 6H), 2.54 (d, 1H, J = 6.5 Hz), 2.67 (d, 1H, J = 6.5 Hz), 3.55 (s, 1H), 3.67 (s, 6H), 4.18-4.29 (m, 2H), 7.08 (s, 2H), 7.11 (s, 2H), 7.24-7.27 (m, 3H), 7.37-7.40 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.42, 16.17, 16.20, 34.87, 45.22, 59.58, 59.60, 61.21, 76.83, 82.48, 84.28, 122.65, 127.72, 127.77, 128.13, 128.32, 130.69, 130.72, 131.96, 136.99, 137.01, 156.17, 167.61 (1 sp^2 C not located); IR (thin film) 2926s, 1734s, 1559s, 1456s, 1221s, 1184s, 1011s cm^{-1} ; mass spectrum: m/z (% rel intensity) 497 M^+ (1), 424 (2), 283 (100), 268 (8), 209 (3), 142 (4), 114 (15); Anal calcd for $\text{C}_{32}\text{H}_{35}\text{NO}_4$: C, 77.24; H, 7.09; N, 2.81. Found: C, 76.85; H, 7.43; N, 2.65. $[\alpha]_{\text{D}}^{20}$ -6.2 (c = 1.0, CH_2Cl_2) on 49% *ee* (2*R*,3*R*)-**138c** from (*S*)-VAPOL.



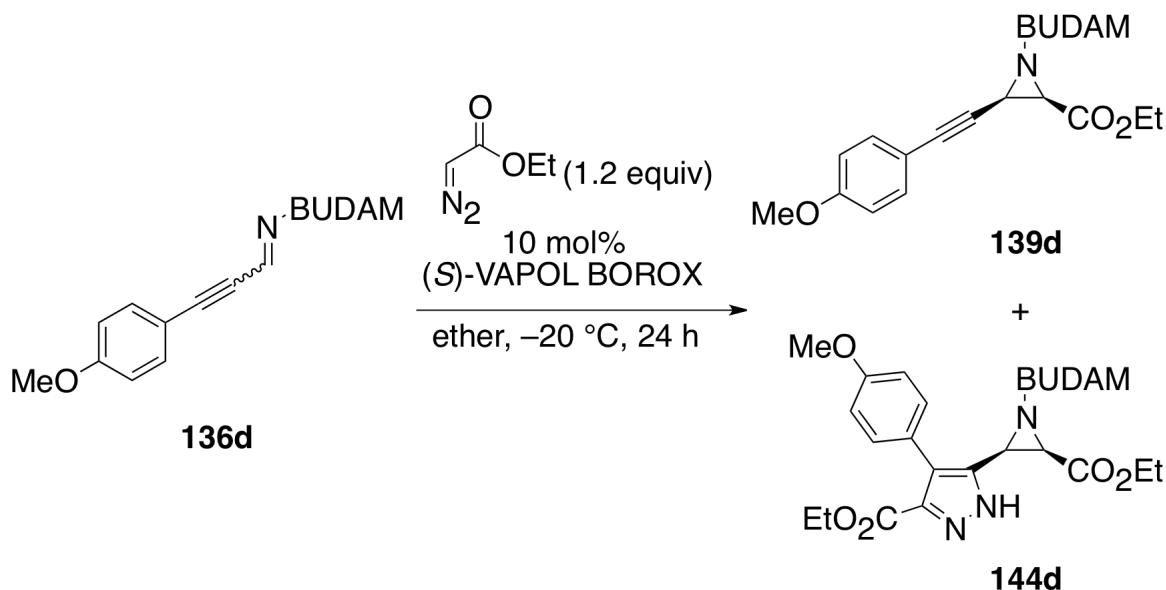
(2*R*,3*R*)-Ethyl 1-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl)-3-((4-(methoxycarbonyl)-phenyl)ethynyl)aziridine-2-carboxylate **139c** (Table 2.5, entry 9): The reaction of **136c** (579 mg, 1.00 mmol) and ethyl diazoacetate (124 μL , 1.2 mmol) was performed according to the general procedure (Procedure F) except that the solvent was ether and the temperature was -20°C . The presence of **144c** in the crude reaction mixture was assigned on the basis of the following absorptions: ^1H NMR (CDCl_3 , 500 MHz) δ 2.76 (d, 1H, $J = 6.0$ Hz), 2.99 (d, 1H, $J = 6.0$ Hz) and the presence of a compound with $R_f = 0.15$ (1:4 EtOAc/hexanes) in TLC. These data are consistent with the corresponding product **144g** isolated and characterized from the reaction of imine **136g**. The yield of **27c** was determined to be 18% by integration against the aziridine **139c** in the ^1H NMR spectrum of the crude reaction mixture and based on the isolated yield of **139c**. The trans isomer of **139c** could not be detected. The major product was purified by column chromatography on silica gel (35 mm x 400 mm, Et_2O /hexanes 1:20) to afford **139c** as a white foamy solid (443 mg, 0.66 mmol, 66%). The optical purity of **139c** was determined to be 97% *ee*

by HPLC (Pirkle covalent (*R,R*) Whelk-O1 column, 225 nm, 98:2 Hexane/2-PrOH, flow rate: 1.0 mL/min). Retention time: R_t = 7.29 min for (*2S,3S*)-**139c** (minor) and R_t = 13.47 min for (*2R,3R*)-**139c** (major). mp 62-64 °C; R_f = 0.20 (1:10 Et₂O/hexanes). The outcomes of this reaction under a number of different conditions are given in Table 2.5 in the text. Spectral data for **139c**: ¹H NMR (CDCl₃, 500 MHz) δ 1.25 (t, 3H, J = 7.0 Hz), 1.37 (s, 36H), 2.62 (d, 1H, J = 6.5 Hz), 2.83 (d, 1H, J = 6.5 Hz), 3.64 (s, 6H), 3.81 (s, 1H), 4.17-4.28 (m, 2H), 7.24-7.28 (m, 7H), 7.36-7.38 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 14.44, 32.10, 32.11, 35.61, 35.79, 35.81, 44.97, 61.20, 64.07, 64.08, 76.40, 82.55, 84.61, 122.79, 125.81, 125.83, 128.13, 128.25, 131.88, 135.44, 135.80, 143.08, 143.21, 158.55, 158.61, 168.00; IR (thin film) 2961s, 1734s, 1456s, 1414s, 1221s, 1013s cm⁻¹; mass spectrum: m/z (% rel intensity) 665 M⁺ (0.47), 592 (5), 451 (100), 379 (12), 305 (2), 142 (19), 114 (45). Anal calcd for C₄₄H₅₉NO₄: C, 79.36; H, 8.93; N, 2.10. Found: C, 79.02; H, 9.10; N, 1.95. $[\alpha]_D^{20}$ -10.4 (c = 1.0, CH₂Cl₂) on 97% *ee* (*2R,3R*)-**139c** from (*S*)-VAPOL.

The aziridination of 136c with 0.9 equiv of ethyl diazo acetate (Table 2.5, entry 12): The reaction of **136c** (579 mg, 1.00 mmol) and ethyl diazoacetate (contains 11 wt% CH₂Cl₂, 105 μ L, 0.9 mmol) was performed according to the general procedure (Procedure F) except that the solvent was ether and the temperature was -20 °C. The yields of **139c** (32%) and **139c** (6%) were determined from the ¹H NMR spectrum of the crude reaction mixture by integration against an internal standard (Ph₃CH).

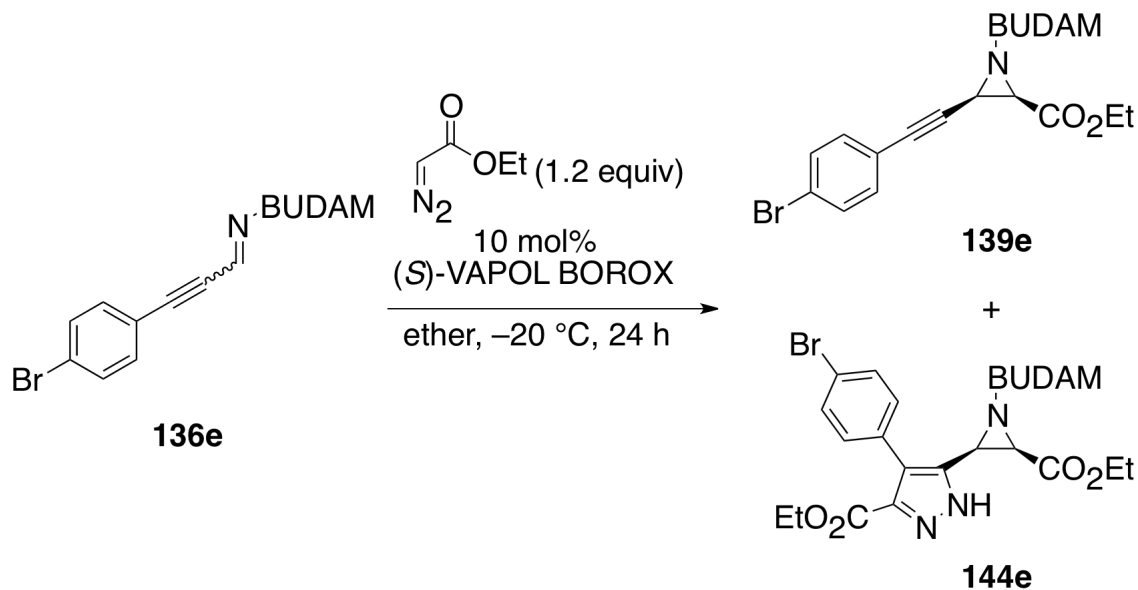
The aziridination of 136c with 4.0 equiv of ethyl diazo acetate (Table 2.5, entry 13): The reaction of **136c** (579 mg, 1.00 mmol) and ethyl diazoacetate (contains 11 wt% CH₂Cl₂, 466

μL , 4.0 mmol) was performed according to the general procedure (Procedure F) except that the solvent was ether and the temperature was $-20\text{ }^{\circ}\text{C}$. The yields of **139c** (58%) and **139c** (3%) were determined from the ^1H NMR spectrum of the crude reaction mixture by integration against an internal standard (Ph_3CH). A third compound was observed in this reaction with the following absorptions: ^1H NMR (CDCl_3 , 500 MHz) δ 2.60 (d, 1H, $J = 6.5$ Hz), 2.95 (d, 1H, $J = 6.5$ Hz). This compound is tentatively assigned as the regioisomer of **144c** resulting from a regioisomeric [3+2] cycloaddition and is formed in 18% yield.



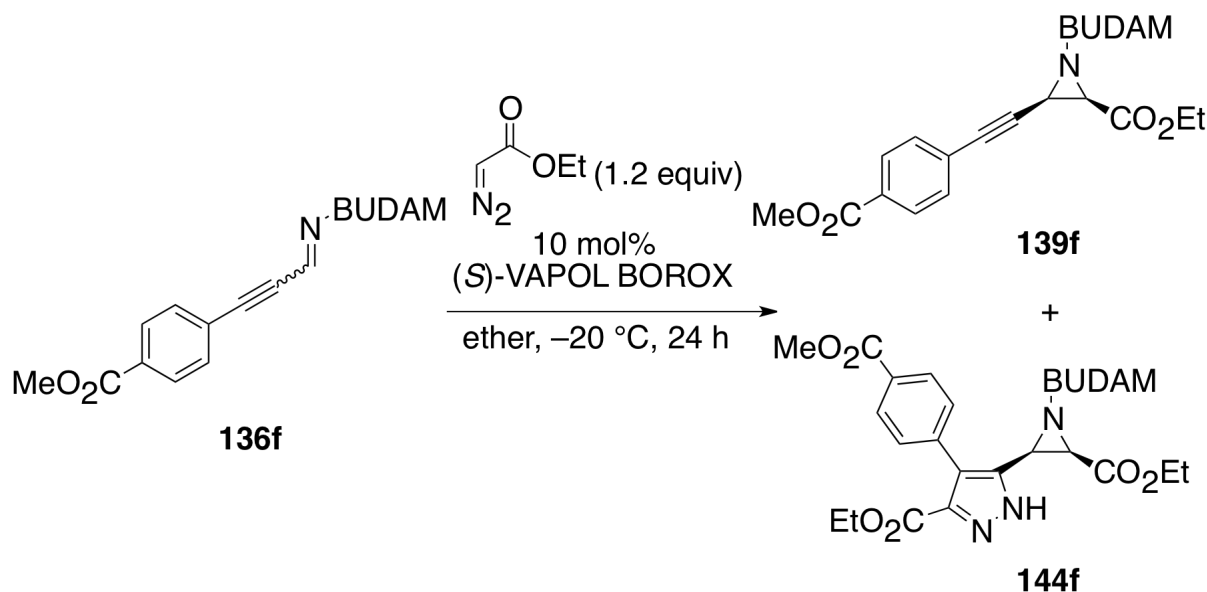
(2*R*,3*R*)-Ethyl 1-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl)-3-((4-methoxyphenyl)-ethynyl)-aziridine-2-carboxylate **139d**: The reaction of **136d** (609 mg, 1.00 mmol) and ethyl diazoacetate (124 μL , 1.2 mmol) was performed according to the general procedure (Procedure F) except that the solvent was ether and the temperature was $-20\text{ }^{\circ}\text{C}$. The presence of **144d** in the crude reaction mixture was assigned on the basis of the following absorptions: ^1H NMR (CDCl_3 , 500 MHz) δ 2.76 (d, 1H, $J = 6.0$ Hz), 2.99 (d, 1H, $J = 6.0$ Hz) and the presence of a compound

with $R_f = 0.15$ (1:4 EtOAc/hexanes) in TLC. These data are consistent with the corresponding product **144g** isolated and characterized from the reaction of imine **136g**. The yield of **144d** was determined to be 27% by integration against the aziridine **139d** in the ^1H NMR spectrum of the crude reaction mixture and based on the isolated yield of **139d**. The trans-isomer of **139d** was not detected. The major product was purified by column chromatography on silica gel (40 mm x 450 mm, Et₂O/hexanes 1:10) to afford **139d** as a white foamy solid (315 mg, 0.45 mmol, 45%). The optical purity of **139d** was determined to be 96% *ee* by HPLC (Pirkle covalent (*R,R*) Whelk-O1 column, 225 nm, 98:2 Hexane/2-PrOH, flow rate: 1.0 mL/min). Retention time: $R_t = 9.85$ min for (2*S*,3*S*)-**139d** (minor) and $R_t = 23.03$ min for (2*R*,3*R*)-**139d** (major). mp 58-61 °C; $R_f = 0.18$ (1:5 Et₂O/hexanes). Spectral data for **139d**: ^1H NMR (CDCl₃, 500 MHz) δ 1.25 (t, 3H, $J = 7.0$ Hz), 1.37 (s, 36H), 2.61 (d, 1H, $J = 6.5$ Hz), 2.84 (d, 1H, $J = 6.5$ Hz), 3.64 (s, 3H), 3.64 (s, 3H), 3.78 (s, 3H), 3.80 (s, 1H), 4.17-4.28 (m, 2H), 6.77-6.79 (m, 2H), 7.23 (s, 2H), 7.25 (s, 2H), 7.29-7.32 (m, 2H); ^{13}C NMR (CDCl₃, 125 MHz) δ 14.45, 32.08, 35.76, 35.79, 35.87, 44.89, 55.21, 61.18, 64.06, 64.08, 76.34, 82.52, 83.03, 113.76, 114.86, 125.83, 125.85, 133.30, 135.38, 135.81, 143.00, 143.17, 158.51, 158.58, 159.54, 168.11 (1 sp^3 C not located); IR (thin film) 2961s, 1734s, 1559s, 1456s cm^{-1} ; mass spectrum, m/z (% rel intensity) 695 M^+ (0.63), 451 (68), 408 (9), 233 (12), 132 (60), 57 (100); Anal calcd for C₄₅H₆₁NO₅: C, 77.66; H, 8.83; N, 2.01. Found: C, 77.91; H, 8.90; N, 1.85. $[\alpha]_{\text{D}}^{20} -9.4$ ($c = 1.0$, CH₂Cl₂) on 96% *ee* (2*R*,3*R*)-**139d** from (*S*)-VAPOL.



(2*R*,3*R*)-Ethyl 1-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl)-3-((4-bromophenyl)-*ethynyl*)-aziridine-2-carboxylate **139e**: The reaction of **136e** (658 mg, 1.00 mmol) and ethyl diazoacetate (124 μ L, 1.2 mmol) was performed according to the general procedure (Procedure F) except that the solvent was ether and the temperature was -20 °C. The presence of **144e** in the crude reaction mixture was assigned on the basis of the following absorptions: ^1H NMR (CDCl_3 , 500 MHz) δ 2.76 (d, 1H, $J = 6.0$ Hz), 2.92 (d, 1H, $J = 6.0$ Hz) and the presence of a compound with $R_f = 0.15$ (1:4 EtOAc/hexanes) in TLC. These data are consistent with the corresponding product **144g** isolated and characterized from the reaction of imine **136g**. The yield of **144e** was determined to be 24% by integration against the aziridine **139e** in the ^1H NMR spectrum of the crude reaction mixture and based on the isolated yield of **139e**. The *trans*-isomer of **139e** was not detected. The major product was purified by column chromatography on silica gel (35 mm x 400 mm, Et_2O /hexanes 1:20) to afford **139e** as a white foamy solid (404 mg, 0.54 mmol, 54%). The optical purity of **139e** was determined to be 97% *ee* by HPLC (Pirkle covalent (*R,R*) Whelk-O1

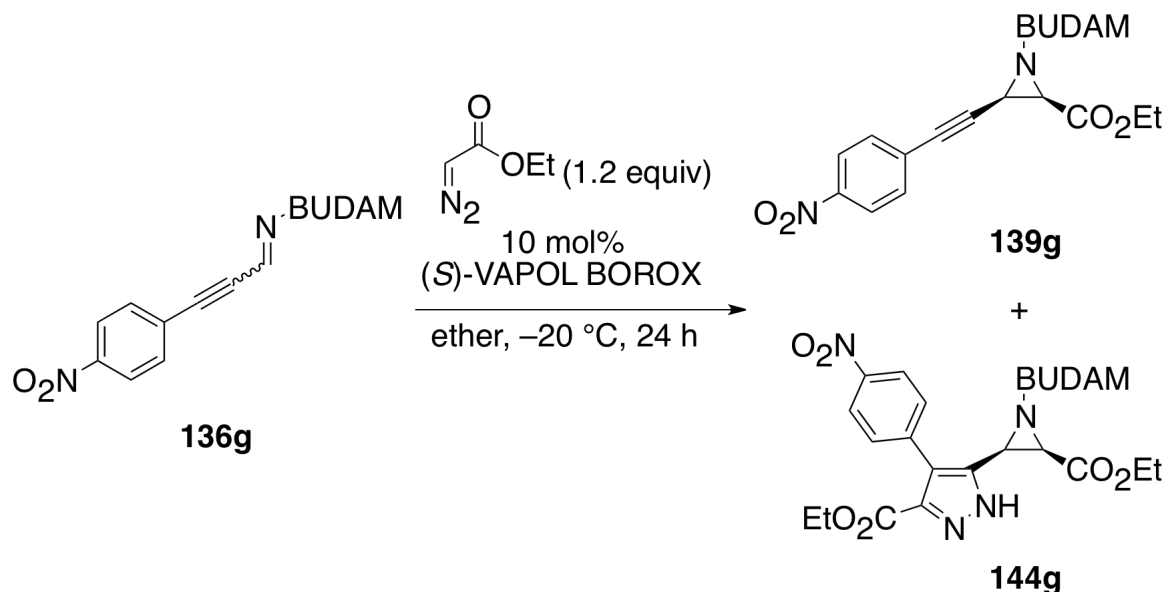
column, 225 nm, 98:2 Hexane/2-PrOH, flow rate: 1.0 mL/min). Retention time: R_t = 5.60 min for (2*S*,3*S*)-**139e** (minor) and R_t = 7.97 min for (2*R*,3*R*)-**139e** (major). mp 68-72 °C; R_f = 0.20 (1:10 Et₂O/hexanes). Spectral data for **139e**: ¹H NMR (CDCl₃, 500 MHz) δ 1.25 (t, 3H, J = 7.5 Hz), 1.37 (s, 36H), 2.64 (d, 1H, J = 6.5 Hz), 2.81 (d, 1H, J = 6.5 Hz) 3.64 (s, 3H), 3.64 (s, 3H) 3.81 (s, 1H), 4.17-4.28 (m, 2H), 7.22-7.24 (m, 6H), 7.37-7.40 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 14.43, 32.07, 35.46, 35.77, 35.79, 44.92, 61.24, 64.08, 76.34, 81.48, 85.85, 121.68, 122.56, 125.75, 125.77, 131.45, 133.28, 135.30, 135.67, 143.08, 143.22, 158.56, 158.62, 167.86 (2 sp³ C not located); IR (thin film) 2961s, 1734s, 1559s, 1456s, 1414s, 1221s, 1011s cm⁻¹; mass spectrum, m/z (% rel intensity) 745 M⁺ (0.60, ⁸¹Br), 743 M⁺ (0.42, ⁷⁹Br), 465 (2), 451 (100), 379 (6), 247 (6). Anal calcd for C₄₄H₅₈BrNO₄: C, 70.95; H, 7.85; N, 1.88. Found: C, 70.80; H, 7.96; N, 1.91. $[\alpha]_D^{20}$ -11.4 (c = 1.0, CH₂Cl₂) on 97% *ee* (2*R*,3*R*)-**139e** from (*S*)-VAPOL.



(2*R*,3*R*)-Ethyl-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-((4-(methoxycarbonyl)-phenyl)-ethynyl)aziridine-2-carboxylate **139f**. The reaction of **136f** (637 mg, 1.00 mmol) and ethyl

diazoacetate (124 μ L, 1.2 mmol) was performed according to the general procedure (Procedure F) except that the solvent was ether and the temperature was -20 $^{\circ}$ C. The presence of **144f** in the crude reaction mixture was assigned on the basis of the following absorptions: ^1H NMR (CDCl_3 , 500 MHz) δ 2.77 (d, 1H, $J = 6.0$ Hz), 2.93 (d, 1H, $J = 6.0$ Hz) and the presence of a compound with $R_f = 0.15$ (1:4 EtOAc/hexanes) in TLC. These data are consistent with the corresponding product **144g** isolated and characterized from the reaction of imine **136g**. The yield of **144f** was determined to be 19% by integration against the aziridine **139f** in the ^1H NMR spectrum of the crude reaction mixture and based on the isolated yield of **139f**. The *trans*-isomer of **139f** was not detected. The major product was purified by column chromatography on silica gel (40 mm x 450 mm, Et₂O/hexanes 1:12) to afford **139f** as a white foamy solid (410 mg, 0.57 mmol, 57%). The optical purity of **139f** was determined to be 94% *ee* by HPLC (Pirkle covalent (*R,R*) Whelk-O1 column, 225 nm, 98:2 Hexane/2-PrOH, flow rate: 1.0 mL/min). Retention time: $R_t = 13.47$ min for (*2S,3S*)-**139f** (minor) and $R_t = 26.15$ min for (*2R,3R*)-**139f** (major). mp $59\text{--}62$ $^{\circ}$ C; $R_f = 0.16$ (1:5 Et₂O/hexanes). Spectral data for **139f**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.25 (t, 3H, $J = 7.0$ Hz), 1.37 (s, 36H), 2.66 (d, 1H, $J = 6.5$ Hz), 2.82 (d, 1H, $J = 6.5$ Hz), 3.64 (s, 3H), 3.64 (s, 3H), 3.82 (s, 1H), 3.89 (s, 3H), 4.17–4.28 (m, 2H), 7.24 (s, 4H), 7.42–7.44 (m, 2H), 7.92–7.94 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.42, 32.09, 32.10, 35.29, 35.79, 35.81, 45.06, 52.17, 61.26, 64.08, 76.43, 81.80, 87.90, 125.75, 125.76, 127.47, 129.36, 129.64, 131.79, 135.38, 135.69, 143.16, 143.28, 158.60, 158.65, 166.50, 167.80 (1 sp^3 C not located); IR (thin film) 2961s, 1728s, 1559s, 1456s, 1277s, 1223s cm^{-1} ; mass spectrum, m/z (% rel intensity) 723 M^+ (0.17),

598 (0.15), 451 (23), 379 (6), 128 (11), 44 (100). Anal calcd for C₄₆H₆₁NO₆: C, 76.31; H, 8.49; N, 1.93. Found: C, 76.43; H, 8.45; N, 1.79. $[\alpha]_D^{20}$ -12.7 (*c* = 1.0, CH₂Cl₂) on 94% *ee* (2*R*,3*R*)-**139f** from (*S*)-VAPOL.



(2*R*,3*R*)-Ethyl-1-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl)-3-((4-nitrophenyl)-

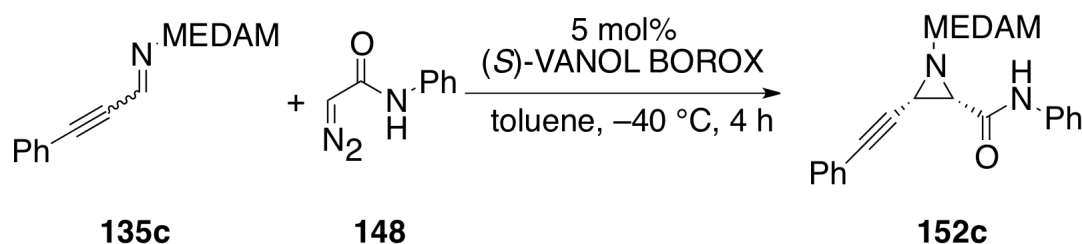
-ethynyl)-aziridine-2-carboxylate **139g**: The reaction of **136g** (624 mg, 1.00 mmol) and ethyl diazoacetate (124 μ L, 1.2 mmol) was performed according to the general procedure (Procedure F) except that the solvent was ether and the temperature was -20 °C. The yield of **144g** was determined to be 22% by integration against the aziridine **139g** in the ¹H NMR spectrum of the crude reaction mixture and based on the isolated yield of **139g**. The trans-isomer of **139g** was not detected. The major product was purified by column chromatography on silica gel (40 mm x 450 mm, Et₂O/hexanes 1:12) to afford **139g** as an off-white foamy solid (252 mg, 0.35 mmol, 35%); mp 73-76 °C; *R*_f = 0.22 (1:5 Et₂O/hexanes). The column was flushed with ethyl acetate, the residue was loaded onto a silica gel column (40 mm x 450 mm) and elution with a 1:5

mixture of ethyl acetate and hexanes gave a few fractions of pure **144g** as a yellow foamy solid (15 mg); mp 91-95 °C; $R_f = 0.15$ (1:4 EtOAc/hexanes). The optical purity of **139g** was determined to be 88% *ee* by HPLC (Pirkle covalent (*R,R*) Whelk-O1 column, 225 nm, 96:4 Hexane/2-PrOH, flow rate: 1.0 mL/min). Retention time: $R_t = 7.06$ min for (*2S,3S*)-**139g** (minor) and $R_t = 8.50$ min for (*2R,3R*)-**139g** (major). Spectral data for **139g**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.25 (t, 3H, $J = 7.0$ Hz), 1.37 (s, 36H), 2.70 (d, 1H, $J = 6.5$ Hz), 2.83 (d, 1H, $J = 6.5$ Hz), 3.64 (s, 3H), 3.65 (s, 3H) 3.83 (s, 1H), 4.18-4.28 (m, 2H), 7.23 (s, 2H), 7.24 (s, 2H), 7.50-7.53 (m, 2H), 8.12-8.15 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.42, 32.08, 32.10, 35.02, 35.79, 35.82, 45.13, 61.33, 64.09, 76.43, 80.69, 90.46, 123.50, 125.68, 125.72, 129.64, 132.60, 135.24, 135.56, 143.21, 143.33, 147.16, 158.65, 158.70, 167.58 (1 sp^3 C not located); IR (thin film) 2961s, 1734s, 1595s, 1522s, 1414s, 1345, 1223s, 1013s cm^{-1} ; mass spectrum, m/z (% rel intensity) 710 M^+ (0.20), 637 (1), 551 (1), 494 (1), 452 (28), 450 (100), 379 (9), 246 (21), 146 (15). Anal calcd for $\text{C}_{44}\text{H}_{58}\text{N}_2\text{O}_6$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.34; H, 8.43; N, 4.27. $[\alpha]_{\text{D}}^{20} -16.2$ ($c = 1.0$, CH_2Cl_2) on 88% *ee* (*2R,3R*)-**139g** from (*S*)-VAPOL. Spectral data for **144g**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.21 (t, 3H, $J = 7.5$ Hz), 1.26 (t, 3H, $J = 7.5$ Hz), 1.28 (s, 18H), 1.36 (s, 18H), 2.81 (d, 1H, $J = 6.0$ Hz), 2.88 (d, 1H, $J = 6.0$ Hz), 3.61 (s, 3H), 3.65 (s, 3H), 3.88 (s, 1H), 4.11-4.20 (m, 2H), 4.24-4.30 (m, 2H), 7.10-7.13 (m, 2H), 7.15 (s, 2H), 7.23 (s, 2H), 8.10-8.13 (m, 2H), 11.48 (br, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.05, 14.13, 31.96, 32.02, 35.74, 35.81, 39.13, 46.83, 61.00, 62.12, 64.10, 64.18, 76.71, 122.64, 123.09, 125.08, 125.38, 131.19, 135.16, 135.46, 137.98, 138.35, 143.56, 143.84, 147.03, 158.70, 158.76, 161.92, 169.16 (1 sp^2 C not

located); IR (thin film) 2961s, 1734s, 1522s, 1414s, 1345s, 1202s, 1115s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{48}\text{H}_{65}\text{N}_4\text{O}_8$ ($\text{M}+\text{H}^+$) 825.4805, meas 825.4790. $[\alpha]_{\text{D}}^{20} -2.5$ ($c = 1.0$, CH_2Cl_2).

6.1.6 Catalytic asymmetric aziridination of alkynyl imines with diazoacetamides

General procedure for catalytic asymmetric aziridination with alkynyl imine with diazoacetamides – illustrated for the synthesis of *(2S,3S)*-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-*N*-phenyl-3-(phenylethynyl)aziridine-2-carboxamide **152c** (Procedure G, Table 2.7, entry 16)^{27a}



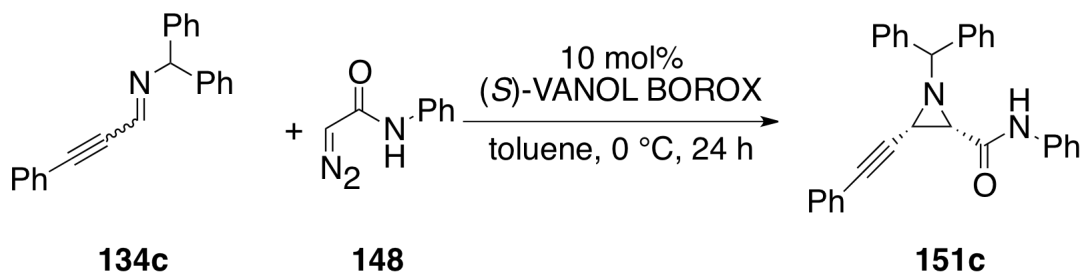
A 25 mL pear-shaped single necked Schlenk flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it) and cooled to room temperature under N_2 and charged with *(S)*-VANOL (11 mg, 0.025 mmol), phenol (4.7 mg, 0.050 mmol), dry toluene (1.0 mL), $\text{BH}_3\cdot\text{SMe}_2$ (2 M solution in toluene, 37.5 μL , 0.075 mmol) and water (1.35 μL , 0.075 mmol). The Teflon valve was closed and the flask was heated at $100\text{ }^{\circ}\text{C}$ for 1 hour. The toluene was then carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After the solvent was removed, the Teflon valve was completely opened and the flask was heated to $100\text{ }^{\circ}\text{C}$ under high vacuum for 30 min. The flask was then removed from the oil bath and allowed to cool to room temperature under N_2 . The

residue was then completely dissolved in 1.25 mL of dry toluene (10 mmol% catalyst) or 2.5 mL of dry toluene (5 mol% catalyst) to afford the stock solution of the catalyst.

A 10 mL round-bottom single-neck (14/20) flask fitted with a magnetic stir bar was flame dried under high vacuum and cooled to room temperature under N₂. To the flask was then added imine **135c** (82 mg, 0.20 mmol, 1 equiv). The flask was then fitted with a rubber septum and a N₂ balloon. To this flask was added 1.00 mL of the catalyst stock solution (5 mol% catalyst) via a plastic syringe fitted with a metallic needle. This catalyst-imine complex was cooled to –40 °C with the aid of an immersion cooler for 15-20 min. Diazoacetamide **148** (45 mg, 0.28 mmol, 1.4 equiv) was then added to the reaction flask, and the reaction stirred at –40 °C for 4 h.

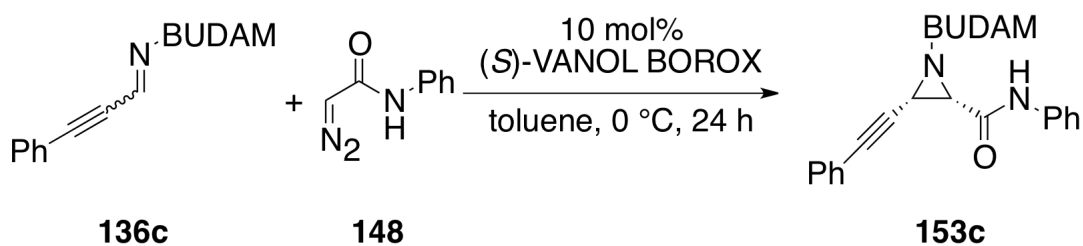
To the reaction mixture was added cold saturated aq. NaHCO₃ (8 mL). The mixture was transferred to a 50 mL separatory funnel. The reaction flask was rinsed with EtOAc (8 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (8 mL x 2) and the organic layers were then combined. This solution was dried over MgSO₄, filtered through a pad of Celite, rinsed with EtOAc, subjected to rotary evaporation until dry and finally exposed to high vacuum (0.5 mm Hg) to afford the crude product as a foamy yellow solid. The conversion was determined from the ¹H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the H on the imine carbon. The *cis/trans* ratio was determined on the crude reaction mixture by ¹H NMR integration of the ring methine protons for each aziridine. The *cis* (*J* = 6-8 Hz) and the *trans* (*J* = 1-3 Hz) coupling constants were used to differentiate the two isomers. This reaction was examined under the variety of conditions and the results are presented in Table 2.7 of the text.

The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 50:1. The major product was purified by column chromatography on silica gel (30 mm x 400 mm, EtOAc/hexanes 1:7 to 1:5 to 1:4) to afford **152c** as an off-white foamy solid (99 mg, 0.182 mmol, 91%). The optical purity of **152c** was determined to be 97% *ee* by HPLC (Chiralpak AD column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: R_t = 15.87 min for (2*R*,3*R*)-**152c** (minor) and R_t = 27.87 min for (2*S*,3*S*)-**152c** (major); mp 74-77 °C; R_f = 0.29 (1:2 EtOAc/hexanes); Spectra data for **152c**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.24 (s, 6H), 2.29 (s, 6H), 2.69 (d, 1H, J = 6.5 Hz), 2.74 (d, 1H, J = 6.5 Hz), 3.67 (s, 3H), 3.71 (s, 3H), 3.76 (s, 1H), 6.98 (s, 2H), 7.07-7.11 (m, 1H), 7.12 (s, 2H), 7.15-7.19 (m, 4H), 7.22-7.26 (m, 1H), 7.27-7.31 (m, 2H), 7.49-7.51 (m, 2H), 8.45 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.28, 16.31, 35.72, 46.44, 59.59, 59.65, 75.50, 83.14, 83.97, 120.13, 122.14, 124.42, 127.43, 127.83, 128.18, 128.49, 128.95, 130.88, 131.16, 131.85, 136.52, 136.77, 137.04, 156.19, 156.54, 165.57; IR (thin film) 3355br m, 2926s, 1686s, 1528s, 1445s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{36}\text{H}_{37}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 545.2804, meas 545.2815. $[\alpha]_D^{20}$ +30.2 (c = 1.0, CH_2Cl_2) on 94% *ee* (2*S*,3*S*)-**152c** from (*S*)-VANOL.



(2*S*,3*S*)-1-Benzhydryl-*N*-phenyl-3-(phenylethynyl)aziridine-2-carboxamide **151c**: The reaction of **134c** (59 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was

performed according to the general procedure except that the temperature was 0 °C and the time was 24 h (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 25:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:7 to 1:5) to afford **151c** as an off-white foamy solid (66 mg, 0.154 mmol, 77%). The optical purity of **151c** was determined to be 89% *ee* by HPLC (Chiralpak AD column, 222 nm, 98:2 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: R_t = 55.12 min for (2*R*,3*R*)-**151c** (minor) and R_t = 71.77 min for (2*S*,3*S*)-**151c** (major); mp 50-55 °C; R_f = 0.17 (1:4 EtOAc/hexanes). Spectral data for **151c**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.79 (d, 1H, J = 7.0 Hz), 2.83 (d, 1H, J = 7.0 Hz), 3.99 (s, 1H), 7.08-7.12 (m, 1H), 7.15-7.18 (m, 4H), 7.22-7.34 (m, 7H), 7.35-7.40 (m, 4H), 7.50-7.53 (m, 4H), 8.45 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 35.87, 46.35, 76.28, 83.29, 83.67, 119.98, 121.98, 124.42, 127.14, 127.48, 127.55, 128.04, 128.15, 128.53, 128.64, 128.90, 128.95, 131.89, 137.00, 141.17, 141.31, 165.29; IR (thin film) 3355br m, 2926s, 1684s, 1528s, 1445s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}$ ($\text{M}+\text{H}^+$) 429.1967, meas 429.1978. $[\alpha]_D^{20}$ +44.6 (c = 1.0, CH_2Cl_2) on 89% *ee* (2*S*,3*S*)-**151c** from (*S*)-VANOL.

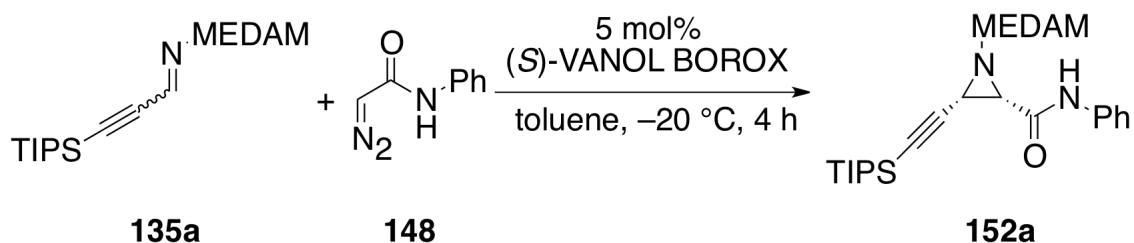


(2*S*,3*S*)-1-(Bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N-phenyl-3-(phenylethynyl)aziridine-2-

-carboxamide **35c**: The reaction of **136c** (116 mg, 0.20 mmol) and diazoacetamide **148** (45 mg,

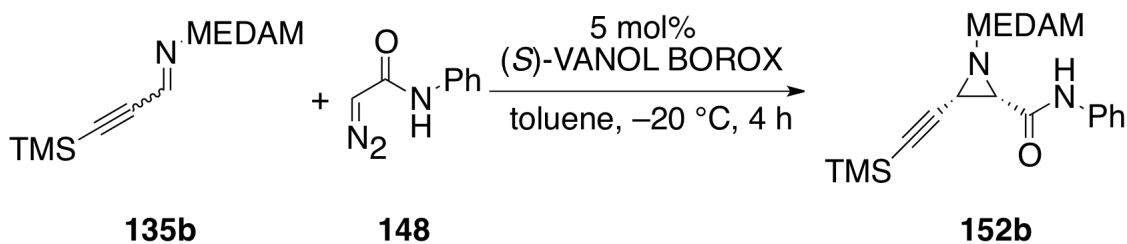
0.28 mmol) was performed according to the general procedure (Procedure G) except that the

temperature was 0 °C and the time was 24 h. The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 2:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:18) to afford **153c** as an off-white foamy solid (49 mg, 0.068 mmol, 34%). The optical purity of **153c** was determined to be 71% *ee* by HPLC (Pirkle covalent (*R,R*) Whelk-O1 column, 222 nm, 95:5 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: R_t = 13.65 min for (*2S,3S*)-**153c** (major) and R_t = 25.65 min for (*2R,3R*)-**153c** (minor); mp 59-65 °C; R_f = 0.27 (1:5 EtOAc/hexanes). Spectral data for **153c**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.36 (s, 18H), 1.41 (s, 18H), 2.76 (d, 1H, J = 7.0 Hz), 2.87 (d, 1H, J = 7.0 Hz), 3.65 (s, 3H), 3.68 (s, 3H), 3.93 (s, 1H), 7.08 (t, 1H, J = 7.7 Hz), 7.15 (s, 2H), 7.16 (d, 2H, J = 7.5 Hz), 7.21-7.24 (m, 3H), 7.28 (t, 2H, J = 7.5 Hz), 7.32 (s, 2H), 7.50 (d, 2H, J = 8.0 Hz), 8.51 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.05, 32.11, 35.75, 35.86, 36.04, 46.54, 64.12, 64.15, 75.72, 83.19, 84.16, 120.02, 122.10, 124.39, 125.43, 125.55, 128.15, 128.45, 128.93, 131.79, 135.36, 135.43, 137.03, 143.37, 143.67, 158.58, 158.83, 165.81; IR (thin film) 3357br m, 2961s, 1700s, 1528s, 1445s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{48}\text{H}_{61}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 713.4682, meas 713.4664. $[\alpha]_D^{20}$ +14.3 (c = 1.0, CH_2Cl_2) on 71% *ee* (*2S,3S*)-**153c** from (*S*)-VANOL.

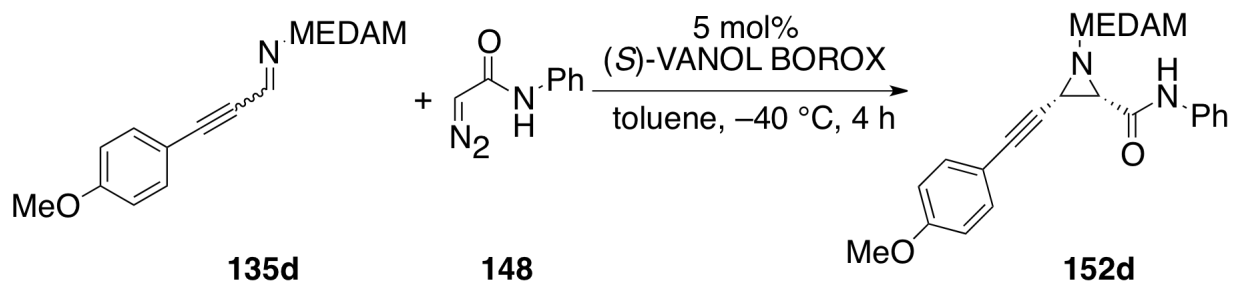


(*2S,3S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-*N*-phenyl-3-((triisopropylsilyl)ethynyl)-aziridine-2-carboxamide **152a**: The reaction of **135a** (98 mg, 0.20 mmol) and diazoacetamide **148**

(45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G) except that the temperature was $-20\text{ }^{\circ}\text{C}$. The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 50:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:7) to afford **152a** as a white foamy solid (107 mg, 0.171 mmol, 86%). The optical purity of **152a** was determined to be 98% *ee* by HPLC (Chiralpak AD column, 222 nm, 98:2 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: $R_t = 10.82$ min for (2*R*,3*R*)-**152a** (minor) and $R_t = 28.42$ min for (2*S*,3*S*)-**152a** (major). A repeat of the reaction gave an 87% yield of **152a** with 98% *ee*; mp $54\text{--}59\text{ }^{\circ}\text{C}$; $R_f = 0.20$ (1:4 EtOAc/hexanes). Spectral data for **152a**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.83-0.93 (m, 21H), 2.22 (s, 6H), 2.27 (s, 6H), 2.56 (d, 1H, $J = 6.5$ Hz), 2.60 (d, 1H, $J = 6.5$ Hz), 3.66 (s, 3H), 3.70 (s, 1H), 3.71 (s, 3H), 6.95 (s, 2H), 7.03-7.07 (m, 1H), 7.10 (s, 2H), 7.25-7.29 (m, 2H), 7.48-7.51 (m, 2H), 8.43 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 10.94, 16.24, 18.39, 18.42, 35.95, 46.12, 59.57, 59.64, 75.26, 84.84, 101.61, 119.34, 124.05, 127.24, 127.85, 128.74, 130.81, 131.17, 136.57, 136.88, 137.24, 156.10, 156.54, 165.15; IR (thin film) 3351br m, 2944s, 2867s, 1694s, 1530s, 1445s, 1223s, 1017s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{39}\text{H}_{53}\text{N}_2\text{O}_3\text{Si}$ ($\text{M}+\text{H}^+$) 625.3825, meas 625.3799. $[\alpha]_D^{20} +24.8$ ($c = 1.0$, CH_2Cl_2) on 98% *ee* (2*S*,3*S*)-**152a** from (*S*)-VANOL.

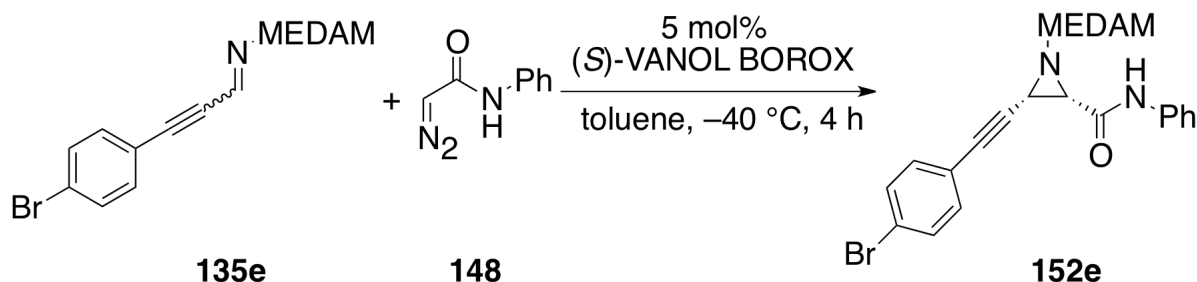


(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-*N*-phenyl-3-((trimethylsilyl)ethynyl)-aziridine-2-carboxamide **152b**: The reaction of **135b** (81 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G) except that the temperature was –20 °C. The ¹H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 5:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:7) to afford **152b** as a white foamy solid (86 mg, 0.159 mmol, 80%). The optical purity of **152b** was determined to be 83% *ee* by HPLC (Chiralpak AD column, 222 nm, 99:1 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: *R*_t = 12.95 min for (2*R*,3*R*)-**152b** (minor) and *R*_t = 15.15 min for (2*S*,3*S*)-**152b** (major). A repeat of the reaction gave an 80% yield of **152b** with 86% *ee*; mp 123-127 °C; *R*_f = 0.20 (1:4 EtOAc/hexanes). Spectral data for **152b**: ¹H NMR (CDCl₃, 500 MHz) δ -0.02 (s, 9H), 2.23 (s, 6H), 2.28 (s, 6H), 2.50 (d, 1H, *J* = 6.5 Hz), 2.59 (d, 1H, *J* = 6.5 Hz), 3.67 (s, 3H), 3.71 (s, 3H), 3.72 (s, 1H), 6.94 (s, 2H), 7.07 (s, 2H), 7.07-7.11 (m, 1H), 7.28-7.32 (m, 2H), 7.48-7.51 (m, 2H), 8.35 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ -0.47, 16.25, 45.45, 45.99, 59.58, 59.65, 75.14, 88.67, 99.99, 119.96, 124.34, 127.42, 127.88, 128.86, 130.78, 131.11, 136.40, 136.68, 136.98, 156.11, 156.51, 165.40 (1 sp³ C not located); IR (thin film) 3357br m, 2957s, 1686s, 1530s, 1445s, 1223s, 1013s cm⁻¹; HRMS (ESI+) *m/z* calcd for C₃₃H₄₁N₂O₃Si (M+H⁺) 541.2886, meas 541.2899. [*α*]_D²⁰ +4.2 (*c* = 1.0, CH₂Cl₂) on 83% *ee* (2*S*,3*S*)-**152b** from (*S*)-VANOL.



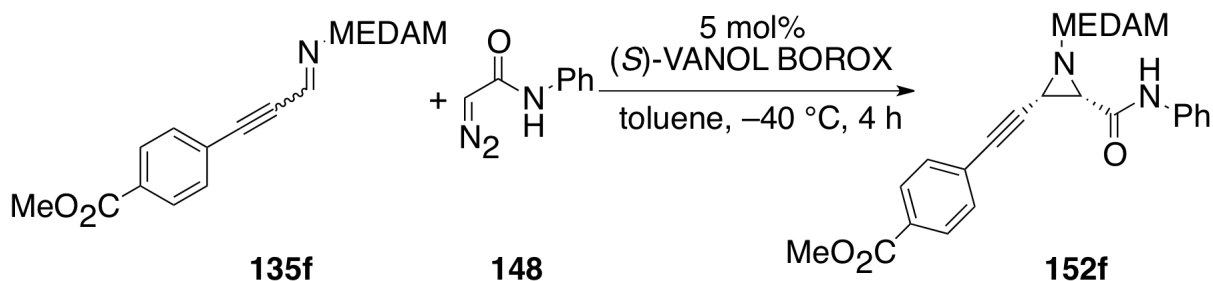
(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((4-methoxyphenyl)ethynyl)-*N*-phenylaziridine-2-carboxamide **152d**: The reaction of **135d** (88 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of >100:1. The major product was purified by column chromatography on silica gel (30 mm x 300 mm, EtOAc/hexanes 1:4 to 1:3) to afford **152d** as an off-white foamy solid (103 mg, 0.179 mmol, 90%). The optical purity of **152d** was determined to be 99% *ee* by HPLC (Chiralpak AD column, 222 nm, 85:15 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: R_t = 9.25 min for (2*R*,3*R*)-**152d** (minor) and R_t = 23.24 min for (2*S*,3*S*)-**152d** (major). A repeat of the reaction gave an 89% yield of **152d** with 99% *ee*; mp 76-79 °C; R_f = 0.42 (1:1 EtOAc/hexanes). Spectral data for **152d**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.24 (s, 6H), 2.29 (s, 6H), 2.67 (d, 1H, J = 6.5 Hz), 2.73 (d, 1H, J = 6.5 Hz), 3.67 (s, 3H), 3.71 (s, 3H), 3.74 (s, 3H), 3.75 (s, 1H), 6.68-6.72 (m, 2H), 6.98 (s, 2H), 7.07-7.14 (s, 3H), 7.12 (s, 2H), 7.27-7.31 (m, 2H), 7.49-7.52 (m, 2H), 8.45 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.28, 16.31, 35.90, 46.40, 55.22, 59.58, 59.65, 75.49, 82.54, 83.12, 113.81, 114.21, 120.14, 124.38, 127.45, 127.84, 128.93, 130.83, 131.12, 133.31, 136.58, 136.82, 137.08, 156.16, 156.50, 159.72, 165.71; IR (thin film) 3351br m, 2932s, 1686s, 1528s, 1510s, 1445s, 1250s,

1223s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{37}\text{H}_{39}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$) 575.2910, meas 575.2896. $[\alpha]_{\text{D}}^{20} +32.9$ ($c = 1.0$, CH_2Cl_2) on 99% *ee* (2*S*,3*S*)-**152d** from (*S*)-VANOL.



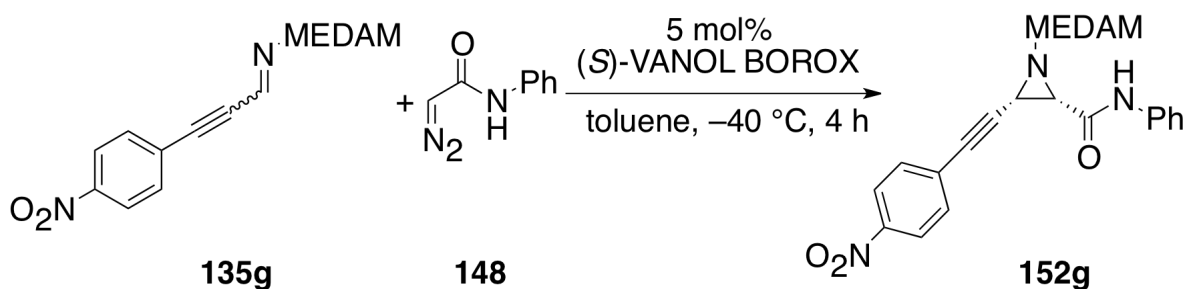
(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((4-bromophenyl)ethynyl)-*N*-phenylaziridine-2-carboxamide **152e**: The reaction of **135e** (98 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of >100:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:7 to 1:5 to 1:4) to afford **152e** as an off-white foamy solid (116 mg, 0.186 mmol, 93%). The optical purity of **152e** was determined to be 98% *ee* by HPLC (Chiralpak AD column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: $R_t = 6.65$ min for (2*R*,3*R*)-**152e** (minor) and $R_t = 23.21$ min for (2*S*,3*S*)-**152e** (major). A repeat of the reaction gave a 92% yield of **152e** with 99% *ee*; mp 74-78 °C; $R_f = 0.32$ (1:2 EtOAc/hexanes). Spectral data for **152e**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.24 (s, 6H), 2.28 (s, 6H), 2.71 (d, 1H, $J = 7.0$ Hz), 2.72 (d, 1H, $J = 7.0$ Hz), 3.67 (s, 3H), 3.71 (s, 3H), 3.76 (s, 1H), 6.98 (s, 2H), 7.00-7.03 (m, 2H), 7.08-7.12 (m, 1H), 7.10 (s, 2H), 7.28-7.32 (m, 4H), 7.48-7.51 (m, 2H), 8.43 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.29, 16.32, 35.55, 46.45, 59.59, 59.65, 75.47, 81.99, 85.24, 119.97, 121.04, 122.84, 124.50, 127.40, 127.79, 129.00, 130.91, 131.20, 131.47, 133.24, 136.42, 136.66, 136.98, 156.22, 156.56,

165.41; IR (thin film) 3353br m, 2928s, 1684s, 1528s, 1445s, 1223s, 1011s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{36}\text{H}_{36}\text{N}_2\text{O}_3^{79}\text{Br}$ ($\text{M}+\text{H}^+$) 623.1909, meas 623.1881. $[\alpha]_{\text{D}}^{20} +31.0$ ($c = 1.0$, CH_2Cl_2) on 98% *ee* (2*S*,3*S*)-**152e** from (*S*)-VANOL.



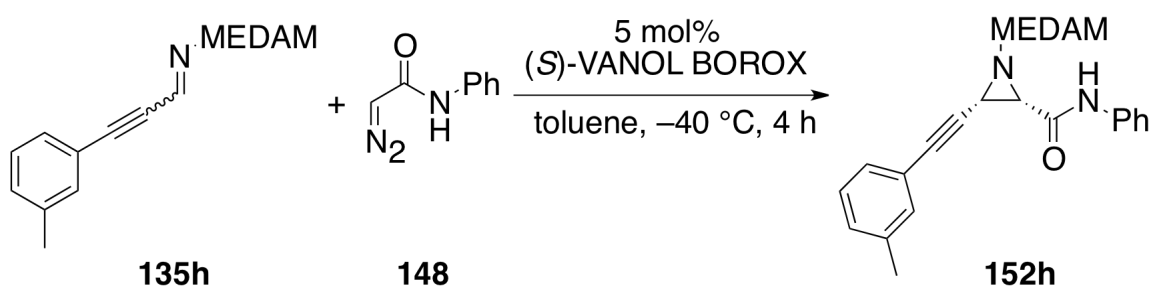
*Methyl 4-(((2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(phenylcarbamoyl)-aziridin-2-yl)ethynyl)benzoate* **152f**: The reaction of **135f** (94 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 23:1. The major product was purified by column chromatography on silica gel (30 mm x 300 mm, EtOAc/hexanes 1:4) to afford **152f** as a light yellow foamy solid (108 mg, 0.179 mmol, 90%). The optical purity of **152f** was determined to be 96% *ee* by HPLC (Chiralpak AD column, 222 nm, 80:20 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 7.58$ min for (2*R*,3*R*)-**152f** (minor) and $R_t = 35.70$ min for (2*S*,3*S*)-**152f** (major). A repeat of the reaction gave an 89% yield of **152f** with 95% *ee*; mp 71-74 $^\circ\text{C}$; $R_f = 0.23$ (1:2 EtOAc/hexanes). Spectral data for **152f**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.24 (s, 6H), 2.28 (s, 6H), 2.73 (d, 1H, $J = 6.5$ Hz), 2.76 (d, 1H, $J = 6.5$ Hz), 3.67 (s, 3H), 3.71 (s, 3H) 3.77 (s, 1H), 3.87 (s, 3H), 6.98 (s, 2H), 7.08-7.12 (m, 1H), 7.11 (s, 2H), 7.20-7.23 (m, 2H), 7.28-7.32 (m, 2H), 7.49-7.52 (m, 2H), 7.82-7.86 (m, 2H), 8.44 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.28, 16.31, 35.46, 46.55, 52.20, 59.58,

59.64, 75.49, 82.25, 87.09, 119.98, 124.56, 126.75, 127.38, 127.78, 129.01, 129.33, 129.77, 130.93, 131.21, 131.74, 136.37, 136.63, 136.93, 156.24, 156.58, 165.32, 166.35; IR (thin film) 3353br m, 2951s, 1725s, 1530s, 1445s, 1277s, 1223s, 1019s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{38}\text{H}_{39}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 603.2859, meas 603.2845. $[\alpha]_{\text{D}}^{20} +34.9$ ($c = 1.0$, CH_2Cl_2) on 96% *ee* (2*S*,3*S*)-**152f** from (*S*)-VANOL.



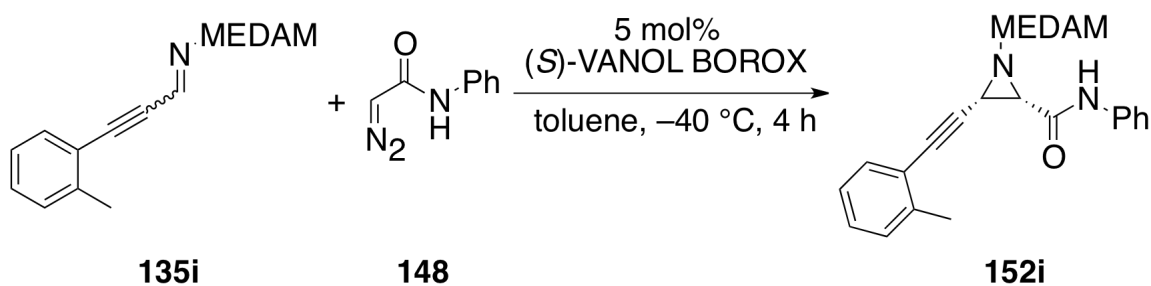
(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((4-nitrophenyl)ethynyl)-*N*-phenylaziridine-2-carboxamide **152g**: The reaction of **135g** (91 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 25:1. The major product was purified by column chromatography on silica gel (30 mm x 300 mm, EtOAc/hexanes 1:4 to 1:3) to afford **152g** as a light yellow foamy solid (107 mg, 0.182 mmol, 91%). The optical purity of **152g** was determined to be 95% *ee* by HPLC (Chiralpak AD column, 222 nm, 80:20 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 8.77$ min for (2*R*,3*R*)-**152g** (minor) and $R_t = 47.72$ min for (2*S*,3*S*)-**152g** (major). A repeat of the reaction gave an 89% yield of **152g** with 96% *ee*; mp 80-83 °C; $R_f = 0.20$ (1:2 EtOAc/hexanes). Spectral data for **152g**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.45 (s, 6H), 2.29 (s, 6H), 2.77 (s, 2H), 3.68 (s, 3H), 3.71 (s, 3H), 3.78 (s, 1H), 6.99 (s, 2H), 7.10 (s, 2H), 7.10-7.14 (m, 1H), 7.25-7.29 (m, 2H), 7.29-7.33 (m, 2H),

7.50-7.53 (m, 2H), 8.01-8.05 (m, 2H), 8.43 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.30, 16.33, 35.21, 46.67, 59.59, 59.66, 75.50, 81.03, 89.57, 119.79, 123.45, 124.66, 127.35, 127.74, 128.90, 129.10, 131.00, 131.31, 132.57, 136.24, 136.48, 136.90, 147.19, 156.31, 156.65, 165.07; IR (thin film) 3351br m, 2930s, 1696s, 1595s, 1522s, 1445s, 1345s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{36}\text{H}_{36}\text{N}_3\text{O}_5$ ($\text{M}+\text{H}^+$) 590.2655, meas 590.2652. $[\alpha]_{\text{D}}^{20} +38.4$ ($c = 1.0$, CH_2Cl_2) on 95% *ee* (2*S*,3*S*)-**152g** from (S)-VANOL.



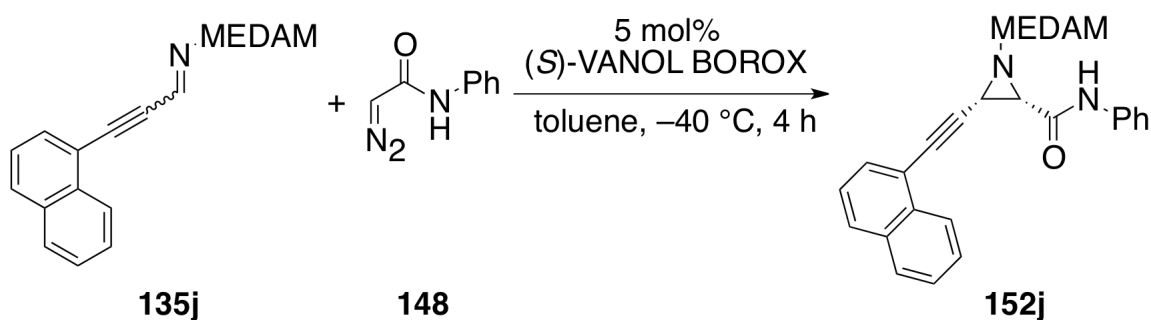
(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-*N*-phenyl-3-(*m*-tolylethynyl)aziridine-2-carboxamide **152h**: The reaction of **135h** (85 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 33:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:6) to afford **152h** as a white foamy solid (99 mg, 0.177 mmol, 89%). The optical purity of **152h** was determined to be 96% *ee* by HPLC (Chiralpak AD column, 222 nm, 85:15 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 9.35$ min for (2*R*,3*R*)-**152h** (minor) and $R_t = 16.21$ min for (2*S*,3*S*)-**152h** (major). A repeat of the reaction gave a 90% yield of **152h** with 96% *ee*; mp 68-72 $^\circ\text{C}$; $R_f = 0.30$ (1:2 EtOAc/hexanes). Spectral data for **152h**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.16 (s, 3H), 2.24 (s, 6H), 2.29 (s, 6H), 2.69 (d, 1H, $J = 6.5$ Hz), 2.73 (d, 1H, $J = 6.5$ Hz), 3.68

(s, 3H), 3.71 (s, 3H), 3.76 (s, 1H), 6.93 (s, 1H), 6.98 (s, 2H), 7.00-7.08 (m, 3H), 7.08 -7.12 (m, 1H), 7.12 (s, 2H), 7.28-7.32 (m, 2H), 7.51-7.54 (m, 2H), 8.46 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.29, 16.31, 21.01, 35.74, 46.44, 59.58, 59.64, 75.47, 83.27, 83.63, 120.09, 121.91, 124.39, 127.43, 127.82, 128.04, 128.77, 128.93, 129.36, 130.86, 131.14, 132.59, 136.52, 136.77, 137.09, 137.86, 156.17, 156.51, 165.62; IR (thin film) 3355br m, 2928s, 1686s, 1528s, 1445s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{37}\text{H}_{39}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 559.2961, meas 559.2941. $[\alpha]_{\text{D}}^{20} +35.2$ ($c = 1.0$, CH_2Cl_2) on 96% *ee* (2*S*,3*S*)-**152h** from (*S*)-VANOL.



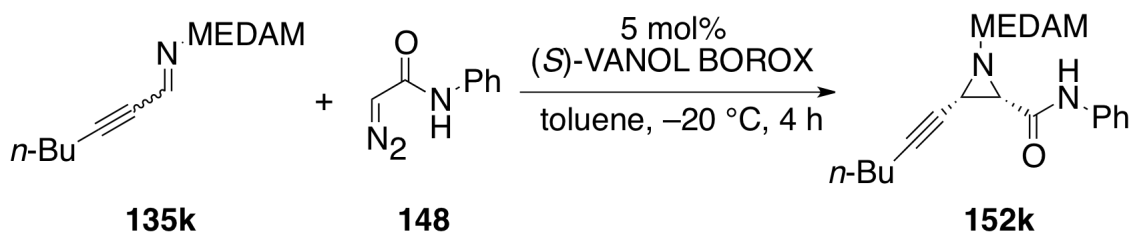
(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-*N*-phenyl-3-(*o*-tolylethynyl)aziridine-2-carboxamide **152i**: The reaction of **135i** (85 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 33:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:6) to afford **152i** as a white foamy solid (106 mg, 0.190 mmol, 95%). The optical purity of **152i** was determined to be 95% *ee* by HPLC (Chiralpak AD column, 222 nm, 85:15 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 10.84$ min for (2*R*,3*R*)-**152i** (minor) and $R_t = 21.46$ min for (2*S*,3*S*)-**152i** (major). A repeat of the reaction gave a 90% yield of **152i** with 96% *ee*; mp 68-73 °C; $R_f = 0.29$ (1:2 EtOAc/hexanes). Spectral data for **34i**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.20 (s,

3H), 2.24 (s, 6H), 2.29 (s, 6H), 2.71 (d, 1H, $J = 6.5$ Hz), 2.80 (d, 1H, $J = 6.5$ Hz), 3.67 (s, 3H), 3.71 (s, 3H), 3.77 (s, 1H), 6.99 (s, 2H), 6.99-7.03 (m, 1H), 7.05-7.09 (m, 2H), 7.13-7.17 (m, 1H), 7.14 (s, 2H), 7.20 (dd, 1H, $J = 8.0, 1.5$ Hz), 7.25-7.29 (m, 2H), 7.47-7.50 (m, 2H), 8.48 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.28, 16.31, 20.44, 36.00, 46.52, 59.59, 59.65, 75.51, 81.98, 87.71, 119.83, 121.93, 124.31, 125.40, 127.35, 127.83, 128.50, 128.90, 129.28, 130.87, 131.18, 132.32, 136.59, 136.84, 137.11, 140.53, 156.16, 156.54, 165.47; IR (thin film) 3353br m, 2967s, 1696s, 1530s, 1445s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{37}\text{H}_{39}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 559.2961, meas 559.2949. $[\alpha]_{\text{D}}^{20} +30.1$ ($c = 1.0$, CH_2Cl_2) on 95% *ee* (2*S*, 3*S*)-**152i** from (*S*)-VANOL.



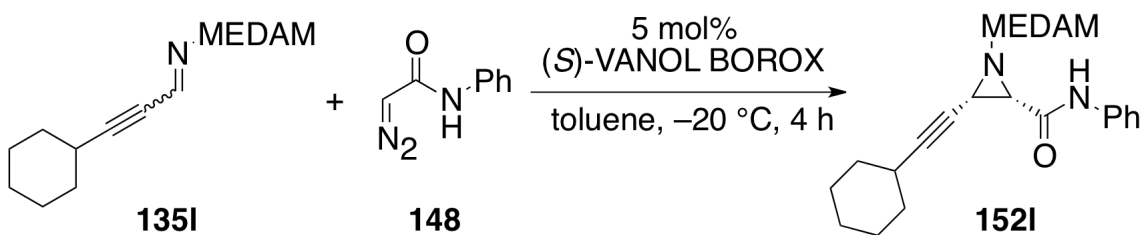
(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(naphthalen-1-ylethynyl)-*N*-phenylaziridine-2-carboxamide **152j**: The reaction of **135j** (92 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 25:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:4) to afford **152j** as an off-white foamy solid (113 mg, 0.190 mmol, 95%). The optical purity of **152j** was determined to be 97% *ee* by HPLC (Chiralpak AD column, 222 nm, 85:15 Hexane/2-PrOH,

flow rate: 0.7 mL/min). Retention time: R_t = 9.03 min for (2*R*,3*R*)-**152j** (minor) and R_t = 26.87 min for (2*S*,3*S*)-**152j** (major). A repeat of the reaction gave a 94% yield of **152j** with 99% *ee*; mp 83-88 °C; R_f = 0.24 (1:2 EtOAc/hexanes). Spectral data for **152j**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.26 (s, 6H), 2.30 (s, 6H), 2.80 (d, 1H, J = 6.5 Hz), 2.91 (d, 1H, J = 6.5 Hz), 3.68 (s, 3H), 3.72 (s, 3H), 3.83 (s, 1H), 7.03 (s, 2H), 7.06-7.11 (m, 1H), 7.11 -7.14 (m, 1H), 7.19 (s, 2H), 7.26-7.32 (m, 3H), 7.37-7.41 (m, 1H), 7.48 (dd, 1H, J = 7.5, 1.5 Hz), 7.53-7.56 (m, 2H), 7.76 (d, 2H, J = 8.5 Hz), 8.07 (dd, 1H, J = 8.5, 1.0 Hz), 8.59 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.29, 16.33, 36.07, 46.68, 59.59, 59.66, 75.58, 81.30, 88.70, 119.77, 119.96, 124.36, 125.00, 125.91, 126.35, 126.71, 127.39, 127.84, 128.08, 128.97, 129.01, 130.93, 131.07, 131.22, 132.92, 133.18, 136.58, 136.84, 137.16, 156.21, 156.57, 165.51; IR (thin film) 3349br m, 2930s, 1684s, 1528s, 1445s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{40}\text{H}_{39}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 595.2961, meas 595.2944. $[\alpha]_D^{20}$ +46.8 (c = 1.0, CH_2Cl_2) on 97% *ee* (2*S*,3*S*)-**152j** from (*S*)-VANOL.



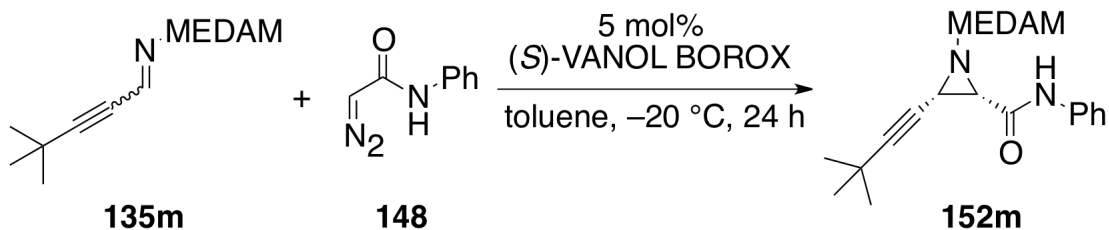
(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(hex-1-yn-1-yl)-*N*-phenylaziridine-2-carboxamide **152k**: The reaction of **135k** (78 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G) except that the temperature was -20°C . The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 25:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:6) to afford **152k** as a white foamy solid (86 mg, 0.164 mmol, 82%).

The optical purity of **152k** was determined to be 97% *ee* by HPLC (Chiralpak AD column, 222 nm, 80:20 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: R_t = 10.05 min for (2*S*,3*S*)-**152k** (major) and R_t = 40.11 min for (2*R*,3*R*)-**152k** (minor). A repeat of the reaction gave an 81% yield of **152k** with 98% *ee*; mp 125-127 °C; R_f = 0.32 (1:2 EtOAc/hexanes). Spectral data for **152k**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.73 (t, 3H, J = 7.5 Hz), 1.22-1.30 (m, 4H), 2.07 (t, 2H, J = 6.5 Hz), 2.22 (s, 6H), 2.28 (s, 6H), 2.51 (dt, 1H, J = 6.5, 1.5 Hz), 2.53 (d, 1H, J = 6.5 Hz), 3.66 (s, 4H), 3.71 (s, 3H), 6.95 (s, 2H), 7.06-7.10 (m, 1H), 7.08 (s, 2H), 7.28-7.32 (m, 2H), 7.48-7.51 (m, 2H), 8.39 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.42, 16.25, 16.26, 18.29, 21.67, 30.41, 35.70, 45.89, 59.57, 59.63, 74.64, 75.38, 84.01, 119.80, 124.19, 127.39, 127.84, 128.88, 130.73, 131.06, 136.68, 136.91, 137.22, 156.08, 156.44, 165.80; IR (thin film) 3353br m, 2930s, 2865m, 1686s, 1530s, 1445s, 1223s, 1017s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{34}\text{H}_{41}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 525.3117, meas 525.3092. $[\alpha]_D^{20}$ -0.7 (c = 1.0, CH_2Cl_2) on 97% *ee* (2*S*,3*S*)-**152k** from (*S*)-VANOL.



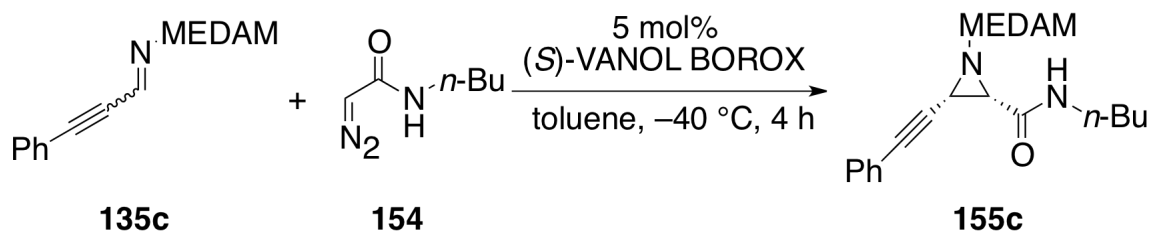
(2*S*,3*S*)-1-Bis(4-methoxy-3,5-dimethylphenyl)methyl-3-(cyclohexylethynyl)-*N*-phenylaziridine-2-carboxamide **152l**: The reaction of **135l** (83 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G) except that the temperature was -20 °C. The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 25:1. The major product was purified by column chromatography on silica gel (30 mm x

350 mm, EtOAc/hexanes 1:6 to 1:5) to afford **152i** as a white foamy solid (92 mg, 0.167 mmol, 84%). The optical purity of **152i** was determined to be 97% *ee* by HPLC (Chiralpak AD column, 222 nm, 80:20 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: R_t = 9.82 min for (2*S*,3*S*)-**152i** (major) and R_t = 34.88 min for (2*R*,3*R*)-**152i** (minor). The same reaction at -40 °C for 4 h gave a 78% yield of **152i** with 99% *ee* and >100:1 *cis/trans* selectivity after 81% conversion; mp 140-145 °C; R_f = 0.18 (1:4 EtOAc/hexanes). Spectral data for **152i**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.16-1.56 (m, 11H), 2.22 (s, 6H), 2.28 (s, 6H), 2.51 (dd, 1H, J = 6.5, 1.5 Hz), 2.54 (d, 1H, J = 6.5 Hz), 3.66 (s, 3H), 3.68 (s, 1H), 3.71 (s, 3H), 6.94 (s, 2H), 7.05-7.09 (m, 3H), 7.27-7.31 (m, 2H), 7.49-7.52 (m, 2H), 8.40 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.25, 16.27, 24.25, 25.76, 28.58, 32.15, 32.19, 35.75, 45.85, 59.58, 59.65, 74.81, 75.23, 87.98, 119.68, 124.14, 127.40, 127.89, 128.84, 130.71, 131.06, 136.70, 136.92, 137.22, 156.05, 156.45, 165.82 (1 sp^3 C not located); IR (thin film) 3353br m, 2930s, 1686s, 1528s, 1445s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{36}\text{H}_{43}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 551.3274, meas 551.3279. $[\alpha]_{\text{D}}^{20}$ +3.0 (c = 1.0, CH_2Cl_2) on 97% *ee* (2*S*,3*S*)-**152i** from (*S*)-VANOL.



(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(3,3-dimethylbut-1-yn-1-yl)-*N*-phenylaziridine-2-carboxamide **152m**: The reaction of **135m** (78 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure (Procedure G) except that

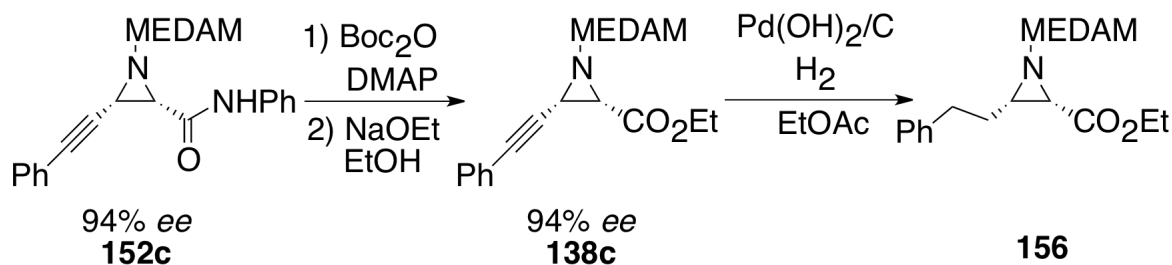
the temperature was $-20\text{ }^{\circ}\text{C}$ and the time was 24 h. The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 4:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:6) to afford **152m** as a white foamy solid (81 mg, 0.154 mmol, 77%). The optical purity of **152m** was determined to be 91% *ee* by HPLC (Chiralpak AD column, 222 nm, 90:10 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 10.94$ min for (2*S*,3*S*)-**152m** (major) and $R_t = 30.61$ min for (2*R*,3*R*)-**152m** (minor). A repeat of the reaction gave a 78% yield of **152m** with 91% *ee*; mp $66\text{--}71\text{ }^{\circ}\text{C}$; $R_f = 0.30$ (1:2 EtOAc/hexanes). Spectral data for **152m**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.03 (s, 9H), 2.22 (s, 6H), 2.28 (s, 6H), 2.47 (d, 1H, $J = 6.5$ Hz), 2.54 (d, 1H, $J = 6.5$ Hz), 3.67 (s, 3H), 3.70 (s, 1H), 3.71 (s, 3H), 6.94 (s, 2H), 7.05–7.09 (m, 1H), 7.08 (s, 2H), 7.28–7.32 (m, 2H), 7.50–7.53 (m, 2H), 8.38 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 16.25, 16.26, 27.26, 30.69, 35.60, 45.69, 59.57, 59.66, 73.21, 75.01, 92.23, 119.67, 124.15, 127.43, 127.96, 128.86, 130.68, 131.05, 136.67, 136.88, 137.14, 156.01, 156.46, 165.84; IR (thin film) 3353br m, 2967s, 1696s, 1530s, 1445s, 1223s, 1015s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{34}\text{H}_{41}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 525.3117, meas 525.3098. $[\alpha]_D^{20} -6.4$ ($c = 1.0$, CH_2Cl_2) on 91% *ee* (2*S*,3*S*)-**152m** from (S)-VANOL.



(2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-butyl-3-(phenylethynyl)aziridine-2-carboxamide **155c**: The reaction of **135c** (82 mg, 0.20 mmol) and diazoacetamide **154**^{27a} (40 mg,

0.28 mmol) was performed according to the general procedure (Procedure G). The ^1H NMR spectrum of the crude reaction mixture gave *cis/trans* ratio of 33:1. The major product was purified by column chromatography on silica gel (30 mm x 350 mm, EtOAc/hexanes 1:3) to afford **155c** as an off-white foamy solid (88 mg, 0.168 mmol, 84%). The optical purity of **155c** was determined to be 94% *ee* by HPLC (Chiralpak AD column, 222 nm, 85:15 Hexane/2-PrOH, flow rate: 0.7 mL/min). Retention time: R_t = 8.19 min for (2*R*,3*R*)-**155c** (minor) and R_t = 13.53 min for (2*S*,3*S*)-**155c** (major). mp 50-55 °C; R_f = 0.32 (1:1 EtOAc/hexanes). Spectral data for **155c**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.78 (t, 3H, J = 6.5 Hz), 1.19-1.28 (m, 2H), 1.35-1.48 (m, 2H), 2.22 (s, 6H), 2.27 (s, 6H), 2.55 (d, 1H, J = 6.5 Hz), 2.63 (d, 1H, J = 6.5 Hz), 3.15-3.23 (m, 1H), 3.24-3.31 (m, 1H), 3.66 (s, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 6.68 (t, 1H, J = 6.0 Hz), 6.92 (s, 2H), 7.09 (s, 2H), 7.25-7.32 (m, 3H), 7.35-7.38 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.67, 16.20, 16.29, 19.94, 31.95, 35.42, 38.65, 46.10, 59.57, 59.63, 75.68, 82.65, 84.47, 122.48, 127.42, 127.82, 128.26, 128.47, 130.74, 130.93, 131.84, 136.78, 136.96, 156.09, 156.41, 167.13; IR (thin film) 3401br m, 2930s, 1676s, 1530s, 1489s, 1223s, 1013s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{34}\text{H}_{41}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$) 525.3117, meas 525.3102. $[\alpha]_D^{20}$ +59.5 (c = 1.0, CH_2Cl_2) on 94% *ee* (2*S*,3*S*)-**155c** from (*S*)-VANOL.

6.1.7 Detemination of the absolute configurations of *cis*-aziridines from diazoacetamides



Conversion of the *cis*-amide aziridine **152c to the *cis*-ester aziridine **138c**** ^{27a,26o}

(2*S*,3*S*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(phenylethynyl)aziridine-2-carboxylate **138c**:

To a 25 mL flame dried round bottom flask charged with N_2 were added the *cis*-aziridine (2*S*,3*S*)-**152c** (56 mg, 0.103 mmol, 94% *ee*), dry CH_3CN (4.5 mL), and dry CH_2Cl_2 (0.5 mL). The flask was then fitted with a rubber septum and a N_2 balloon. This was followed by the addition of DMAP (26 mg, 0.213 mmol) and di-*tert*-butyl dicarbonate (68 mg, 0.312 mmol). The reaction mixture was then stirred at room temperature for 12 h. The reaction mixture was then subjected to rotary evaporation to afford a yellow oil, which was loaded onto a silica gel chromatography column (20 mm $\times$ 200 mm, 1:5 EtOAc /hexanes) to afford the intermediate product as a white foamy solid. R_f = 0.16 (1:4 EtOAc /hexanes). This intermediate was added to a 25 mL round bottom flask fitted with a magnetic stir bar and then EtOH (2 mL) was added. The flask was fitted with a rubber septum and a N_2 balloon and the solution was cooled to 0 $^\circ\text{C}$ in an ice bath, and then NaOEt (21 wt% solution of NaOEt in EtOH , 77 μL , 0.206 mmol) was added. This reaction mixture was stirred at 0 $^\circ\text{C}$ for 1 h. The reaction was then quenched by the addition of NH_4Cl (sat. aq. 1mL) and the reaction mixture was concentrated by rotary evaporation. This was followed by the addition of water (1 mL) and the mixture was extracted with CH_2Cl_2 (5 mL $\times$ 3). The organic layers were combined, dried over Na_2SO_4 , filtered through a pad of Celite and

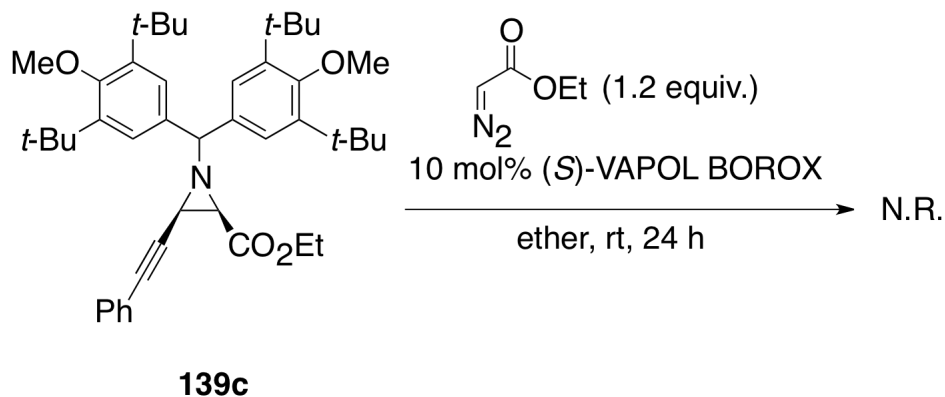
the solvents removed. Purification of the major product by silica gel chromatography (20 mm × 200 mm, 1:12 EtOAc/hexanes) afforded the *cis*-ester aziridine **138c** (40 mg, 0.080 mmol, 80%). The optical purity of **138c** was determined to be 94% *ee* by HPLC (Chiralcel OD-H column, 225 nm, 99:1 Hexane/2-PrOH, flow rate: 1 mL/min). Retention time: $R_t = 8.37$ min for (2*R*,3*R*)-**21c** (major) and $R_t = 10.59$ min for (2*S*,3*S*)-**138c** (minor). $[\alpha]_D^{20} +59.5$ ($c = 1.0$, CH₂Cl₂) on 94% *ee* (2*S*,3*S*)-**138c**.

Conversion of the aziridine **138c** to the aziridine **156** by alkyne reduction

(2*S*,3*S*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenethylaziridine-2-carboxylate

156: A flame dried 10 mL round bottom flask was charged with (2*S*,3*S*)-**138c** (25 mg, 0.050 mmol), Pearlman's catalyst (20% Pd(OH)₂ on carbon, moisture *ca* 60%, 9 mg, 0.005 mmol) and EtOAc (1 mL) under N₂. The flask was equipped with a 3-way valve connected with vacuum and a H₂ balloon. The valve to vacuum was opened for a few seconds and switched to the H₂ balloon. This process was repeated 3 additional times. The suspension was stirred under a H₂ balloon for 24 h. Then the mixture was filtered through a Celite pad on a sintered glass funnel and washed well with EtOAc. The filtrate was concentrated by rotary evaporation. Purification of the major product by silica gel chromatography (20 mm × 300 mm, 1:15 EtOAc/hexanes) afforded the *cis*-aziridine **156** as a colorless oil (16 mg, 0.032 mmol, 64%). $R_f = 0.27$ (1:4 EtOAc/hexanes). Spectral data for **156**: ¹H NMR (CDCl₃, 500 MHz) δ 1.23 (t, 3H, $J = 7.0$ Hz), 1.80-1.92 (m, 2H), 1.95 (q, 1H, $J = 7.0$ Hz), 2.19 (d, 1H, $J = 7.0$ Hz), 2.22 (s, 6H), 2.25 (s, 6H), 2.28-2.33 (m, 1H), 2.45-2.52 (m, 1H), 3.39 (s, 1H), 3.66 (s, 3H), 3.67 (s, 3H), 4.11-4.20 (m, 2H),

6.89 (d, 2H, $J = 7.5$ Hz), 7.06 (s, 2H), 7.08 (s, 2H), 7.10-7.13 (m, 1H), 7.16-7.20 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.32, 16.15, 16.18, 29.60, 33.26, 43.36, 46.15, 59.58, 59.64, 60.76, 77.26, 125.72, 127.27, 128.07, 128.17, 128.39, 130.54, 130.62, 137.77, 138.30, 141.37, 155.80, 156.22, 169.57. $[\alpha]_{\text{D}}^{20} = -58.9$ ($c = 1.0$, EtOAc) on 94% *ee* material; lit.^{26m} $[\alpha]_{\text{D}}^{20} -62.3$ ($c = 1.0$, EtOAc) on 96 % *ee* material.



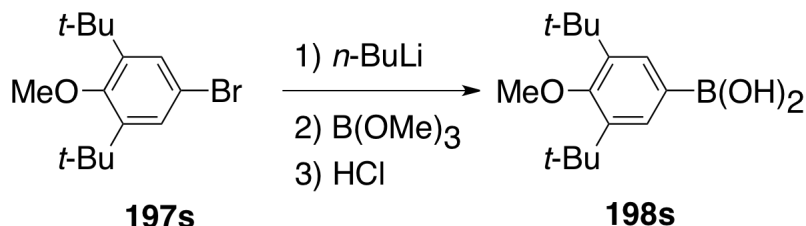
A 25 mL pear-shaped single necked Schlenk flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it) and cooled to room temperature under N_2 and charged with (*S*)-VAPOL (54 mg, 0.10 mmol) and triphenyl borate (116 mg, 0.40 mmol). The mixture was dissolved in 2 mL distilled toluene. After the addition of H_2O (1.8 μL , 0.10 mmol), the Teflon valve was closed and the flask was heated at 80 $^\circ\text{C}$ for 1 h. Toluene was carefully removed by exposing to high vacuum (0.1 mm Hg) by slightly cracking the Teflon valve. After removal of the volatile, the Teflon valve was completely opened and the flask was heated to 80 $^\circ\text{C}$ under high vacuum (0.5 mm Hg) for 30 min. To the Schlenk flask containing the catalyst were added benzhydryl phenyl imine (27.1 mg, 0.10 mmol) and dry ether (2 mL). The reaction mixture was stirred at room temperature for 5 minutes. At the same time, to

a flame dried 25 mL round bottom flask was added aziridine **139c** (266 mg, 0.4 mmol) under N₂. The VAPOL-BOROX catalyst solution (0.8 mL) in the Schlenk flask was then transferred to the flask. The resulting mixture was stirred at room temperature for 5 min and then ethyl diazoacetate (50 μ L, 0.48 mmol) was added via syringe. The reaction mixture was stirred at room temperature for 24 h. The mixture was then diluted with hexanes (5 mL). Rotary evaporation of the solvent followed by exposure to high vacuum (0.5 mm Hg) for 30 minutes gave the crude mixture as a yellow amorphous solid. The ¹H NMR of the crude mixture didn't show any [3+2] cycloaddition product **144c**.

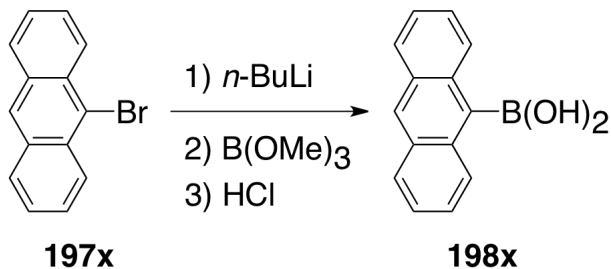
6.2 Experimental for chapter three

6.2.1 Preparation of boronic acids

General procedure for the preparation of boronic acids – illustrated for the synthesis of *(3,5-di-tert-butyl-4-methoxyphenyl)boronic acid 198s* (Procedure H)⁸⁰

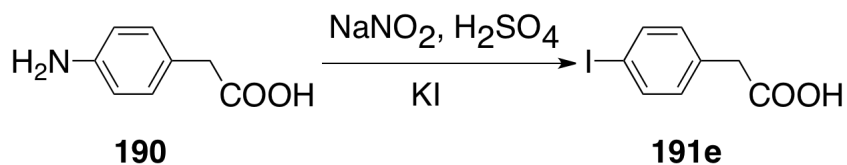


To a flame-dried 250 mL round bottom flask was added 5-bromo-1,3-di-*tert*-butyl-2-methoxybenzene **197s** (5.98 g, 20.0 mmol) and anhydrous THF (100 mL). The mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-BuLi (2.5 M in hexanes, 8.4 mL, 21.0 mmol) was added dropwise. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and then B(OMe)₃ (5.60 mL, 50.2 mmol) was added all at once. The mixture was warmed up to room temperature and stirred overnight. H₂O (80 mL) was added to the mixture. The mixture was acidified with 10% HCl to pH 3-5. The organic layer was separated and the aqueous layer was extracted with ether (80 mL x 2). The combined organic layer was washed with brine (25 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. Petroleum ether (50 mL) was added to the residue. After filtration through filter paper, the product was obtained as a white solid (1.66 g, 6.29 mmol, 31% yield). Spectral data for **198s**: ¹H NMR (CDCl₃, 500 MHz) δ 1.50 (s, 18H), 3.74 (s, 3H), 8.15 (s, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 32.00, 35.73, 64.37, 134.14, 143.30, 163.80 (1 sp² C not located).



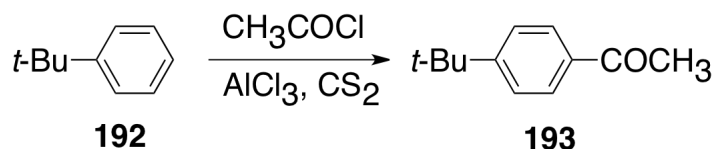
anthracene-9-boronic acid 198x:⁸¹ The reaction of 9-bromoanthracene **197x** (5.14 g, 20.0 mmol) with *n*-BuLi (2.5 M in hexanes, 8.4 mL, 21.0 mmol) and B(OMe)₃ (5.60 mL, 50.2 mmol) was performed according to the general procedure (Procedure A). Purification of the crude product by column chromatography on silica gel (50 mm x 200 mm, CH₂Cl₂/hexanes 1:1, then acetone/hexanes 1:3) gave **198x** as a yellow solid (2.34 g, 10.5 mmol, 53%). Spectral data for **198x**: ¹H NMR (DMSO-*d*₆, 500 MHz) δ 7.46-7.52 (m, 4H), 7.98-8.01 (m, 2H), 8.04-8.07 (m, 2H), 8.51 (s, 1H), 8.77 (br s, 2H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 124.89, 125.05, 125.84, 128.35, 128.99, 130.73, 132.70 (1 sp² C not located).

6.2.2 Preparation of 4-substituted-phenylacetic acids



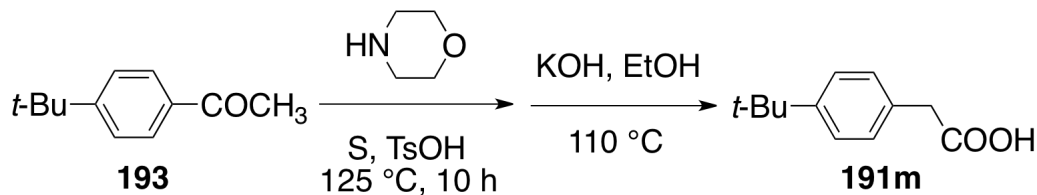
4-iodophenylacetic acid 191e:⁷⁴ To a 500 mL round bottom flask was added 4-aminophenylacetic acid **190** (15.1 g, 100 mol), H₂O (150 mL) and H₂SO₄ (20 mL). To the resulting mixture was added a solution of NaNO₂ (8.28 g, 120 mmol) in H₂O (30 mL). The mixture was stirred at 0 °C for 30 min prior to the addition of a cooled solution of KI (33.2 g,

200 mmol) in H₂O (120 mL). The reaction was stirred at 0 °C for 2.5 h. The mixture was extracted with EtOAc (150 mL x 4). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm x 200 mm, CH₂Cl₂/hexanes 1:1, then acetone/hexanes 1:3) gave **191e** as a yellow solid (15.9 g, 60.7 mmol, 61%). mp 137-138 °C (lit.⁷⁴ mp 138-140 °C); R_f = 0.20 (1:3 acetone:hexanes). Spectral data for **191e**: ¹H NMR (CDCl₃, 500 MHz) δ 3.57 (s, 2H), 6.99-7.03 (m, 2H), 7.62-7.66 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 40.46, 92.96, 131.34, 132.76, 137.75, 177.17; IR (thin film) 1698s, 1487s, 1406s cm⁻¹.



4-tert-butylacetophenone 193:⁷⁵ The following procedure was adapted from one for a related compound:⁷⁴ To a flame-dried 500 mL round bottom flask was added AlCl₃ (147 g, 1.1 mol) and CS₂ (200 mL). To the stirred mixture was added a solution of *t*-butylbenzene (155 mL, 1.0 mol), acetyl chloride (71.1 mL, 1.0 mol) in CS₂ (100 mL) at 0 °C. After stirring at 0 °C for 2 h, the mixture was refluxed overnight. The mixture was cooled to room temperature and poured into a mixture of ice (600 g) and H₂SO₄ (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layer was washed with brine (100 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. Vacuum distillation (94 °C at 1 mm Hg) gave **193** as a clear colorless oil (160 g, 0.91 mol, 91%). Spectral data for **193**: ¹H NMR (CDCl₃, 500 MHz) δ 1.32 (s, 9H), 2.57 (s, 3H), 7.44-7.48 (m, 2H),

7.86-7.90 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.52, 31.06, 35.07, 125.48, 128.26, 134.60, 156.80, 197.84; IR (thin film) 2965s, 1684s, 1406s, 1360s, 1271s, 1113s cm^{-1} .

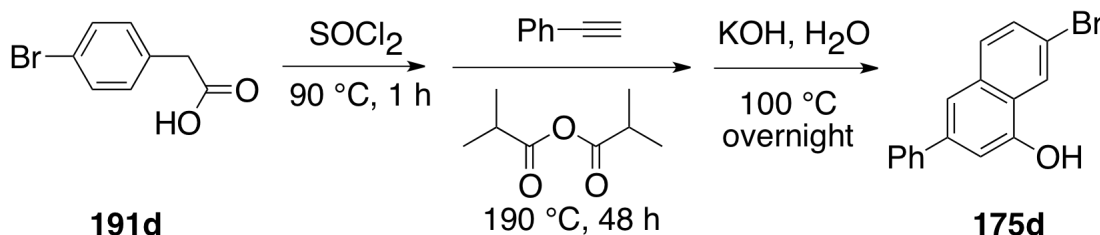


4-tert-butylphenylacetic acid **191m**:⁷⁶ The following procedure was adapted from one for a related compound:⁷ To a 1 L round bottom flask was added 4-*tert*-butylacetophenone **193** (26.4 g, 150 mmol), morpholine (45 mL, 0.5 mol), sulfur (9.6 g, 0.3 mol) and *p*-toluene sulfonic acid monohydrate (0.4 g, 2 mmol). The mixture was stirred at 125 °C for 10 h. After cooling down to room temperature, alcoholic KOH (3M, 250 mL) was added and the mixture was stirred at 110 °C overnight. After cooling down to room temperature, H_2O (200 mL) was added to the mixture. The mixture was acidified with 6N HCl to pH 2. CH_2Cl_2 (300 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined organic layer was dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm column, CH_2Cl_2 /hexanes 1:3, then CH_2Cl_2 , and then acetone/hexanes 1:3 as eluent) gave **191m** as an off-white solid (25.2 g, 132 mmol, 88%). mp 77-79 °C; R_f = 0.20 (CH_2Cl_2). Spectral data for **191m**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.30 (s, 9H), 3.61 (s, 2H), 7.19-7.22 (m, 2H), 7.33-7.36 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 31.31, 34.47, 40.50, 125.59, 129.01, 130.19, 150.24, 177.88; IR (thin film) 2957s, 1715s, 1520s, 1458s, 1402s cm^{-1} .

6.2.3 Preparation of 7-substituted-3-phenyl-1-naphthols

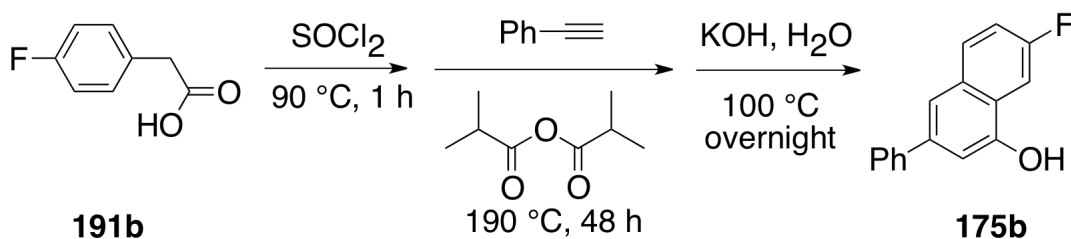
General procedure for the preparation of 7-substituted-3-phenyl-1-naphthols – illustrated

for the synthesis of 7-bromo-3-phenyl-1-naphthol **175d** (Procedure I)^{13g,73}



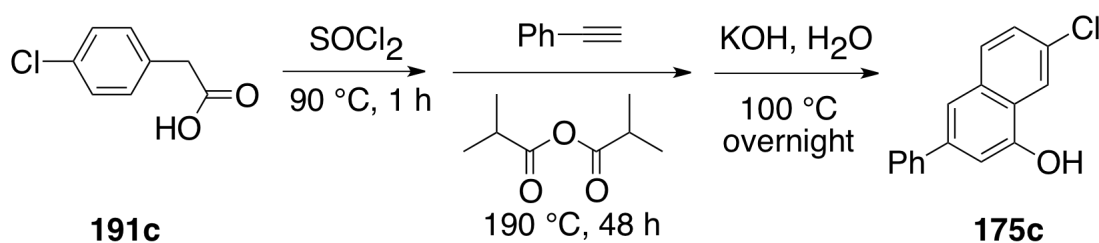
A single-neck 500 mL round bottom flask equipped with a condenser was charged with 4-bromo-phenylacetic acid **191d** (19.35 g, 90 mmol), and SOCl_2 (24 mL, 329 mmol). The top of the condenser was vented to a bubbler and then into a beaker filled with NaOH (sat. aq.) to trap acidic gases. The mixture was heated to reflux for 1 h in a $90\text{ }^\circ\text{C}$ oil bath, and then all of the volatiles were carefully removed by swirling it under high vacuum (1 mm Hg) for 1 h with a 2nd liquid N_2 trap to protect the pump. To the flask containing the acyl chloride was added phenylacetylene (13.2 mL, 120 mmol) and $(i\text{-PrCO})_2\text{O}$ (30 mL, 181 mmol) under N_2 . The mixture was stirred at $190\text{ }^\circ\text{C}$ for 48 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled down to below $100\text{ }^\circ\text{C}$ (*ca.* $60\text{ }^\circ\text{C}$, oil bath temperature) and a solution of KOH (30 g, 536 mmol) in H_2O (120 mL) was then added slowly. This two-phase mixture was stirred at $100\text{ }^\circ\text{C}$ overnight. The mixture was cooled to room temperature and ethyl acetate (200 mL) was added and the mixture stirred for 10 min before the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate ($100\text{ mL} \times 3$) and the combined organic layer was washed with brine (100 mL), dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography

on silica gel (50 mm × 250 mm, CH₂Cl₂:hexanes 1:3 to 1:2 to 1:1 to 1:0) gave **175d** as an off-white solid (17.94 g, 60.0 mmol, 67%). mp 94-95 °C; R_f = 0.33 (CH₂Cl₂). Spectral data for **175d**: ¹H NMR (CDCl₃, 500 MHz) δ 5.24 (s, 1H), 7.07 (d, 1H, *J* = 1.5 Hz), 7.35-7.39 (m, 1H), 7.43-7.47 (m, 2H), 7.56 (dd, 1H, *J* = 8.5, 1.5 Hz), 7.59 (s, 1H), 7.62-7.65 (m, 2H), 7.70 (d, 1H, *J* = 9.0 Hz), 8.35 (d, 1H, *J* = 1.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 109.28, 118.62, 119.30, 124.27, 124.65, 127.24, 127.69, 128.90, 129.59, 130.31, 133.36, 139.41, 140.49, 150.84; IR (thin film) 3526br m, 3058w, 1590s, 1495s, 1408s, 1248m cm⁻¹; mass spectrum, *m/z* (% rel intensity) 300 M⁺ (90, ⁸¹Br), 298 M⁺ (100, ⁷⁹Br), 269 (3), 218 (8), 191 (58, ⁸¹Br), 189 (68, ⁷⁹Br), 150 (18). Anal calcd for C₁₆H₁₁BrO: C, 64.24; H, 3.71. Found: C, 64.61; H, 3.65.

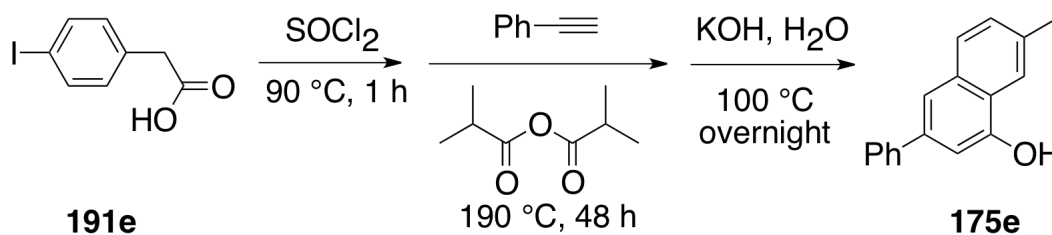


7-fluoro-3-phenylnaphthalen-1-ol **175b**: The reaction of 4-fluoro-phenylacetic acid **191b** (3.66 g, 23.8 mmol), SOCl₂ (6.35 mL, 87 mmol), phenylacetylene (3.49 mL, 31.8 mmol) and (*i*-PrCO)₂O (7.93 mL, 47.9 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:3 to 1:2 to 1:1 to 1:0) gave **175b** as an off-white solid (3.66 g, 15.4 mmol, 65%). mp 82-84 °C; R_f = 0.28 (CH₂Cl₂). Spectral data for **175b**: ¹H NMR (CDCl₃, 500 MHz) δ 5.21 (s, 1H), 7.09 (s, 1H), 7.27 (td, 1H, *J* = 8.5, 2.5 Hz), 7.34-7.38 (m, 1H), 7.43-7.47 (m, 2H), 7.62-7.66 (m, 3H), 7.78 (dd, 1H, *J* = 10.0, 2.5 Hz), 7.83 (dd, 1H, *J* = 9.0, 5.5 Hz); ¹³C NMR

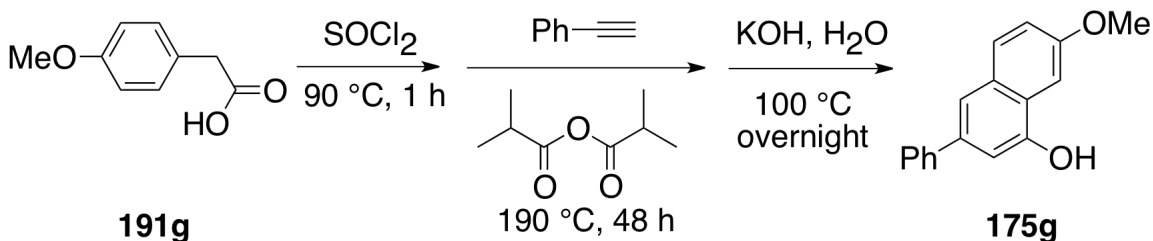
(CDCl₃, 125 MHz) δ 105.59 ($^2J_{\text{CF}} = 22.6$ Hz), 109.11, 117.25 ($^2J_{\text{CF}} = 25.3$ Hz), 118.61 ($^4J_{\text{CF}} = 1.4$ Hz), 124.25 ($^3J_{\text{CF}} = 8.9$ Hz), 127.35 ($^2J_{\text{CF}} = 36.9$ Hz), 128.86, 130.35 ($^3J_{\text{CF}} = 8.9$ Hz), 131.92, 138.13 ($^4J_{\text{CF}} = 2.8$ Hz), 140.60, 151.19, 151.23, 160.42 ($^1J_{\text{CF}} = 244.5$ Hz); ^{19}F NMR (CDCl₃, 283 Hz) δ -112.77; IR (thin film) 3528br s, 3063m, 1501s, 1414s, 1244s cm⁻¹; mass spectrum, m/z (% rel intensity) 238 M⁺ (100), 209 (73), 183 (29), 157 (6). Anal calcd for C₁₆H₁₁OF: C, 80.66; H, 4.65. Found: C, 80.65; H, 4.60.



7-chloro-3-phenylnaphthalen-1-ol **175c**: The reaction of 4-chloro-phenylacetic acid **191c** (10.10 g, 59.2 mmol), SOCl₂ (15.8 mL, 217 mmol), phenylacetylene (8.8 mL, 80 mmol) and (i-PrCO)₂O (19.7 mL, 119 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:3 to 1:1 to 1:0) gave **175c** as a white solid (10.73 g, 42.1 mmol, 71%). mp 94.5-95.5 °C; R_f = 0.33 (CH₂Cl₂). Spectral data for **175c**: ^1H NMR (CDCl₃, 500 MHz) δ 5.27 (s, 1H), 7.07 (d, 1H, $J = 1.0$ Hz), 7.35-7.39 (m, 1H), 7.42-7.48 (m, 3H), 7.60 (s, 1H), 7.62-7.65 (m, 2H), 7.76 (dd, 1H, $J = 8.0, 0.5$ Hz), 8.17 (d, 1H, $J = 1.5$ Hz); ^{13}C NMR (CDCl₃, 125 MHz) δ 109.26, 118.54, 120.96, 124.18, 127.23, 127.65, 127.82, 128.89, 129.52, 131.15, 133.15, 139.20, 140.47, 150.92; IR (thin film) 3308br s, 1593s, 1497s, 1410s, 1275s cm⁻¹; HRMS (ESI-) m/z calcd for C₁₆H₁₀³⁵ClO (M-H⁺) 253.0420, meas 253.0423.

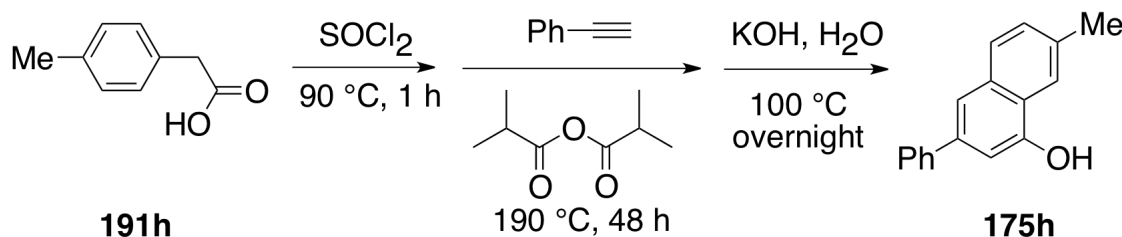


7-iodo-3-phenylnaphthalen-1-ol 175e: The reaction of 4-iodo-phenylacetic acid **191e** (15.72 g, 60.0 mmol), SOCl_2 (16 mL, 219 mmol), phenylacetylene (8.8 mL, 80 mmol) and $(i\text{-PrCO})_2\text{O}$ (20 mL, 120 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:3 to 1:1 to 1:0) gave **175e** as a yellow solid (10.76 g, 31.0 mmol, 52%). mp $95\text{--}97\text{ }^\circ\text{C}$; $R_f = 0.31$ (CH_2Cl_2). Spectral data for **175e**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.23 (s, 1H), 7.06 (d, 1H, $J = 1.5$ Hz), 7.35–7.39 (m, 1H), 7.43–7.47 (m, 2H), 7.56 (d, 1H, $J = 8.5$ Hz), 7.60 (s, 1H), 7.62–7.65 (m, 2H), 7.73 (dd, 1H, $J = 8.5, 1.5$ Hz), 8.56–8.58 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 90.62, 109.14, 118.63, 125.09, 127.24, 127.71, 128.89, 129.49, 130.86, 133.61, 135.47, 139.62, 140.48, 150.62; IR (thin film) 3526br s, 3056m, 1581s, 1493s, 1406s, 1248s cm^{-1} ; mass spectrum, m/z (% rel intensity) 346 M^+ (76), 218 (7), 189 (71), 173 (44), 165 (24), 109 (15), 94 (100). Anal calcd for $\text{C}_{16}\text{H}_{11}\text{IO}$: C, 55.51; H, 3.20. Found: C, 55.52; H, 3.02.



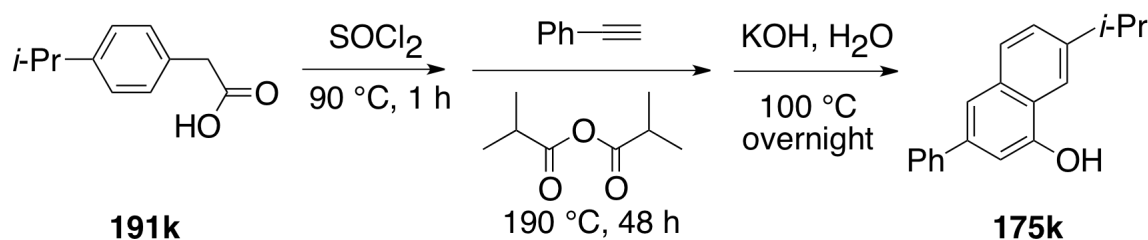
7-methoxy-3-phenylnaphthalen-1-ol 175g: The reaction of 4-methoxy-phenylacetic acid **191g** (12.46 g, 75.0 mmol), SOCl_2 (20 mL, 274 mmol), phenylacetylene (11 mL, 100 mmol) and

(*i*-PrCO)₂O (25 mL, 150 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:2 to 1:1 to 1:0) gave **175g** as a yellow solid (9.35 g, 37.4 mmol, 50%). mp 81-82 °C; R_f = 0.16 (CH₂Cl₂). Spectral data for **175g**: ¹H NMR (CDCl₃, 500 MHz) δ 3.95 (s, 3H), 5.24 (s, 1H), 7.06 (d, 1H, *J* = 1.5 Hz), 7.18 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.31-7.36 (m, 1H), 7.41-7.46 (m, 3H), 7.59 (s, 1H), 7.62-7.65 (m, 2H), 7.75 (d, 1H, *J* = 9.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 55.42, 99.85, 108.84, 118.65, 119.75, 124.45, 127.11, 127.16, 128.79, 129.62, 130.45, 136.46, 140.94, 150.74, 157.50; IR (thin film) 3397br s, 2940m, 1597s, 1501s, 1401s, 1257s, 1213s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 250 M⁺ (100), 235 (34), 207 (71), 178 (41), 176 (11), 152 (10), 125 (18). Anal calcd for C₁₇H₁₄O₂: C, 81.58; H, 5.64. Found: C, 81.37; H, 5.59.

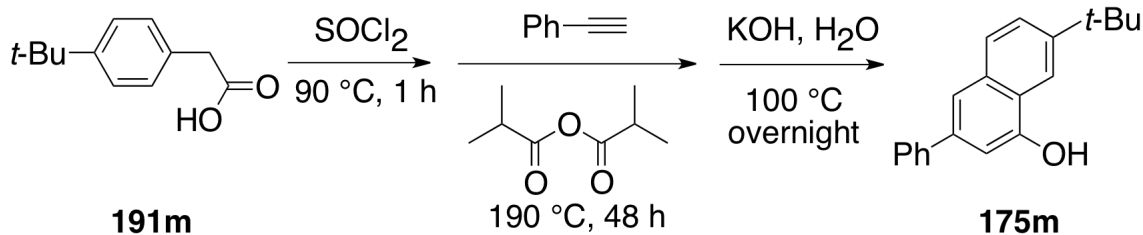


7-methyl-3-phenylnaphthalen-1-ol 175h: The reaction of 4-methyl-phenylacetic acid **191h** (11.25 g, 75 mmol), SOCl₂ (20 mL, 274 mmol), phenylacetylene (11 mL, 100 mmol) and (*i*-PrCO)₂O (25 mL, 150 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:3 to 1:2 to 1:1 to 1:0) gave **175h** as a yellow solid (9.88 g, 42.2 mmol, 56%). mp 91-92 °C; R_f = 0.30 (CH₂Cl₂). Spectral data for **175h**: ¹H NMR (CDCl₃, 500 MHz) δ 2.54 (s, 3H), 5.23 (s, 1H), 7.05 (d, 1H, *J* = 1.5 Hz), 7.33-7.37 (m, 2H), 7.42-7.47 (m, 2H), 7.60 (s, 1H),

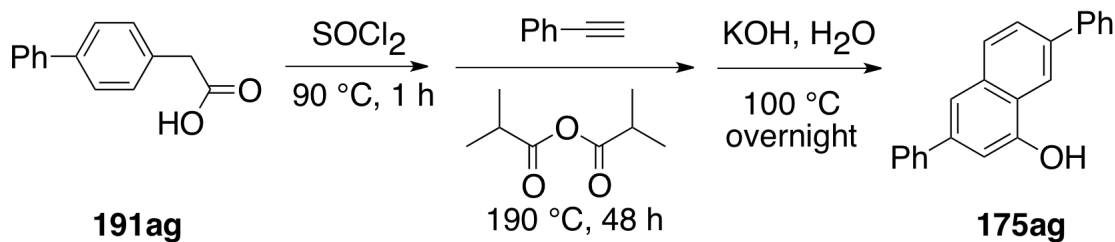
7.64-7.67 (m, 2H), 7.75 (d, 1H, $J = 8.5$ Hz), 7.92 (d, 1H, $J = 1.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.91, 108.46, 118.61, 120.31, 123.61, 127.22, 127.29, 127.94, 128.79, 129.14, 133.23, 135.15, 137.90, 141.00, 151.18; IR (thin film) 3335br s, 3054m, 2919w, 1572s, 1501s, 1410s, 1258s cm^{-1} ; mass spectrum, m/z (% rel intensity) 234 M^+ (30), 191 (17), 165 (5). Anal calcd for $\text{C}_{17}\text{H}_{14}\text{O}$: C, 87.15; H, 6.02. Found: C, 87.00; H, 6.05.



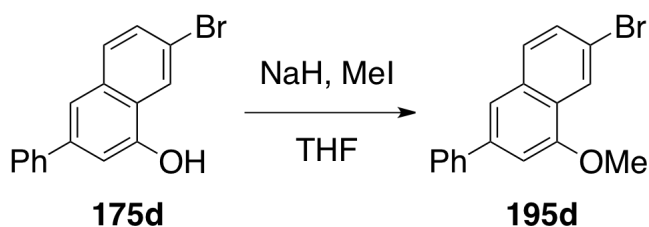
7-isopropyl-3-phenylnaphthalen-1-ol **175k**: The reaction of 4-isopropylphenylacetic acid **191k** (14.79 g, 83.1 mmol), SOCl_2 (22.1 mL, 303 mmol), phenylacetylene (12.2 mL, 111 mmol) and $(i\text{-PrCO})_2\text{O}$ (27.6 mL, 167 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:3 to 1:1 to 1:0) gave **175k** as an off-white solid (13.19 g, 50.3 mmol, 61%). mp $100\text{--}101^\circ\text{C}$; $R_f = 0.42$ (CH_2Cl_2). Spectral data for **175k**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.36 (d, 6H, $J = 7.0$ Hz), 3.07-3.14 (m, 1H), 5.32 (s, 1H), 7.05 (d, 1H, $J = 1.5$ Hz), 7.33-7.38 (m, 1H), 7.42-7.47 (m, 3H), 7.62 (s, 1H), 7.64-7.67 (m, 2H), 7.80 (d, 1H, $J = 8.5$ Hz), 7.97 (d, 1H, $J = 0.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 23.96, 34.47, 108.40, 117.59, 118.57, 123.57, 126.74, 127.22, 127.28, 128.08, 128.78, 133.61, 137.99, 141.00, 146.09, 151.41; IR (thin film) 3225br s, 2955s, 1496s, 1398s, 1254s cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{19}\text{H}_{19}\text{O}$ ($\text{M}+\text{H}^+$) 263.1436, found 263.1431.



7-(*tert*-butyl)-3-phenylnaphthalen-1-ol **175m**: The reaction of 4-*tert*-butylphenylacetic acid **191m** (13.44 g, 70.0 mmol), SOCl_2 (18.7 mL, 256 mmol), phenylacetylene (10.3 mL, 94 mmol) and $(i\text{-PrCO})_2\text{O}$ (23.4 mL, 141 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:3 to 1:1 to 1:0) gave **175m** as an off-white solid (9.78 g, 35.4 mmol, 51%). mp $135\text{--}137\text{ }^\circ\text{C}$; $R_f = 0.40$ (CH_2Cl_2). Spectral data for **175m**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.43 (s, 9H), 5.25 (s, 1H), 7.06 (d, 1H, $J = 2.0$ Hz), 7.32–7.37 (m, 1H), 7.42–7.47 (m, 2H), 7.59–7.62 (m, 2H), 7.64–7.67 (m, 2H), 7.80 (d, 1H, $J = 8.5$ Hz), 8.08–8.10 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 31.31, 35.10, 108.41, 116.25, 118.40, 123.31, 125.80, 127.24, 127.29, 127.81, 128.78, 133.22, 138.19, 141.06, 148.30, 151.66; IR (thin film) 3505br s, 2961s, 1601s, 1559s, 1458s, 1408s, 1273s cm^{-1} ; mass spectrum, m/z (% rel intensity) 276 M^+ (54), 261 (96), 233 (15), 202 (24), 189 (15), 165 (9), 130 (13), 116 (100). Anal calcd for $\text{C}_{20}\text{H}_{20}\text{O}$: C, 86.92; H, 7.29. Found: C, 86.92; H, 7.04.

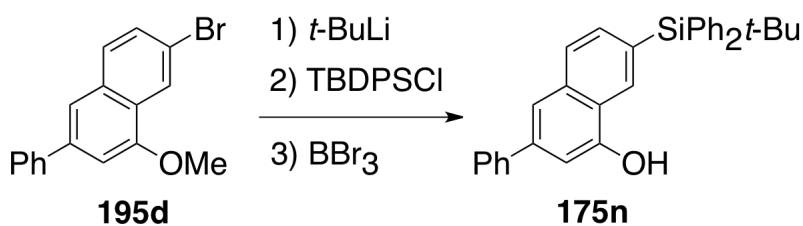


3,7-diphenylnaphthalen-1-ol 175ag: The reaction of 4-phenyl-phenylacetic acid **191ag** (15.92 g, 75 mmol), SOCl₂ (20 mL, 274 mmol), phenylacetylene (11 mL, 100 mmol) and (*i*-PrCO)₂O (25 mL, 150 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:3 to 1:2 to 1:1 to 1:0) gave **175ag** as a yellow solid (14.42 g, 48.7 mmol, 65%). mp 202-207 °C; R_f = 0.38 (CH₂Cl₂). Spectral data for **175ag**: ¹H NMR (CDCl₃, 500 MHz) δ 5.30 (s, 1H), 7.10 (d, 1H, *J* = 1.5 Hz), 7.35-7.39 (m, 2H), 7.45-7.50 (m, 4H), 7.66-7.70 (m, 3H), 7.74-7.80 (m, 3H), 7.92 (d, 1H, *J* = 8.5 Hz), 8.38 (d, 1H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 108.76, 118.55, 119.49, 123.81, 126.56, 127.26, 127.35, 127.41, 127.50, 128.58, 128.85, 134.13, 138.06, 138.96, 140.85, 141.15, 151.98 (1 sp² C not located); IR (thin film) 3473br s, 1557s, 1507s, 1456s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 296 M⁺ (100), 295 (10), 267 (11), 265 (10), 252 (8), 189 (11), 165 (6), 148 (21), 119 (7). Anal calcd for C₂₂H₁₆O: C, 89.16; H, 5.44. Found: C, 89.09; H, 5.42.



7-bromo-1-methoxy-3-phenylnaphthalene 195d: To a flame-dried 250 mL round bottom flask was added 7-bromo-3-phenylnaphthalen-1-ol **175d** (4.49 g, 15.0 mmol) and dry THF (75 mL) under N₂. The resulting solution was cooled to 0 °C and NaH (1.2 g, 60% in mineral oil, 30 mmol) was added. The resulting mixture was stirred at 0 °C for 15 minutes. MeI (3.8 mL, 61 mmol) was then added to the mixture at 0 °C. The mixture was warmed up to room temperature

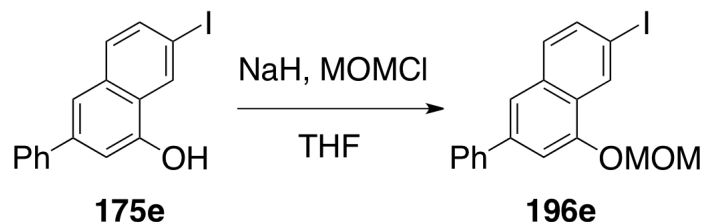
and stirred for an additional 24 h. NH_4Cl (sat. aq. 20 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The residue was extracted with CH_2Cl_2 (20 mL $\times$ 3). The combined organic layer was washed with $\text{Na}_2\text{S}_2\text{O}_3$ (sat. aq. 20 mL $\times$ 2) and brine (20 mL) and then dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm $\times$ 300 mm, CH_2Cl_2 :hexanes 1:8) gave **195d** as a white solid (4.25 g, 13.5 mmol, 90%). mp 99-100 °C; R_f = 0.30 (1:4 CH_2Cl_2 /hexanes). Spectral data for **195d**: ^1H NMR (CDCl_3 , 500 MHz) δ 4.05 (s, 3H), 7.06 (d, 1H, J = 7.5 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.45-7.49 (m, 2H), 7.54-7.57 (m, 2H), 7.67-7.70 (m, 3H), 8.41 (d, 1H, J = 2.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.69, 104.77, 118.14, 119.27, 124.60, 125.89, 127.38, 127.61, 128.86, 129.42, 130.20, 133.04, 139.52, 141.27, 154.97; IR (thin film) 1588s, 1491s, 1372s, 1229s, 1119s cm^{-1} ; mass spectrum, m/z (% rel intensity) 314 M^+ (66, ^{81}Br), 312 M^+ (70, ^{79}Br), 271 (34, ^{81}Br), 269 (39, ^{79}Br), 218 (35), 202 (29), 189 (80), 157 (33). Anal calcd for $\text{C}_{17}\text{H}_{13}\text{BrO}$: C, 65.19; H, 4.18. Found: C, 65.15; H, 3.95.



7-(tert-butyldiphenylsilyl)-3-phenylnaphthalen-1-ol 175n: The following procedure was adapted from one for a related compound:¹⁵ To a 250 mL flame-dried round bottom flask was added 7-bromo-1-methoxy-3-phenylnaphthalene **195d** (2.75 g, 8.80 mmol) and dry THF (10 mL)

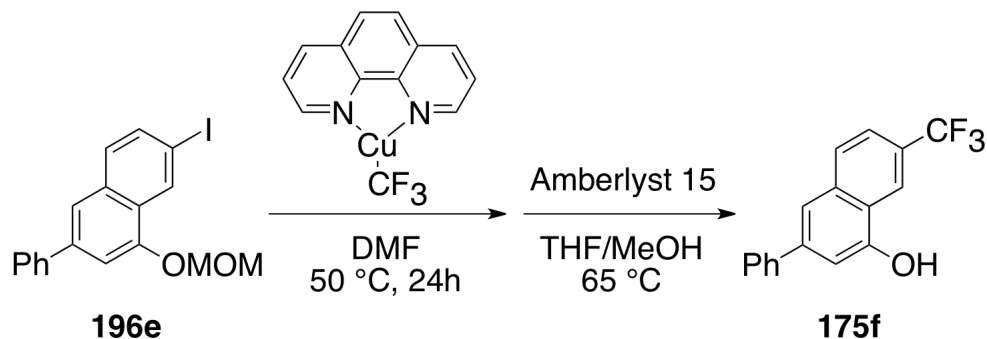
under N₂. The resulting solution was cooled to -78 °C and *t*-BuLi (1.7 M in pentane, 10.6 mL, 18.0 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h. TBDPSCl (2.5 mL, 9.8 mmol) was then added to the mixture at -78 °C. The mixture was warmed up to room temperature and stirred for an additional 24 h. NaHCO₃ (sat. aq. 6 mL) was added to the mixture. The reaction mixture was partitioned between ethyl acetate (100 mL) and NaHCO₃ (sat. aq. 100 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. The product was partially purified by column chromatography on silica gel (30 mm x 300 mm, CH₂Cl₂:hexanes 1:5). The partially purified product was dissolved in CH₂Cl₂ (70 mL) and BBr₃ (1 M in CH₂Cl₂, 26.4 mL, 26.4 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature overnight under an argon balloon. The mixture was cooled to 0 °C and H₂O (140 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (30 mL x 3). The combined organic layer was washed with brine (50 mL) and dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm x 200 mm, CH₂Cl₂:hexanes 1:1) gave **175n** as a yellow foamy solid in 63% yield over two steps (2.53 g, 5.52 mmol). mp 72-74 °C; R_f = 0.21 (2:1 CH₂Cl₂/hexanes). Spectral data for **175n**: ¹H NMR (CDCl₃, 500 MHz) δ 1.23 (s, 9H), 5.17 (s, 1H), 7.08 (d, 1H, *J* = 1.5 Hz), 7.33-7.37 (m, 5H), 7.39-7.43 (m, 2H), 7.43-7.47 (m, 2H), 7.61-7.64 (m, 5H), 7.64-7.68 (m, 3H), 7.81 (d, 1H, *J* = 8.0 Hz), 8.44 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 18.88, 28.90, 108.63, 118.54, 122.81, 126.70, 127.33, 127.54, 127.72, 128.83, 129.24, 130.61, 131.89, 133.56, 134.79,

135.15, 136.60, 139.82, 140.88, 151.85; IR (thin film) 3384br s, 2930s, 1588s, 1428s, 1404s, 1260s, 1105s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{32}\text{H}_{29}\text{OSi}$ ($\text{M}-\text{H}^+$) 457.1988, meas 457.1994.



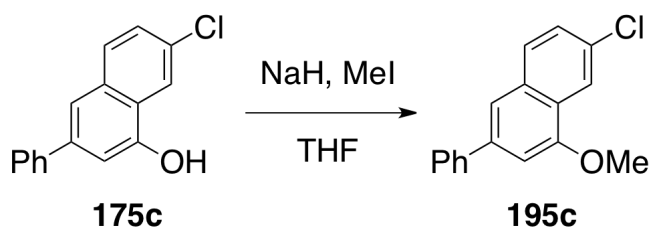
7-iodo-1-(methoxymethoxy)-3-phenylnaphthalene 196e: To a flame-dried 250 mL round bottom flask was added 7-iodo-3-phenylnaphthalen-1-ol **175e** (4.57 g, 13.2 mmol) and dry THF (50 mL) under N_2 . The resulting solution was cooled to 0 °C and NaH (580 mg, 60% in mineral oil, 14.5 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h. MOMCl (1.11 mL, 14.6 mmol) was then added to the mixture at 0 °C. The mixture was warmed up to room temperature and stirred for additional 24 h. NH_4Cl (sat. aq. 10 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The two phase residue was extracted with CH_2Cl_2 (15 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm $\times$ 250 mm, CH_2Cl_2 :hexanes 1:3) gave **196e** as a white solid (4.22 g, 10.8 mmol, 82%). mp 100-101 °C; R_f = 0.19 (1:3 CH_2Cl_2 /hexanes). Spectral data for **196e**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.56 (s, 3H), 5.43 (s, 2H), 7.35-7.39 (m, 2H), 7.44-7.48 (m, 2H), 7.56 (d, 1H, J = 8.5 Hz), 7.61 (s, 1H), 7.66-7.69 (m, 2H), 7.73 (dd, 1H, J = 8.5, 2.0 Hz), 8.64 (d, 1H, J = 2.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 56.40, 90.85, 94.87, 108.44, 119.13, 126.51, 127.39, 127.64, 128.84, 129.45, 131.06, 133.32,

135.28, 139.71, 140.86, 152.25; IR (thin film) 3056w, 2955m, 1578s, 1485s, 1366s, 1233m, 1154s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{18}\text{H}_{16}\text{IO}_2$ ($\text{M}+\text{H}^+$) 391.0195, meas 391.0207.



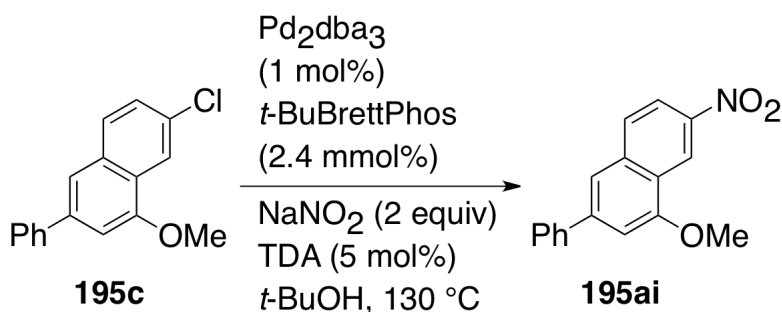
3-phenyl-7-(trifluoromethyl)naphthalen-1-ol 175f: The following procedure was adapted from one for a related compound:⁷⁹ To a flame-dried 25 mL Schlenk flask were added 7-iodo-1-(methoxymethoxy)-3-phenylnaphthalene **196e** (858 mg, 2.20 mmol) and trifluoromethyl(1,10-phenanthroline)copper (1.05 g, 3.34 mmol) under N_2 . The Schlenk flask was evacuated and backfilled with N_2 three times. Dry DMF (9 mL) was added to the mixture under N_2 . The Schlenk flask was sealed and the mixture was stirred at $50\text{ }^\circ\text{C}$ for 24 h. The mixture was cooled to room temperature, diluted with Et_2O and filtered through a pad of Celite. The Celite was washed with Et_2O . The combined filtrate was washed with HCl (aq. 1 M, 10 mL), NaHCO_3 (sat. aq. 10 mL), brine (10 mL), dried over MgSO_4 , filtered through Celite and concentrated to dryness. The ^1H NMR spectrum of the crude mixture indicated incomplete conversion. The mixture was exposed to the above trifluoromethylation procedure with another portion of trifluoromethyl(1,10-phenanthroline)copper (344 mg, 1.10 mmol) and dry DMF (3 mL). The workup was repeated as mentioned above. The product was purified by column chromatography on silica gel (30 mm x 200 mm, Et_2O :hexanes 1:10). The purified product was

obtained as a white solid and was dissolved in a mixture of THF and MeOH (44 mL, 1:1) and Amberlyst 15 (0.55 g) was added. The mixture was stirred at 65 °C for 15 h under N₂ in a balloon. After cooling down to room temperature, the mixture was filtered through filter paper and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 2:1) gave **175f** as a white solid in 97% yield over two steps (617 mg, 2.14 mmol). mp 108-109 °C; R_f = 0.35 (CH₂Cl₂). Spectral data for **175f**: ¹H NMR (CDCl₃, 500 MHz) δ 5.49 (s, 1H), 7.12 (d, 1H, *J* = 1.5 Hz), 7.38-7.42 (m, 1H), 7.45-7.50 (m, 2H), 7.64-7.67 (m, 4H), 7.92 (d, 1H, *J* = 8.5 Hz), 8.52 (d, 1H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 109.43, 118.50, 120.04 (q, ³*J*_{CF} = 4.5 Hz), 122.46, 122.52 (q, ³*J*_{CF} = 3.3 Hz), 124.33 (q, ¹*J*_{CF} = 271.0 Hz), 126.95 (q, ²*J*_{CF} = 32.0 Hz), 127.34, 127.97, 128.87, 128.95, 136.08, 140.26, 141.31, 152.40; ¹⁹F NMR (CDCl₃, 283 Hz) δ -62.28; IR (thin film) 3517br s, 1482s, 1412s, 1323s, 1235s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₁₇H₁₀OF₃ (M-H⁺) 287.0684, meas 287.0678.



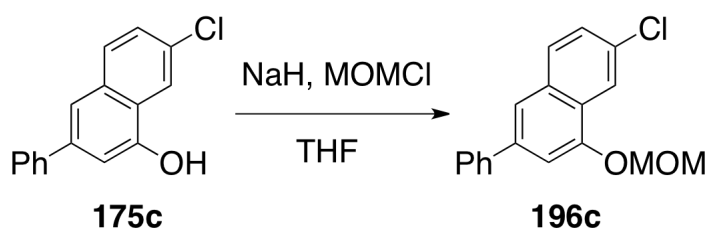
7-chloro-1-methoxy-3-phenylnaphthalene 195c: To a flame-dried 250 mL round bottom flask was added 7-chloro-3-phenylnaphthalen-1-ol **175c** (1.27 g, 5.00 mmol) and dry THF (20 mL) under N₂. The resulting solution was cooled to 0 °C and NaH (220 mg, 60% in mineral oil, 5.5 mmol) was added. The resulting mixture was stirred at 0 °C for 15 minutes. MeI (1.25 mL, 20 mmol) was then added to the mixture at 0 °C. The mixture was warmed up to room

temperature and stirred for an additional 24 h. NH_4Cl (sat. aq. 5 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The residue was extracted with CH_2Cl_2 (5 mL $\times$ 3). The combined organic layer was washed with $\text{Na}_2\text{S}_2\text{O}_3$ (sat. aq. 5 mL $\times$ 2) and brine (5 mL) and then dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm $\times$ 250 mm, CH_2Cl_2 :hexanes 1:10) gave **195c** as a white solid (1.23 g, 4.58 mmol, 92%). mp $^{\circ}\text{C}$; R_f = 0.21 (1:8 CH_2Cl_2 /hexanes). Spectral data for **195c**: ^1H NMR (CDCl_3 , 500 MHz) δ 4.05 (s, 3H), 7.06 (d, 1H, J = 1.5 Hz), 7.36-7.41 (m, 1H), 7.43 (dd, 1H, J = 8.5, 2.0 Hz), 7.45-7.50 (m, 2H), 7.57 (s, 1H), 7.67-7.70 (m, 2H), 7.75 (d, 1H, J = 8.5 Hz), 8.23 (d, 1H, J = 2.5 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.65, 104.70, 118.05, 121.28, 125.41, 127.36, 127.57, 127.68, 128.85, 129.32, 131.09, 132.80, 139.31, 141.23, 155.01; IR (thin film) 3058w, 2936w, 1591s, 1495s, 1234s, 1123s cm^{-1} ; HRMS (EI+) m/z calcd for $\text{C}_{17}\text{H}_{13}^{35}\text{ClO}$ (M^+) 268.0655, meas 268.0656.



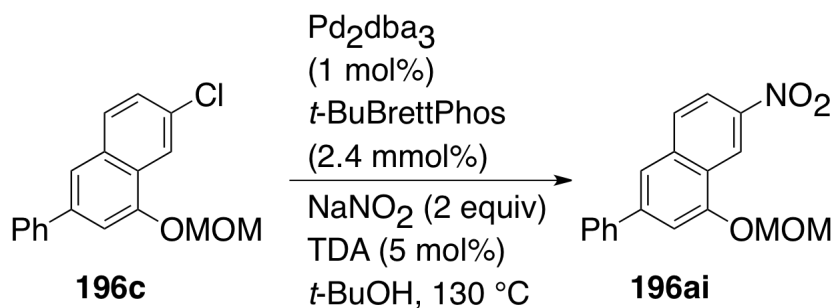
1-methoxy-7-nitro-3-phenylnaphthalene 195ai: The following procedure was adapted from one for a related compound:⁵ To a flame-dried 25 mL Schlenk flask were added 7-chloro-1-methoxy-3-phenylnaphthalene **195c** (268 mg, 1.00 mmol), Pd_2dba_3 (9.2 mg, 0.0100mol), $t\text{-BuBrettPhos}$ (11.6 mg, 0.024 mmol) and NaNO_2 (138 mg, 2.00 mmol) under N_2 . The Schlenk flask was evacuated and backfilled with N_2 three times.

Tris[2-(2-methoxyethoxy)ethyl]amine (16 mL, 0.050 mmol) and *t*-BuOH (2 mL) were added to the mixture under N₂. The Schlenk flask was sealed and the mixture was stirred at 130 °C for 24 h. The mixture was cooled to room temperature, diluted with CH₂Cl₂ (10 mL). The organic layer was washed with H₂O (10 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave **195ai** as a yellow solid (254 mg, 0.91 mmol, 91%). mp 148-150 °C; R_f = 0.27 (1:1 CH₂Cl₂/hexanes). Spectral data for **195ai**: ¹H NMR (CDCl₃, 500 MHz) δ 4.09 (s, 3H), 7.13 (d, 1H, *J* = 1.5 Hz), 7.41-7.45 (m, 1H), 7.48-7.52 (m, 2H), 7.64 (s, 1H), 7.68-7.71 (m, 2H), 7.88 (d, 1H, *J* = 9.0 Hz), 8.22 (dd, 1H, *J* = 9.0, 2.5 Hz), 9.18 (d, 1H, *J* = 2.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 55.84, 105.43, 117.90, 119.74, 120.32, 123.45, 127.48, 128.31, 129.01, 129.05, 137.07, 140.52, 143.51, 144.82, 157.22; IR (thin film) 1559s, 1458s, 1335s, 1130s cm⁻¹; HRMS (ESI+) *m/z* calcd for C₁₇H₁₄NO₃ (M+H⁺) 280.0974, found 280.0963.



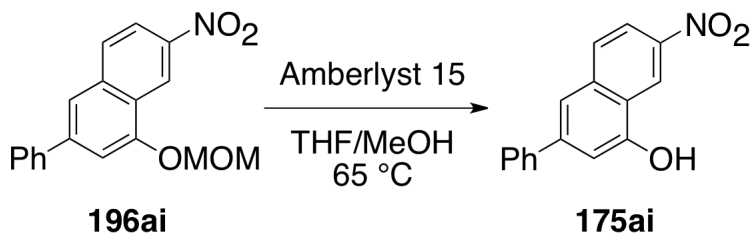
7-chloro-1-(methoxymethoxy)-3-phenylnaphthalene 196c: To a flame-dried 250 mL round bottom flask was added 7-chloro-3-phenylnaphthalen-1-ol **175c** (2.54 g, 10.0 mmol) and dry THF (40 mL) under N₂. The resulting solution was cooled to 0 °C and NaH (440 mg, 60% in mineral oil, 11.0 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h. MOMCl (0.84 mL, 11.1 mmol) was then added to the mixture at 0 °C. The mixture was warmed up to

room temperature and stirred for additional 24 h. NH_4Cl (sat. aq. 10 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The two phase residue was extracted with CH_2Cl_2 (15 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm $\times$ 250 mm, CH_2Cl_2 :hexanes 1:3) gave **196c** as a white solid (2.71 g, 9.1 mmol, 91%). mp 77-79 °C; R_f = 0.24 (1:3 CH_2Cl_2 /hexanes). Spectral data for **196c**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.56 (s, 3H), 5.44 (s, 2H), 7.35-7.40 (m, 2H), 7.42-7.49 (m, 3H), 7.65 (s, 1H), 7.66-7.69 (m, 2H), 7.77 (d, 1H, J = 8.5 Hz), 8.24 (d, 1H, J = 2.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 56.38, 94.86, 108.61, 119.08, 121.17, 125.69, 127.39, 127.59, 127.63, 128.84, 129.47, 131.27, 132.89, 139.34, 140.89, 152.55; IR (thin film) 3058w, 2955m, 1591s, 1493s, 1372s, 1235m, 1154s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{18}\text{H}_{16}^{35}\text{ClO}_2$ ($\text{M}+\text{H}^+$) 299.0839, meas 299.0843.



1-(methoxymethoxy)-7-nitro-3-phenylnaphthalene 196ai: The following procedure was adapted from one for a related compound:⁵ To a flame-dried 25 mL Schlenk flask were added 7-chloro-1-(methoxymethoxy)-3-phenylnaphthalene **196c** (299 mg, 1.00 mmol), Pd_2dba_3 (9.2 mg, 0.0100mol), $t\text{-BuBrettPhos}$ (11.6 mg, 0.024 mmol) and NaNO_2 (138 mg, 2.00 mmol) under

N₂. The Schlenk flask was evacuated and backfilled with N₂ three times. Tris[2-(2-methoxyethoxy)ethyl]amine (16 mL, 0.050 mmol) and *t*-BuOH (2 mL) were added to the mixture under N₂. The Schlenk flask was sealed and the mixture was stirred at 130 °C for 24 h. The mixture was cooled to room temperature, diluted with CH₂Cl₂ (10 mL). The organic layer was washed with H₂O (10 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 2:3) gave **196ai** as a yellow solid (278 mg, 0.90 mmol, 90%). mp 127-129 °C; R_f = 0.20 (1:1 CH₂Cl₂/hexanes). Spectral data for **196ai**: ¹H NMR (CDCl₃, 500 MHz) δ 3.58 (s, 3H), 5.49 (s, 2H), 7.39-7.44 (m, 1H), 7.47-7.51 (m, 3H), 7.68-7.73 (m, 3H), 7.92 (d, 1H, *J* = 9.0 Hz), 8.24 (dd, 1H, *J* = 9.0, 2.5 Hz), 9.21 (d, 1H, *J* = 2.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 56.60, 94.91, 109.19, 118.89, 119.68, 120.25, 123.72, 127.53, 128.33, 129.01, 129.26, 137.08, 140.23, 143.51, 145.00, 154.87; IR (thin film) 2961m, 1605s, 1493s, 1337s, 1238m, 1157s cm⁻¹; HRMS (EI+) *m/z* calcd for C₁₈H₁₅NO₄ (M⁺) 309.1001, found 309.1010.

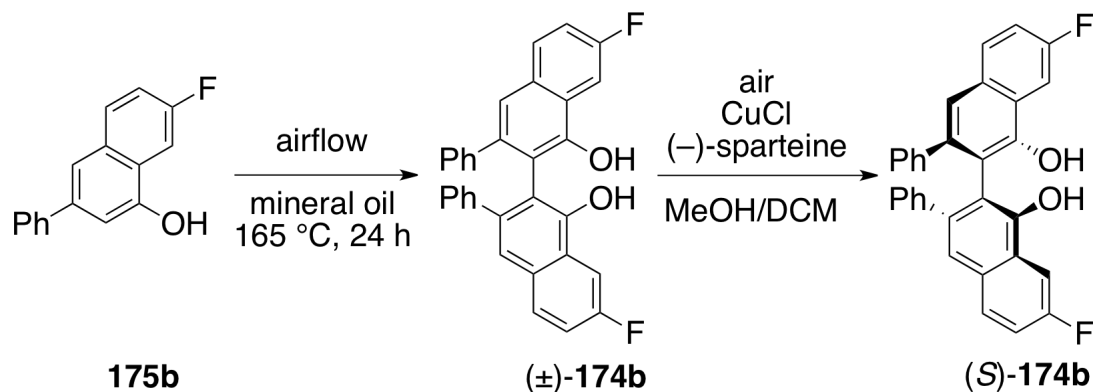


7-nitro-3-phenylnaphthalen-1-ol 175ai: 1-(methoxymethoxy)-7-nitro-3-phenyl-naphthalene **196ai** (1.24 g, 4.00 mmol) was dissolved in a mixture of THF and MeOH (80 mL, 1:1) and Amberlyst 15 (1.00 g) was added. The mixture was stirred at 65 °C for 15 h under N₂ in a balloon. After cooling down to room temperature, the mixture was filtered through filter paper

was stirred at 165 °C for 24 h. After cooling down to room temperature, CH₂Cl₂ (50 mL) and hexanes (100 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (–20 °C) and then filtered through filter paper. The yellow powder was washed with chilled CH₂Cl₂/hexanes and dried under vacuum to afford a yellow solid (11.41 g). Purification of the product remaining in the mother liquor by column chromatography on silica gel (35 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave racemic **174d** as a white solid (0.46 g). The total yield is 84% (11.87 g, 19.9 mmol).

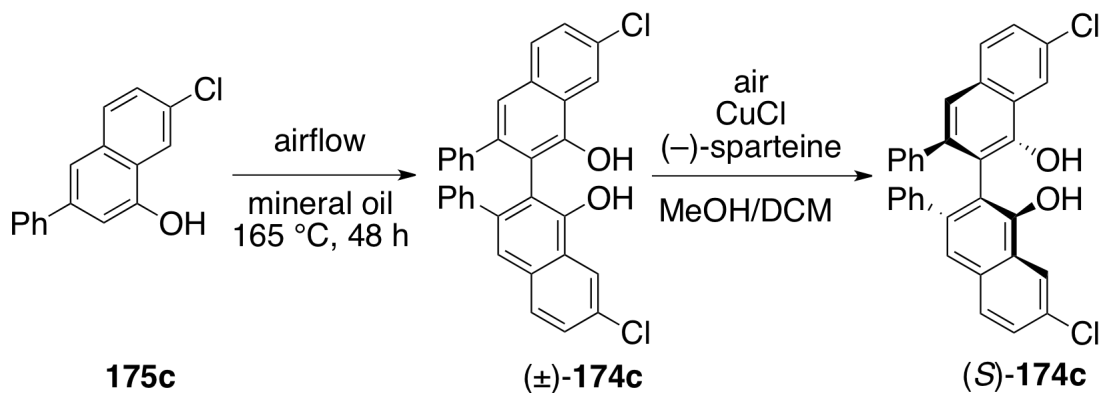
De-racemization:^{13c} The original procedure involves sonification to presumably facilitate reaction. However, it was later found that the deracemization of VAPOL gives the same result whether or not sonification is employed.¹⁷ The following procedure follows the original report: To a 500 mL round bottom flask was added (–)-sparteine (8.20 g, 35.0 mmol), CuCl (1.68 g, 17.0 mmol) and MeOH (270 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 2 L flame-dried round bottom flask was added racemic **174d** (5.96 g, 10.0 mmol) and CH₂Cl₂ (1080 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 **174d** 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. 125 mL), H_2O (400 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with CH_2Cl_2 (300 mL $\times$ 3). The combined organic layer was dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm $\times$ 250 mm, CH_2Cl_2 :hexanes 1:2) gave the product (*S*)-**174d** as an off-white foamy solid (4.97 g, 83.3 mmol, 83%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 26.47 min for (*R*)-**174d** (minor) and R_t = 30.62 min for (*S*)-**174d** (major). mp 136-138 °C; R_f = 0.27 (1:1 CH_2Cl_2 /hexanes). Spectral data for **174d**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.75 (s, 2H), 6.58-6.61 (m, 4H), 6.94-6.98 (m, 4H), 7.06-7.10 (m, 2H), 7.27 (s, 2H), 7.62-7.63 (m, 4H), 8.49-8.50 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 113.55, 119.90, 121.93, 123.96, 125.30, 126.95, 127.57, 128.76, 129.37, 131.06, 133.03, 139.64, 141.07, 149.49; IR (thin film) 3501br m, 1561s, 1487s, 1373s, 1265s cm^{-1} ; mass spectrum, m/z (% rel intensity) 598 M^+ (2, $^{81}\text{Br}^{81}\text{Br}$), 596 M^+ (5, $^{81}\text{Br}^{79}\text{Br}$), 594 M^+ (2, $^{79}\text{Br}^{79}\text{Br}$), 299 (5, ^{81}Br), 297 (5, ^{79}Br), 209 (10), 193 (12). Anal calcd for $\text{C}_{32}\text{H}_{20}\text{Br}_2\text{O}_2$: C, 64.45; H, 3.38. Found: C, 64.52; H, 3.33. $[\alpha]_{\text{D}}^{20} = -190.3$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**174d** (HPLC).



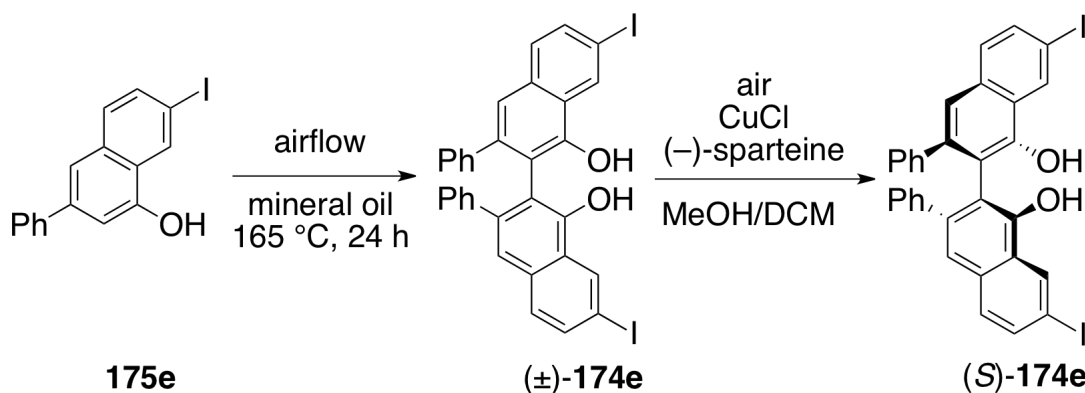
7,7'-di-fluoro VANOL **174b**: The synthesis of racemic **174b** was performed according to the general procedure (Procedure J) with 7-fluoro-3-phenylnaphthalen-1-ol **175b** (3.81 g, 16.0 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:3 to 2:3) gave racemic **174b** as a yellow solid (3.44 g, 7.26 mmol, 91% yield). After de-racemization of racemic **174b** (2.46 g, 5.19 mmol) with CuCl (873 mg, 8.82 mmol) and (–)-sparteine (4.26 g, 18.2 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:2) to afford (*S*)-**174b** as an off-white foamy solid (1.11 g, 2.34 mmol, 45%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 19.71 min for (*R*)-**174b** (minor) and *R*_t = 22.75 min for (*S*)-**174b** (major). mp 190-192 °C; *R*_f = 0.26 (1:1 CH₂Cl₂/hexanes). Spectral data for **174b**: ¹H NMR (CDCl₃, 500 MHz) δ 5.75 (s, 2H), 6.61 (dd, 4H, *J* = 8.5, 1.5 Hz), 6.96 (t, 4H, *J* = 7.5 Hz), 7.07 (t, 2H, *J* = 7.5 Hz), 7.30-7.35 (m, 4H), 7.76 (dd, 2H, *J* = 9.0, 5.5 Hz), 7.93 (dd, 2H, *J* = 10.0, 2.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 106.70 (²*J*_{CF} = 22.4 Hz), 113.50, 117.96 (²*J*_{CF} = 25.6 Hz), 121.90, 123.65 (³*J*_{CF} = 9.1 Hz), 126.78, 127.52, 128.83, 130.17 (³*J*_{CF} = 8.8 Hz), 131.62, 139.81 (⁴*J*_{CF}

= 2.4 Hz), 149.78, 149.82, 160.71 ($^1J_{\text{CF}} = 244.9$ Hz); ^{19}F NMR (CDCl_3 , 283 Hz) δ -111.93; IR (thin film) 3519br s, 3059w, 1597s, 1497s, 1385s, 1267s, 1156s cm^{-1} ; mass spectrum, m/z (% rel intensity) 474 M^+ (100), 397 (8), 338 (15), 307 (7), 249 (26), 237 (93), 209 (64). Anal calcd for $\text{C}_{32}\text{H}_{20}\text{O}_2\text{F}_2$: C, 81.00; H, 4.25. Found: C, 80.93; H, 4.18. $[\alpha]_{\text{D}}^{20} = -226.2$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**174b** (HPLC).



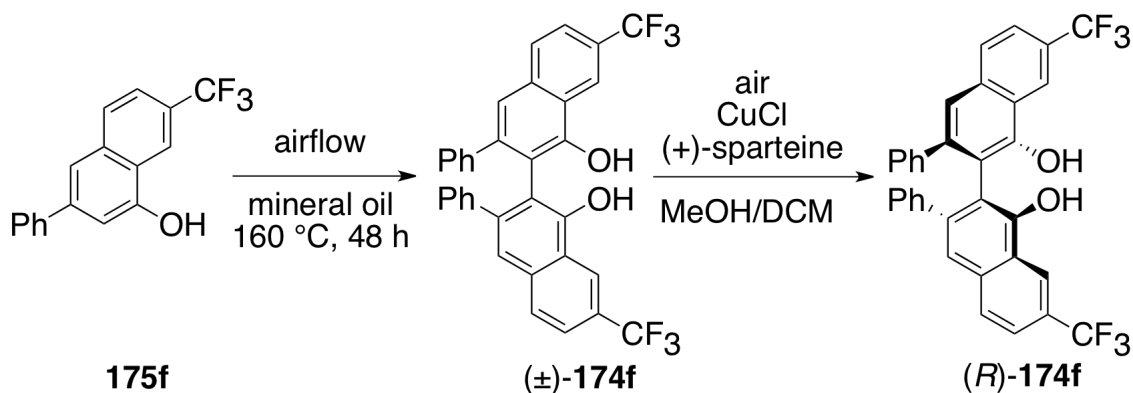
7,7'-di-chloro VANOL 174c: The synthesis of racemic **174c** was performed according to the general procedure (Procedure J) with 7-chloro-3-phenylnaphthalen-1-ol **175c** (1.27 g, 5.0 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH_2Cl_2 /hexanes 1:2) gave racemic **174c** as a white solid (919 mg, 1.81 mmol, 73% yield). After de-racemization of racemic **174c** (406 mg, 0.80 mmol) with CuCl (135 mg, 1.36 mmol) and (–)-sparteine (655 mg, 2.80 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH_2Cl_2 /hexanes 1:2) to afford (*S*)-**174c** as a white foamy solid (336 mg, 0.66 mmol, 83%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: $R_t = 23.87$ min for (*R*)-**174c** (minor) and $R_t = 27.98$ min for (*S*)-**174c** (major). mp 214-215

°C; $R_f = 0.27$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **174c**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.77 (s, 2H), 6.58-6.61 (m, 4H), 6.94-6.99 (m, 4H), 7.06-7.10 (m, 2H), 7.27 (s, 2H), 7.49 (dd, 2H, $J = 8.0, 2.0$ Hz), 7.70 (d, 2H, $J = 8.0$ Hz), 8.31-8.32 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 113.54, 121.85, 122.00, 123.50, 126.91, 127.55, 128.56, 128.76, 129.30, 131.74, 132.81, 139.62, 140.87, 149.55; IR (thin film) 3507br s, 3058m, 1590s, 1489s, 1377s, 1265s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{32}\text{H}_{21}^{35}\text{Cl}_2\text{O}_2$ ($\text{M}+\text{H}^+$) 507.0919, meas 507.0907. $[\alpha]_D^{20} = -206.0$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**174c** (HPLC).



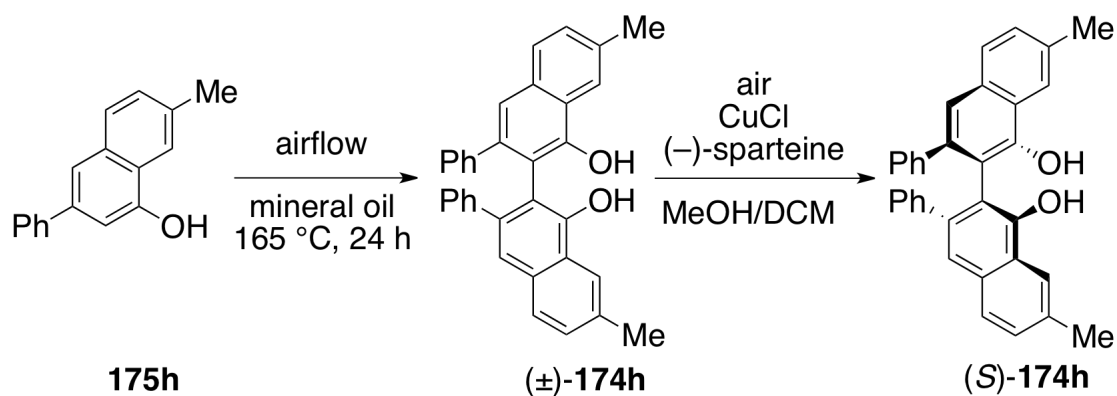
7,7'-di-iodo VANOL 174e: The synthesis of racemic **174e** was performed according to the general procedure (Procedure J) with 7-iodo-3-phenylnaphthalen-1-ol **175e** (1.43 g, 4.13 mmol). Purification by column chromatography on silica gel (30 mm $\times$ 250 mm, EtOAc/hexanes 1:10) gave racemic **174e** as a yellow solid (1.22 g, 1.77 mmol, 86%). After de-racemization of racemic **174e** (5.06 g, 7.33 mmol) with CuCl (1.23 g, 12.4 mmol) and (–)-sparteine (6.01 g, 25.9 mmol), the crude product was purified by column chromatography on silica gel (30 mm $\times$ 250 mm, CH_2Cl_2 /hexanes 1:2) to afford (*S*)-**6e** as a yellow solid (3.82 g, 5.54 mmol, 76%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2

hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 29.63 min for (*R*)-**174e** (minor) and R_t = 33.56 min for (*S*)-**174e** (major). mp 292-294 °C; R_f = 0.36 (1:1 CH₂Cl₂/hexanes). Spectral data for **174e**: ¹H NMR (CDCl₃, 500 MHz) δ 5.73 (s, 2H), 6.57-6.60 (m, 4H), 6.94-6.98 (m, 4H), 7.06-7.10 (m, 2H), 7.24 (d, 2H, J = 4.0 Hz), 7.49 (d, 2H, J = 9.0 Hz), 7.79 (dd, 2H, J = 8.5, 2.0 Hz), 8.72-8.73 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 91.28, 113.36, 121.96, 124.35, 126.95, 127.57, 128.74, 129.24, 131.86, 133.28, 136.23, 139.62, 141.28, 149.26; IR (thin film) 3463br s, 3056m, 1559s, 1485s, 1373s, 1265s cm⁻¹; mass spectrum, m/z (% rel intensity) 690 M⁺ (91), 599 (2), 564 (6), 486 (6), 389 (24), 345 (100), 300 (40), 194 (93). Anal calcd for C₃₂H₂₀I₂O₂: C, 55.68; H, 2.92. Found: C, 55.53; H, 2.78. $[\alpha]_D^{20}$ = -111.6 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**174e** (HPLC).



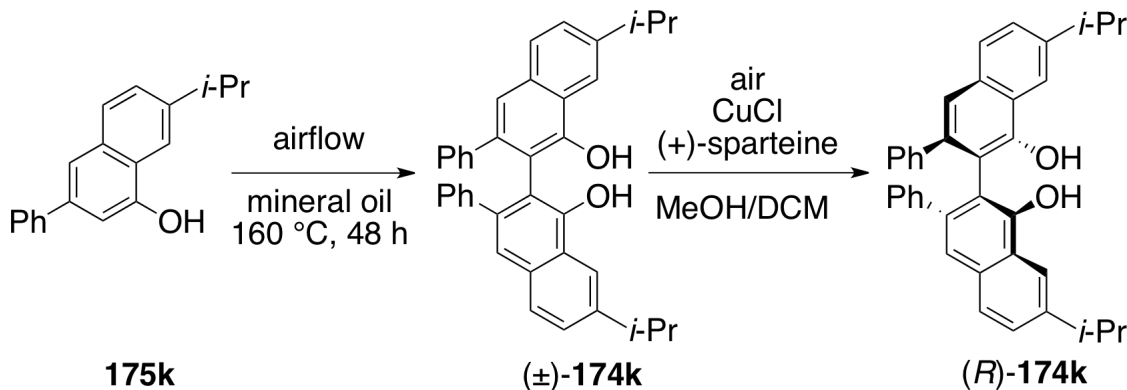
7,7'-di-trifluoromethyl VANOL 174f. The synthesis of racemic **174f** was performed according to the general procedure (Procedure J) with 3-phenyl-7-(trifluoromethyl)naphthalen-1-ol **175f** (576 mg, 2.00 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:3) gave racemic **174f** as an off-white solid (292 mg, 0.51 mmol, 51%). After de-racemization of racemic **174f** (208 mg, 0.36 mmol) with CuCl (61 mg, 0.62 mmol) and (+)-sparteine (297 mg, 1.27 mmol), the crude product

was purified by column chromatography on silica gel (30 mm × 250 m, CH₂Cl₂/hexanes 1:2) to afford (*R*)-**174f** as an off-white solid (165 mg, 0.29 mmol, 79%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 15.50 min for (*R*)-**174f** (major) and *R*_t = 17.18 min for (*S*)-**174f** (minor). mp 215-218 °C; *R*_f = 0.38 (1:1 CH₂Cl₂/hexanes). Spectral data for **174f**: ¹H NMR (CDCl₃, 500 MHz) δ 5.90 (s, 2H), 6.59-6.62 (m, 4H), 6.97-7.01 (m, 4H), 7.09-7.13 (m, 2H), 7.36 (s, 2H), 7.73 (dd, 2H, *J* = 8.5, 1.5 Hz), 7.87 (d, 2H, *J* = 8.5 Hz), 8.68 (d, 2H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 113.64, 121.06 (q, ³*J*_{CF} = 4.5 Hz), 121.84, 121.95, 123.36 (q, ³*J*_{CF} = 3.1 Hz), 124.38 (q, ¹*J*_{CF} = 270.9 Hz), 127.21, 127.64 (q, ²*J*_{CF} = 32.6 Hz), 127.66, 128.73, 128.75, 135.75, 139.33, 142.98, 151.06; ¹⁹F NMR (CDCl₃, 283 Hz) δ -62.81; IR (thin film) 3524br s, 1572s, 1466s, 1377s, 1319s, 1296s, 1123s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₃₄H₁₉O₂F₆ (M-H⁺) 573.1289, meas 573.1272. [α]_D²⁰ = +187.7 (c 1.0, CH₂Cl₂) on >99% *ee* (*R*)-**174f** (HPLC).

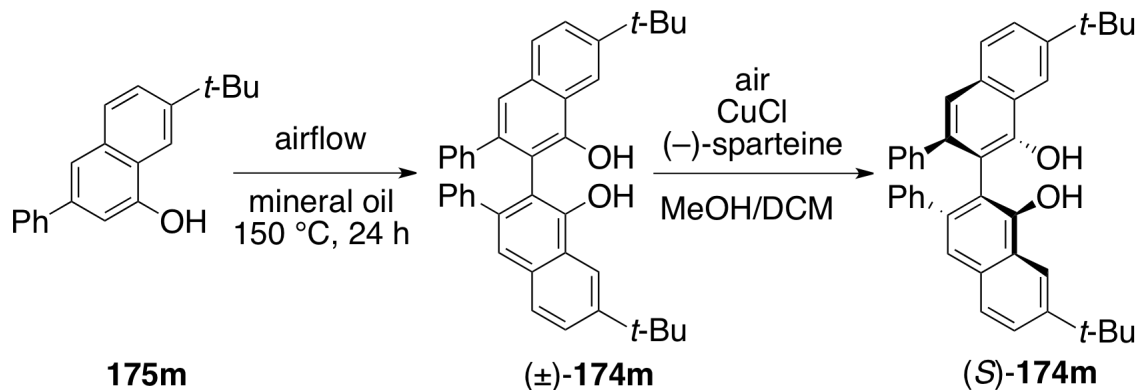


7,7'-di-methyl VANOL 174h: The synthesis of racemic **174h** was performed according to the general procedure (Procedure J) with 7-methyl-3-phenylnaphthalen-1-ol **175h** (3.77 g, 16.1 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm,

CH₂Cl₂/hexanes 1:2) gave racemic **174h** as a yellow solid (2.02 g, 4.33 mmol, 54%). After de-racemization of racemic **174h** (932 mg, 2.00 mmol) with CuCl (337 mg, 3.40 mmol) and (–)-sparteine (1.64 g, 7.00 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:2) to afford (*S*)-**174h** as an off-white solid (509 mg, 1.09 mmol, 55%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 16.70 min for (*R*)-**174h** (minor) and *R*_t = 18.60 min for (*S*)-**174h** (major). mp 132-134 °C; *R*_f = 0.26 (1:1 CH₂Cl₂/hexanes). Spectral data for **174h**: ¹H NMR (CDCl₃, 500 MHz) δ 2.58 (s, 6H), 5.77 (s, 2H), 6.63 (dd, 4H, *J* = 8.5, 1.5 Hz), 6.94 (t, 4H, *J* = 8.0 Hz), 7.02-7.06 (m, 2H), 7.27 (s, 2H), 7.39 (dd, 2H, *J* = 8.0, 1.5 Hz), 7.68 (d, 2H, *J* = 8.0 Hz), 8.11 (d, 2H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 21.94, 112.82, 121.68, 121.80, 122.97, 126.46, 127.40, 127.58, 128.88, 129.71, 132.86, 135.51, 139.70, 140.32, 149.80; IR (thin film) 3509br s, 3054m, 2920m, 1599s, 1497s, 1387s, 1294s, 1265s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 466 M⁺ (86), 389 (8), 302 (9), 233 (100), 194 (65). Anal calcd for C₃₄H₂₆O₂: C, 87.52; H, 5.62. Found: C, 87.47; H, 5.74. [α]_D²⁰ = –292.4 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**174h** (HPLC).

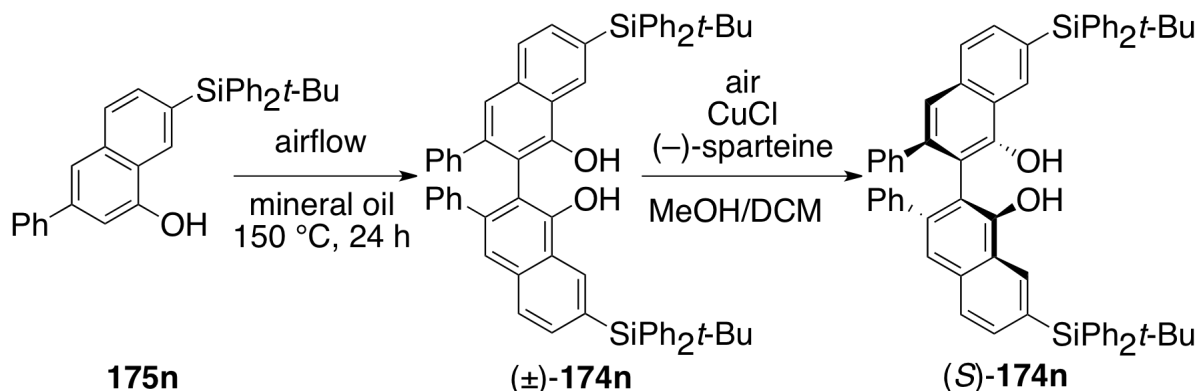


7,7'-di-isopropyl VANOL 174k: The synthesis of racemic **174k** was performed according to the general procedure (Procedure J) with 7-isopropyl-3-phenylnaphthalen-1-ol **175k** (1.31 g, 5.00 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:3) gave racemic **174k** as a white solid (1.08 g, 2.07 mmol, 82%). After de-racemization of racemic **174k** (418 mg, 0.80 mmol) with CuCl (135 mg, 1.36 mmol) and (+)-sparteine (655 mg, 2.80 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 1:3) to afford (*R*)-**174k** as a white foamy solid (300 mg, 0.57 mmol, 72%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 99:1 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 12.60 min for (*R*)-**174k** (major) and *R*_t = 13.87 min for (*S*)-**174k** (minor). mp 123-129 °C; *R*_f = 0.20 (1:2 CH₂Cl₂/hexanes). Spectral data for **6k**: ¹H NMR (CDCl₃, 500 MHz) δ 1.40 (d, 12H, *J* = 7.0 Hz), 3.12-3.19 (m, 2H), 5.81 (s, 2H), 6.61-6.64 (m, 4H), 6.93-6.98 (m, 4H), 7.03-7.08 (m, 2H), 7.29 (s, 2H), 7.48 (dd, 2H, *J* = 8.5, 1.5 Hz), 7.73 (d, 2H, *J* = 8.5 Hz), 8.15-8.17 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 23.95, 24.02, 35.52, 112.76, 119.06, 121.81, 122.96, 126.41, 127.28, 127.42, 127.73, 128.89, 133.25, 139.85, 140.38, 146.38, 150.05; IR (thin film) 3513br s, 3054m, 2959s, 1561s, 1497s, 1387s, 1265m, 1173s cm⁻¹; HRMS (ESI+) *m/z* calcd for C₃₈H₃₅O₂ (M+H⁺) 523.2637, meas 523.2645. [α]_D²⁰ = +207.6 (c 1.0, CH₂Cl₂) on >99% *ee* (*R*)-**174k** (HPLC).



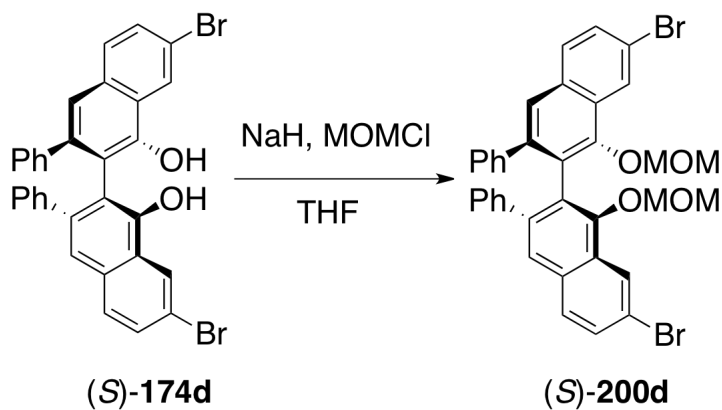
7,7'-di-*t*-butyl VANOL 174m: The synthesis of racemic **174m** was performed according to the general procedure (Procedure J) with 7-(*tert*-butyl)-3-phenylnaphthalen-1-ol **175m** (201 mg, 0.73 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:2) gave racemic **174m** as an off-white solid (145 mg, 0.26 mmol, 72%). After de-racemization of racemic **174m** (525 mg, 0.95 mmol) with CuCl (160 mg, 1.62 mmol) and (–)-sparteine (782 mg, 3.34 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 250 m, CH₂Cl₂/hexanes 1:2) to afford (*S*)-**174m** as an off-white foamy solid (404 mg, 0.73 mmol, 77%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 99:1 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 8.67 min for (*R*)-**174m** (minor) and *R*_t = 10.19 min for (*S*)-**174m** (major). mp 154-156 °C; *R*_f = 0.26 (1:2 CH₂Cl₂/hexanes). Spectral data for **174m**: ¹H NMR (CDCl₃, 500 MHz) δ 1.48 (s, 18H), 5.81 (s, 2H), 6.61 (dd, 4H, *J* = 8.0, 1.0 Hz), 6.95 (t, 4H, *J* = 8.0 Hz), 7.03-7.07 (m, 2H), 7.28 (s, 2H), 7.66 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.73 (d, 2H, *J* = 8.5 Hz), 8.29-8.30 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 31.33, 35.19, 112.72, 117.71, 121.63, 122.65, 126.39, 127.43, 127.45, 128.90, 132.83, 140.01, 140.40, 148.58, 150.24 (1 sp² C not located); IR

(thin film) 3519br s, 3058w, 2961s, 1597s, 1497s, 1385s, 1265s cm^{-1} ; mass spectrum, m/z (% rel intensity) 550 M^+ (47), 535 (13), 275 (29), 260 (89), 232 (29). Anal calcd for $\text{C}_{40}\text{H}_{38}\text{O}_2$: C, 87.23; H, 6.95. Found: C, 86.90; H, 7.16. $[\alpha]_{\text{D}}^{20} = -215.2$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**174n** (HPLC).

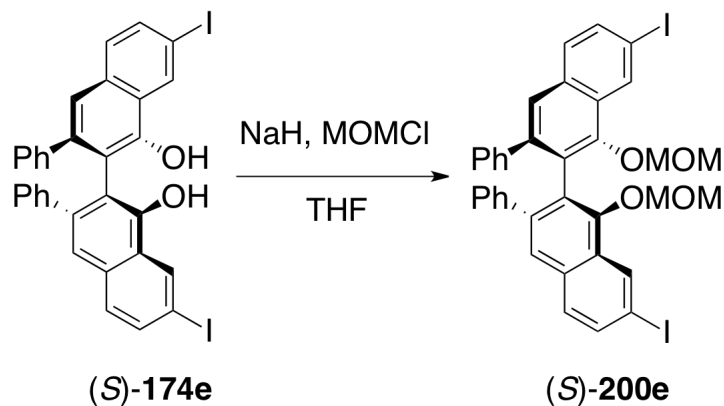


The synthesis of racemic **174n** was performed according to the general procedure (Procedure J) with 7-(*tert*-butyldiphenylsilyl)-3-phenylnaphthalen-1-ol **175n** (2.49 g, 5.43 mmol). Purification by column chromatography on silica gel (30 mm $\times$ 250 mm, CH_2Cl_2 /hexanes 2:5) gave racemic **174n** as an off-white solid (2.07 mg, 2.26 mmol, 84%). After de-racemization of racemic **174n** (2.05 g, 2.23 mmol) with CuCl (376 mg, 3.80 mmol) and (–)-sparteine (1.84 g, 7.86 mmol), the crude product was purified by column chromatography on silica gel (30 mm $\times$ 250 m, CH_2Cl_2 /hexanes 1:2) to afford (*S*)-**174n** as an off-white foamy solid (1.64 g, 1.79 mmol, 80%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: $R_t = 8.74$ min for (*R*)-**174n** (minor) and $R_t = 9.99$ min for (*S*)-**174n** (major). mp 152–155 $^\circ\text{C}$; $R_f = 0.27$ (1:2 CH_2Cl_2 /hexanes). Spectral data for **174n**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.26 (s, 18H), 5.79 (s, 2H), 6.58 (dd, 4H, $J = 8.0, 1.0$ Hz), 6.96 (t, 4H, $J = 7.5$ Hz), 7.07 (t, 2H, $J = 7.5$

product by column chromatography on silica gel (30 mm x 300 mm, CH₂Cl₂:hexanes 1:3) gave (*S*)-**199d** as an off-white solid (3.58 g, 5.74 mmol, 82%). mp 235-236 °C; *R*_f = 0.24 (1:2 CH₂Cl₂/hexanes). Spectral data for **199d**: ¹H NMR (CDCl₃, 500 MHz) δ 3.67 (s, 6H), 6.75-6.77 (m, 4H), 6.93-6.97 (m, 4H), 7.05-7.09 (m, 2H), 7.50 (s, 2H), 7.58 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.71 (d, 2H, *J* = 9.0 Hz), 8.33 (d, 2H, *J* = 2.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 61.20, 120.24, 125.06, 125.25, 126.25, 126.51, 127.58, 128.18, 128.94, 129.88, 130.03, 132.98, 140.38, 140.65, 153.42; IR (thin film) 1559s, 1480s, 1352s, 1105s cm⁻¹; HRMS (ESI+) *m/z* calcd for C₃₄H₂₄O₂⁷⁹Br₂Na (M+Na⁺) 645.0041, meas 645.0068. [α]_D²⁰ = -44.8 (c 1.0, CH₂Cl₂).



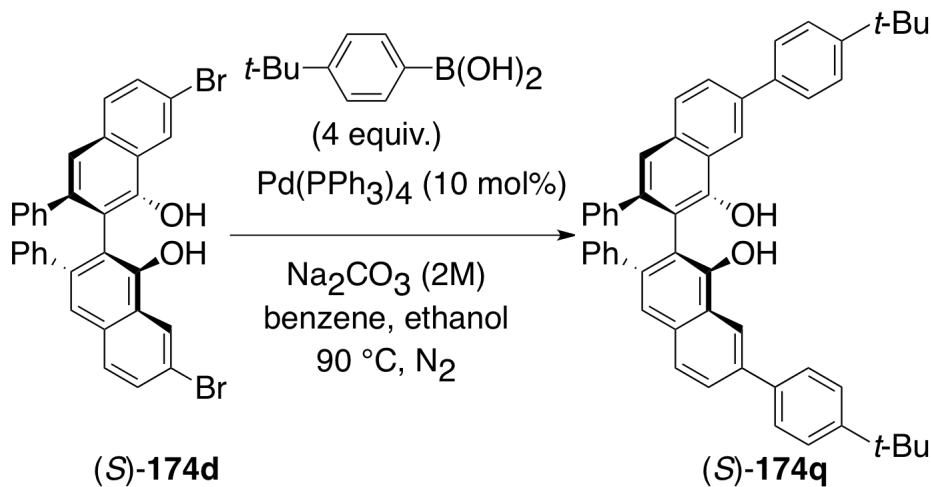
CH₂Cl₂ (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:2 to 3:4 to 1:1) gave (*S*)-**200d** as an off-white solid (2.24 g, 3.27 mmol, 82%). mp 96-98 °C; R_f = 0.22 (1:1 CH₂Cl₂/hexanes). Spectral data for **200d**: ¹H NMR (CDCl₃, 500 MHz) δ 2.76 (s, 6H), 5.04-5.09 (m, 4H), 6.71 (dd, 4H, *J* = 8.5, 1.0 Hz), 6.89-6.93 (m, 4H), 7.03-7.08 (m, 2H), 7.47 (s, 2H), 7.57 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.69 (d, 2H, *J* = 9.0 Hz), 8.32-8.34 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 56.48, 99.50, 120.43, 125.17, 125.48, 126.29, 127.51, 127.53, 128.16, 129.03, 129.86, 130.02, 132.84, 140.42, 141.13, 151.52; IR (thin film) 3056m, 2930s, 1572s, 1482s, 1352s, 1159s cm⁻¹; HRMS (ESI+) *m/z* calcd for C₃₆H₂₈O₂Na⁷⁹Br₂ (M+Na⁺) 705.0252, meas 705.0273. [α]_D²⁰ = -118.2 (c 1.0, CH₂Cl₂).



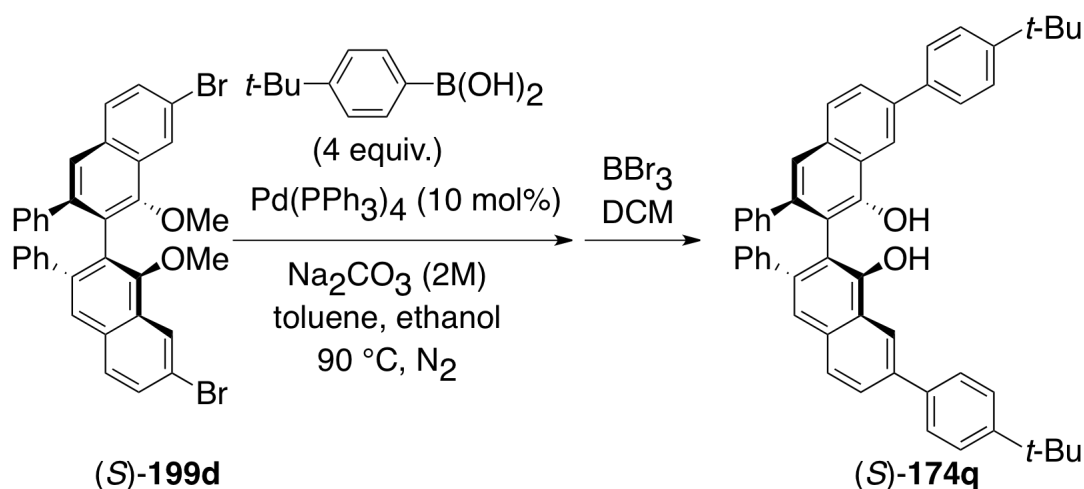
To a flame-dried 250 mL round bottom flask were added NaH (352 mg, 60% in mineral oil, 8.8 mmol) and THF (18 mL). The resulting mixture was cooled to 0 °C and a solution of (*S*)-**174e** (2.76 g, 4.00 mmol) in THF (6 mL) was added. The mixture was stirred at 0 °C for 1 h and then allowed to warm up to room temperature for 15 minutes. The mixture was re-cooled to 0 °C and MOMCl (0.67 mL, 8.8 mmol) was added. The mixture was warmed up to room

temperature and stirred for additional 24 h. NH_4Cl (sat. aq. 6 mL) was added to the mixture and the organic solvent was removed. The residue was extracted with CH_2Cl_2 (10 mL $\times$ 3). The combined organic layer was washed with brine (10 mL), dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm $\times$ 280 mm, CH_2Cl_2 :hexanes 1:1) gave (*S*)-**200e** as an off-white solid in 90% isolated yield (2.81 g, 3.61 mmol). mp 110-114 °C; R_f = 0.24 (1:1 CH_2Cl_2 /hexanes). Spectral data for **200e**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.76 (s, 6H), 5.04-5.08 (m, 4H), 6.70 (dd, 4H, J = 8.5, 1.5 Hz), 6.90 (t, 4H, J = 7.5 Hz), 7.03-7.07 (m, 2H), 7.45 (s, 2H), 7.54 (d, 2H, J = 9.0 Hz), 7.74 (dd, 2H, J = 8.5, 1.5 Hz), 8.57 (d, 2H, J = 1.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 56.50, 91.94, 99.52, 125.50, 126.29, 127.32, 127.51, 128.57, 129.02, 129.70, 131.84, 133.07, 135.15, 140.41, 141.32, 151.30; IR (thin film) 2953s, 1570s, 1480s, 1350s, 1159s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{36}\text{H}_{29}\text{O}_4\text{I}_2$ ($\text{M}+\text{H}^+$) 779.0155, meas 779.0159. $[\alpha]_{\text{D}}^{20} = -74.7$ (c 1.0, CH_2Cl_2).

Suzuki coupling – illustrated for the synthesis of (*S*)-**174q**

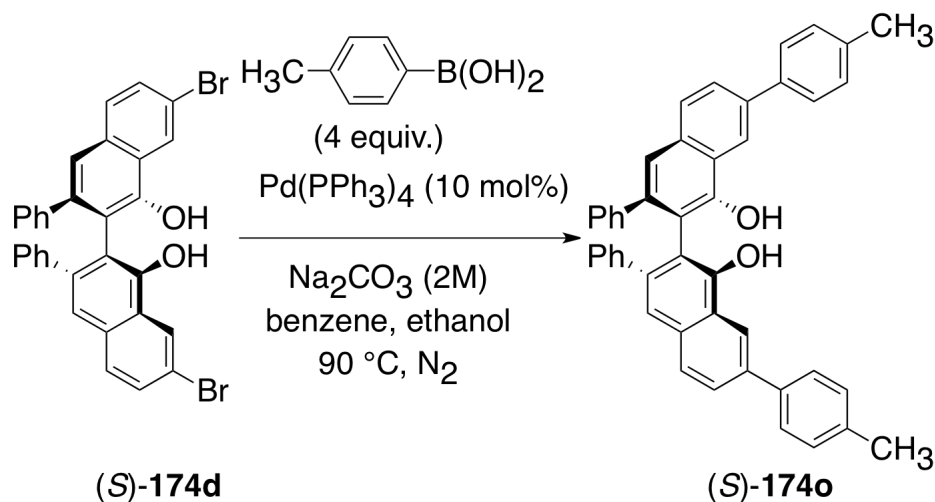


Procedure K:¹⁵ Benzene, ethanol and Na₂CO₃ (aq. 2 M) were purged (>10 min) with inert gas (Ar or N₂) prior to use. To a 25 mL round bottom flask was added (*S*)-**174d** (60 mg, 0.10 mmol), tetrakis(triposphine)palladium (12 mg, 0.010 mmol), benzene (1 mL) and Na₂CO₃ (aq. 2 M, 0.5 mL) under argon. To the stirred mixture was added 4-*tert*-butylphenylboronic acid (71 mg, 0.40 mmol) and ethanol (0.5 mL). The mixture was stirred at 90 °C for 14 h with an argon balloon attached to the condenser. After cooling down to room temperature, the mixture was partitioned between EtOAc (10 mL) and brine (5 mL). The organic layer was separated, dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave (*S*)-**174q** as a white solid (29 mg, 0.041 mmol, 41%).

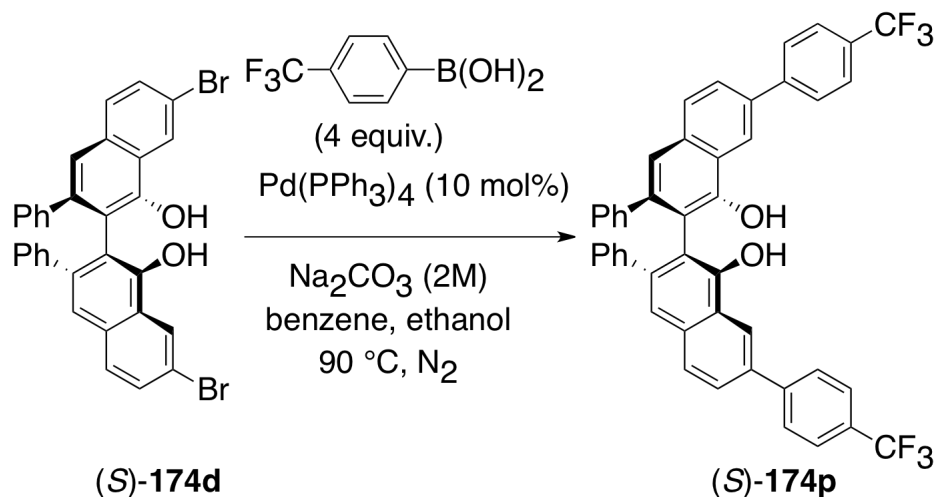


Procedure L:¹⁵ Toluene, ethanol and Na₂CO₃ (aq. 2 M) were purged (>10 min) with inert gas (Ar or N₂) prior to use. To a 100 mL round bottom flask was added (*S*)-**199d** (780 mg, 1.25 mmol), tetrakis(triposphine)palladium (144 mg, 0.125 mmol), toluene (15 mL) and Na₂CO₃ (aq. 2 M, 7.5 mL). To the stirred mixture was added 4-*tert*-butylphenylboronic acid (890 mg, 5.0 mmol) and ethanol (7.5 mL). The mixture was stirred at 90 °C for 14 h with an

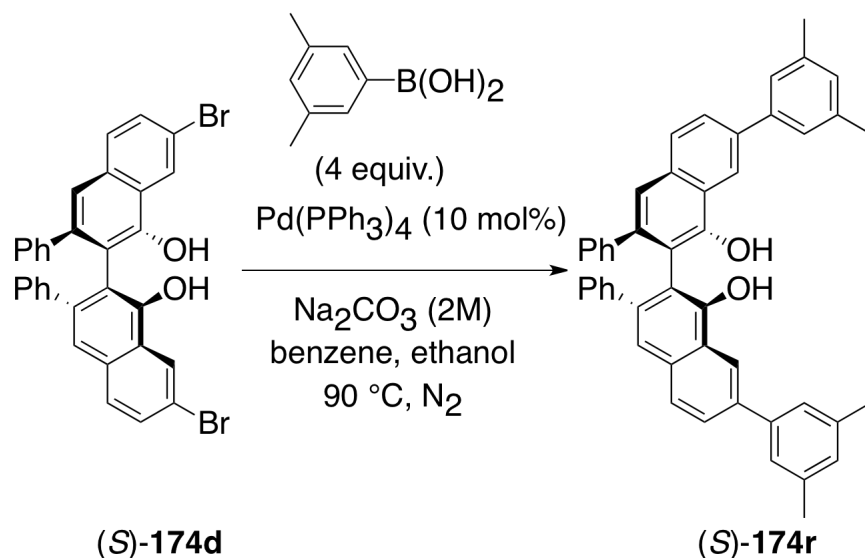
argon balloon attached. After cooling down to room temperature, the mixture was partitioned between EtOAc (40 mL) and brine (20 mL). The organic layer was separated, dried over MgSO₄ and passed through a pad of silica gel (eluted with EtOAc). The crude product was concentrated to dryness. The residue was dissolved in CH₂Cl₂ (20 mL) and cooled to 0 °C, and then BBr₃ (1 M in CH₂Cl₂, 7.5 mL, 7.5 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred at room temperature overnight with an argon balloon attached to the flask. The mixture was then cooled to 0 °C and H₂O (40 mL) was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave (*S*)-**174q** as a white solid in 89% yield over two steps (785 mg, 1.12 mmol). mp >300 °C; R_f = 0.21 (1:2 CH₂Cl₂/hexanes). Spectral data for **174q**: ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 18H), 5.89 (s, 2H), 6.67 (dd, 4H, *J* = 8.5, 1.5 Hz), 6.96-7.00 (m, 4H), 7.06-7.10 (m, 2H), 7.34 (d, 2H, *J* = 1.0 Hz), 7.51-7.55 (m, 4H), 7.73-7.76 (m, 4H), 7.84 (d, 4H, *J* = 1.5 Hz), 8.56 (d, 2H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 31.39, 34.60, 113.11, 120.45, 121.80, 123.24, 125.86, 126.64, 127.09, 127.11, 127.50, 128.21, 128.90, 133.66, 138.11, 138.31, 140.25, 140.58, 150.55, 150.61; IR (thin film) 3517br s, 2961s, 1559s, 1456s, 1387s, 1267s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₅₂H₄₅O₂ (M-H⁺) 701.3420, meas 701.3448. [α]_D²⁰ = +29.2 (c 1.0, CH₂Cl₂).



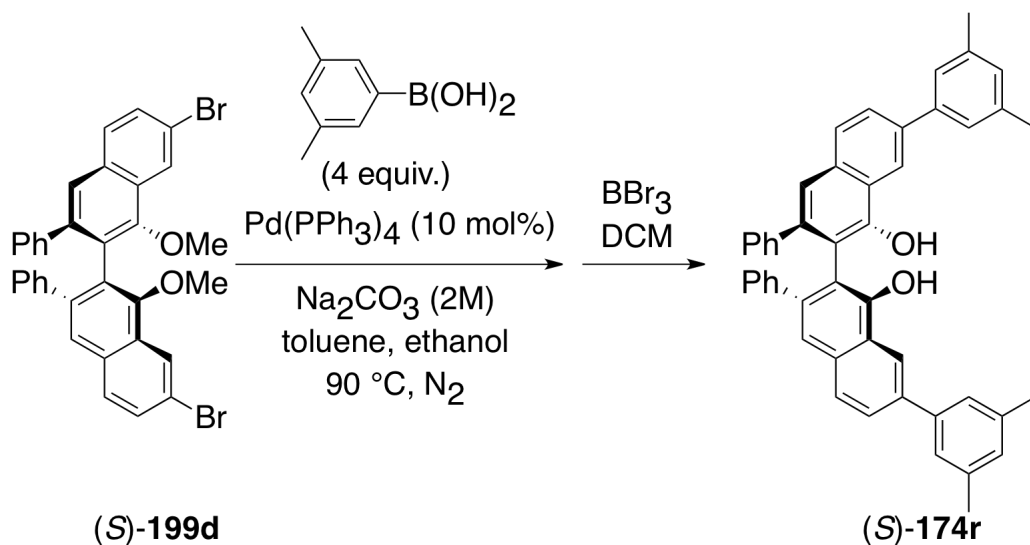
The reaction of **(S)-174d** (179 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na_2CO_3 (aq. 2 M, 1.5 mL), *p*-tolylboronic acid (162 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH_2Cl_2 :hexanes 3:4) gave **(S)-174o** as a white solid (64 mg, 0.104 mmol, 35%). mp > 260°C; R_f = 0.29 (1:1 CH_2Cl_2 /hexanes). Spectral data for **174o**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.42 (s, 6H), 5.88 (s, 2H), 6.64-6.67 (m, 4H), 6.95-6.99 (m, 4H), 7.05-7.10 (m, 2H), 7.30-7.32 (m, 4H), 7.34 (d, 2H, J = 0.5 Hz), 7.69-7.71 (m, 4H), 7.83-7.84 (m, 4H), 8.54-8.55 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.41, 113.29, 120.57, 122.03, 123.43, 126.87, 127.33, 127.51, 127.74, 128.47, 129.13, 129.88, 133.86, 137.53, 138.33, 138.58, 140.42, 140.79, 150.80; IR (thin film) 3503br s, 2922m, 1595s, 1493s, 1388s, 1275m cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{46}\text{H}_{33}\text{O}_2$ ($\text{M}-\text{H}^+$) 617.2481, meas 617.2493. $[\alpha]_{\text{D}}^{20} = +7.8$ (c 1.0, CH_2Cl_2).



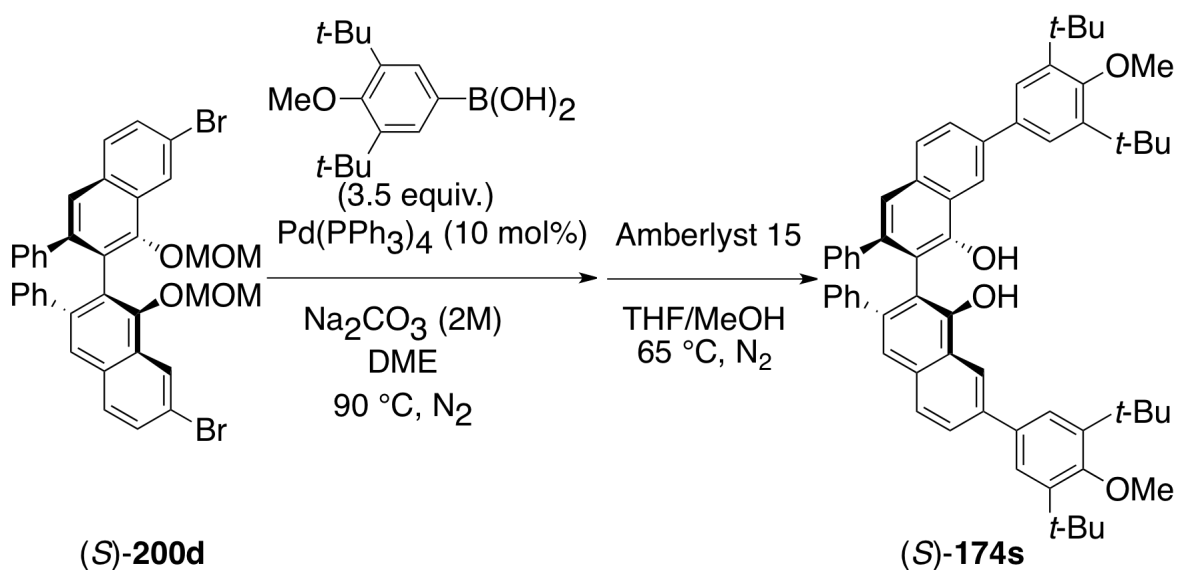
The reaction of **(S)-174d** (179 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na_2CO_3 (aq. 2 M, 1.5 mL), 4-(trifluoromethyl)phenylboronic acid (228 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH_2Cl_2 :hexanes 2:5) gave **(S)-174p** as a white solid (67 mg, 0.092 mmol, 31%). mp > 260 °C; R_f = 0.39 (1:1 CH_2Cl_2 /hexanes). Spectral data for **174p**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.91 (s, 2H), 6.64-6.67 (m, 4H), 6.96-7.00 (m, 4H), 7.07-7.11 (m, 2H), 7.35 (s, 2H), 7.74 (d, 4H, J = 8.0 Hz), 7.82 (dd, 2H, J = 8.0, 1.5 Hz), 7.86-7.90 (m, 6H), 8.57-8.59 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 113.25, 121.33, 121.86, 123.04, 124.31 (q, $^1J_{\text{CF}}$ = 270.4 Hz), 125.84 (q, $^3J_{\text{CF}}$ = 3.8 Hz), 126.84, 127.56, 127.67, 128.62, 128.83, 129.48 (q, $^2J_{\text{CF}}$ = 32.6 Hz), 134.09, 136.90, 139.88, 141.26, 144.46, 150.68 (1 sp^2 C not located); ^{19}F NMR (CDCl_3 , 283 Hz) δ -62.34; IR (thin film) 3517br s, 3058m, 1560s, 1497s, 1387s, 1325s, 1281s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{46}\text{H}_{27}\text{O}_2\text{F}_6$ ($\text{M}-\text{H}^+$) 725.1915, meas 725.1930. $[\alpha]_{\text{D}}^{20}$ = -11.8 (c 1.0, CH_2Cl_2).



The reaction of **(S)-174d** (119 mg, 0.20 mmol), tetrakis(triphenylphosphine)palladium (23 mg, 0.020 mmol), benzene (2 mL), Na_2CO_3 (aq. 2 M, 1 mL), 3,5-dimethylphenylboronic acid (120 mg, 0.80 mmol) and ethanol (1 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH_2Cl_2 :hexanes 1:2) gave **(S)-174r** as an off-white solid (67 mg, 0.092 mmol, 31%).

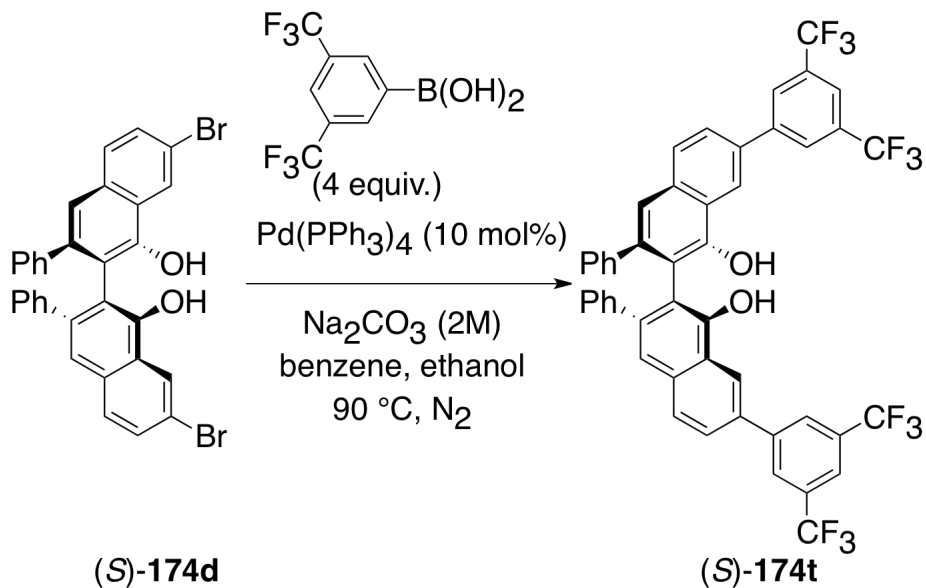


The reaction of (*S*)-**174d** (119 mg, 0.20 mmol), tetrakis(triphenylphosphine)palladium (23 mg, 0.020 mmol), benzene (2 mL), Na₂CO₃ (aq. 2 M, 1 mL), (3,5-di-*tert*-butyl-4-methoxyphenyl)boronic acid (120 mg, 0.80 mmol) and ethanol (1 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (20 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave (*S*)-**174s** as an off-white solid (105 mg, 0.12 mmol, 60%).

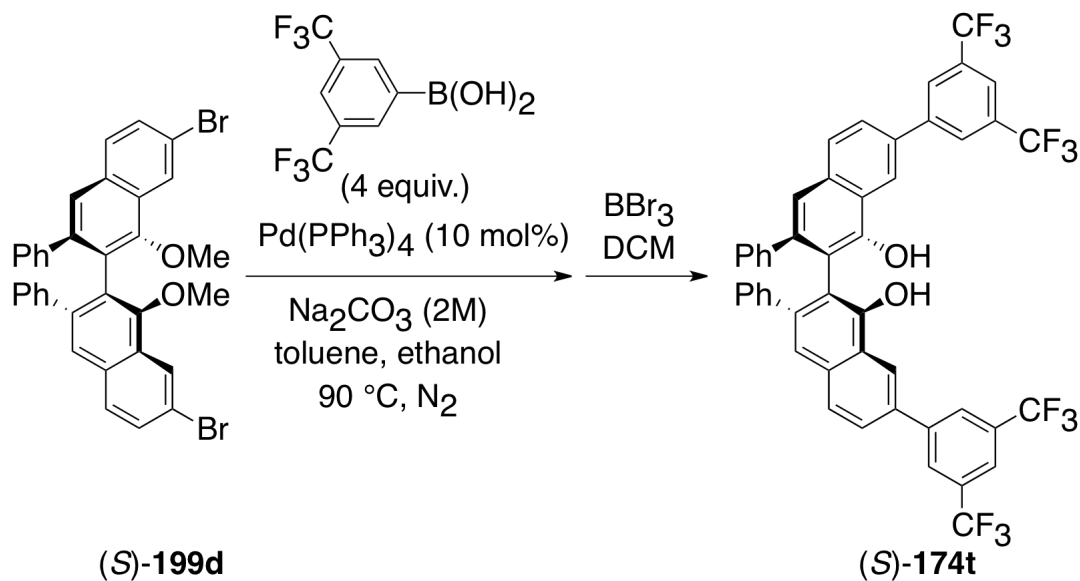


The following procedure was adapted from one for a related compound:¹² To a 25 mL round bottom flask filled with argon were added (*S*)-**200d** (171 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol) and DME (1.7 mL). To the stirred mixture was added (3,5-di-*tert*-butyl-4-methoxyphenyl)boronic acid (230 mg, 0.87 mmol) and Na₂CO₃ (aq. 2 M, 0.7 mL). The mixture was stirred at 90 °C for 14 h with an argon balloon attached to the condenser. After cooling down to room temperature, the mixture was passed through a pad of Celite and washed with CH₂Cl₂. After removal of the solvents, the residue was dissolved in

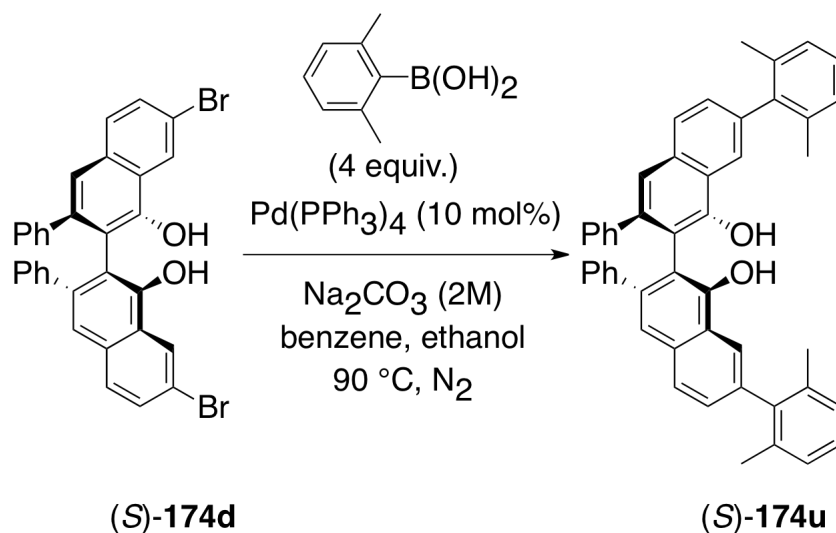
CH₂Cl₂ (20 mL) and washed with NH₄Cl (sat. aq. 5 mL) and brine (5 mL). The organic layer was separated, dried over MgSO₄, filtered through Celite and concentrated to dryness. The product was purified by column chromatography on silica gel (20 mm x 200 mm, CH₂Cl₂:hexanes 1:1). The purified product was dissolved in a mixture of THF and MeOH (10 mL, 1:1) and Amberlyst 15 (0.125g) was added. The mixture was stirred at 65 °C for 15 h with an argon balloon attached to the condenser. After cooling down to room temperature, the mixture was filtered through filter paper and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave the pure product as an off-white solid in 86% yield over two steps (189 mg, 0.216 mmol,). mp 176-179 °C; R_f = 0.29 (1:2 CH₂Cl₂/hexane). Spectral data for **174s**: ¹H NMR (CDCl₃, 500 MHz) δ 1.52 (s, 36H), 3.76 (s, 6H), 5.90 (s, 2H), 6.66 (dd, 4H, *J* = 8.5, 1.0 Hz), 6.95-6.99 (m, 4H), 7.05-7.09 (m, 2H), 7.35 (s, 2H), 7.64 (s, 4H), 7.80 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.84 (d, 2H, *J* = 8.5 Hz), 8.47-8.49 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 32.20, 36.00, 64.35, 113.10, 120.33, 121.82, 123.19, 125.83, 126.60, 127.43, 127.49, 128.13, 128.91, 133.49, 135.34, 139.22, 140.25, 140.41, 144.11, 150.49, 159.45; IR (thin film) 3521br s, 2959s, 1559s, 1456s, 1387s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 875 M+1 (8), 437 (10). Anal calcd for C₆₂H₆₆O₄: C, 85.09; H, 7.60. Found: C, 84.95; H, 7.91. [α]_D²⁰ = +22.1 (c 1.0, CH₂Cl₂).



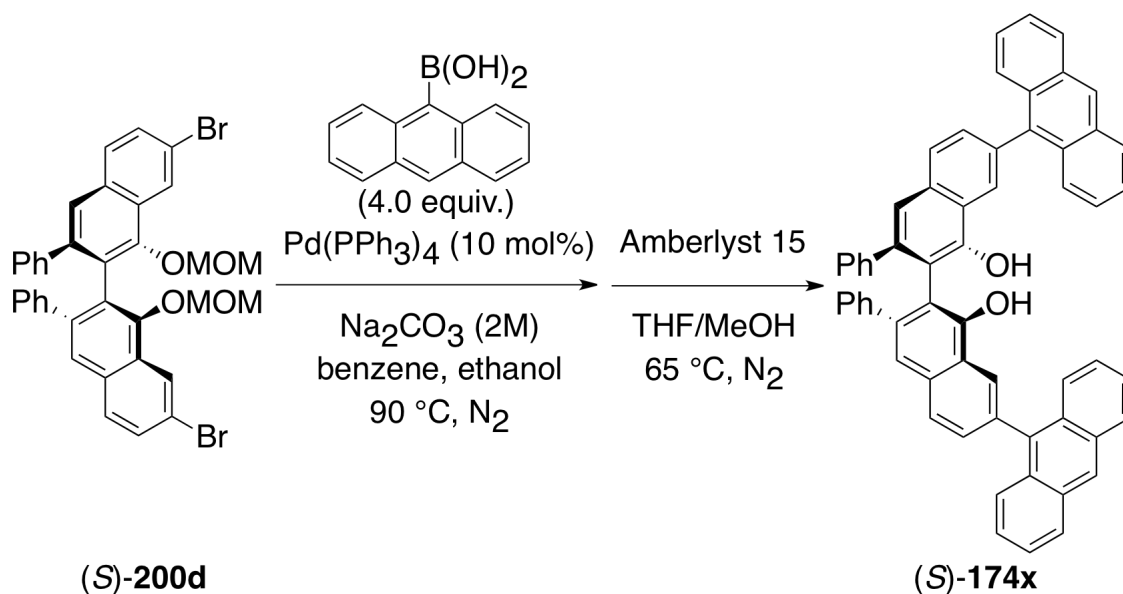
The reaction of **(S)-174d** (179 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na_2CO_3 (aq. 2 M, 1.5 mL), 3,5-bis(trifluoromethyl)phenylboronic acid (228 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH_2Cl_2 :hexanes 1:4) gave **(S)-174t** as a yellow solid (85 mg, 0.099 mmol, 33%).



The reaction of **(S)-199d** (312 mg, 0.50 mmol), tetrakis(triphenylphosphine)palladium (58 mg, 0.050 mmol), toluene (6 mL), Na_2CO_3 (aq. 2 M, 3 mL), 3,5-bis(trifluoromethyl)phenylboronic acid (516 mg, 2.00 mmol) and ethanol (3 mL) was performed according to Procedure L. Purification of the crude product by column chromatography on silica gel (25 mm x 250 mm, CH_2Cl_2 :hexanes 1:2) gave **(S)-174t** as a yellow solid (362 mg, 0.099 mmol, 84%). mp 155-159 °C; $R_f = 0.27$ (1:2 CH_2Cl_2 /hexanes). Spectral data for **174t**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.94 (s, 2H), 6.63-6.66 (m, 4H), 6.96-7.00 (m, 4H), 7.07-7.11 (m, 2H), 7.36 (s, 2H), 7.81 (dd, 2H, $J = 8.5, 2.0$ Hz), 7.89 (s, 2H), 7.91 (d, 2H, $J = 8.5$ Hz), 8.19 (s, 4H), 8.56-8.57 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 113.46, 121.03 (m), 121.62, 121.91, 123.01, 123.41 (q, $^1J_{\text{CF}} = 271.0$ Hz), 126.49, 126.99, 127.45 (q, $^3J_{\text{CF}} = 3.3$ Hz), 127.60, 128.80, 129.03, 132.25 (q, $^2J_{\text{CF}} = 32.5$ Hz), 134.30, 135.36, 139.67, 141.70, 143.11, 150.71; ^{19}F NMR (CDCl_3 , 283 Hz) δ -62.76; IR (thin film) 3528br s, 3059m, 1563s, 1472s, 1372s, 1277s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{48}\text{H}_{25}\text{O}_2\text{F}_{12}$ (M-H^+) 861.1663, meas 861.1635. $[\alpha]_{\text{D}}^{20} = -27.3$ (c 1.0, CH_2Cl_2).

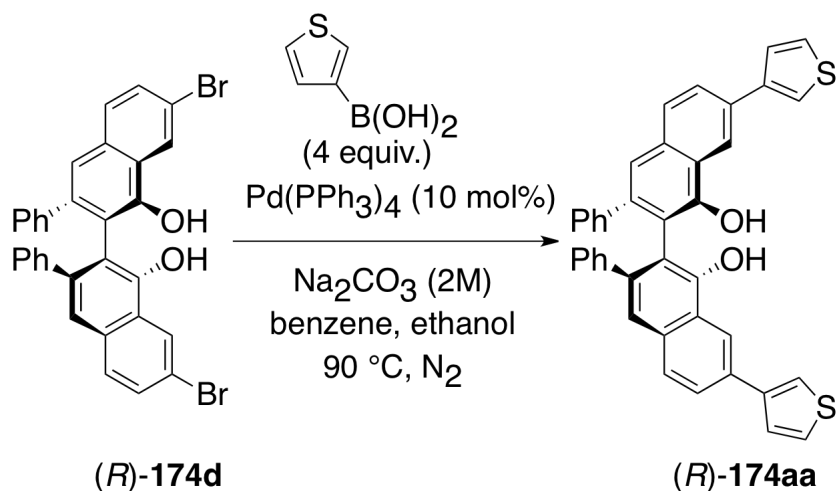


The reaction of **(S)-174d** (238 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na_2CO_3 (aq. 2 M, 2 mL), 2,6-dimethylphenylboronic acid (240 mg, 1.60 mmol) and ethanol (2 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (25 mm x 250 mm, CH_2Cl_2 :hexanes 1:2) gave **(S)-174u** as an off-white solid (148 mg, 0.229 mmol, 57%). mp $>260^\circ\text{C}$; $R_f = 0.37$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **174u**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.11 (s, 6H), 2.15 (s, 6H), 5.86 (s, 2H), 6.67-6.70 (m, 4H), 6.98-7.02 (m, 4H), 7.08-7.13 (m, 2H), 7.15-7.23 (m, 6H), 7.36-7.38 (m, 4H), 7.84 (d, 2H, $J = 8.5$ Hz), 8.12-8.14 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.04, 21.08, 112.99, 121.86, 122.59, 123.02, 126.61, 127.22, 127.39, 127.42, 127.47, 127.83, 128.93, 129.31, 133.40, 136.21, 136.26, 138.60, 140.33, 140.59, 141.70, 150.53; IR (thin film) 3519br s, 3056s, 2923s, 1559s, 1474s, 1383s, 1265s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{48}\text{H}_{37}\text{O}_2$ (M-H^+) 645.2794, meas 645.2820. $[\alpha]_{\text{D}}^{20} = -186.9$ (c 1.0, CH_2Cl_2).



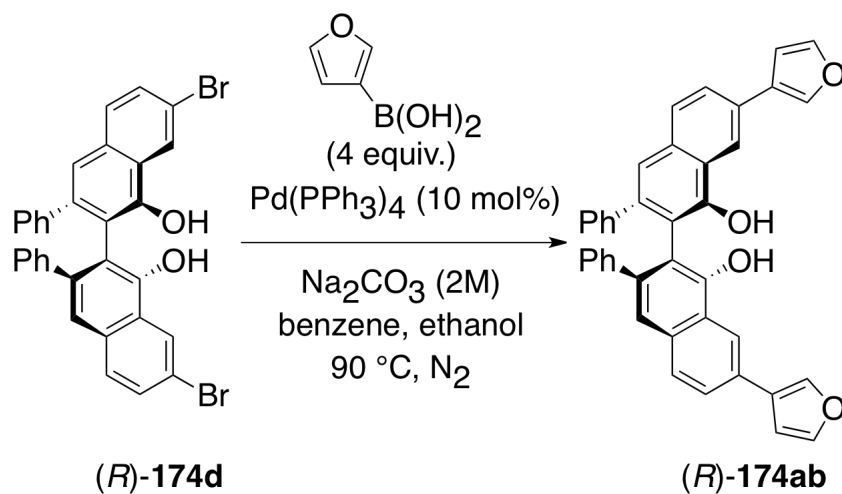
Benzene, ethanol and Na_2CO_3 (aq. 2 M) were purged (>10 min) with inert gas (Ar or N_2) prior to use. To a 100 mL round bottom flask was added **(S)-200d** (171 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol), benzene (5 mL) and Na_2CO_3 (aq. 2 M, 2 mL). To the stirred mixture was added anthracene-9-boronic acid (222 mg, 1.00 mmol) and ethanol (2 mL). The mixture was stirred at 90 °C for 14 h with an argon balloon attached to the condenser. After cooling down to room temperature, the mixture was partitioned between EtOAc (20 mL) and brine (10 mL). The organic layer was separated, dried over MgSO_4 , filtered through Celite and concentrated to dryness. The product was purified by column chromatography on silica gel (30 mm x 200 mm, CH_2Cl_2 :hexanes 1:2). The purified product was dissolved in a mixture of THF and MeOH (10 mL, 1:1) and Amberlyst 15 (0.125g) was added. The mixture was stirred at 65 °C for 15 h with an argon balloon attached to the condenser. After cooling down to room temperature, the mixture was filtered through filter paper and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm,

CH₂Cl₂:hexanes 2:1) gave (*S*)-**174x** as a brownish pink solid in 95% yield over two steps (188 mg, 0.238 mmol). mp >260 °C; R_f = 0.29 (1:1 CH₂Cl₂/hexanes). Spectral data for **174x**: ¹H NMR (THF-*d*8, 500 MHz) δ 8.71-8.74 (m, 4H), 8.89-8.93 (m, 4H), 8.95-8.99 (m, 2H), 9.12-9.16 (m, 2H), 9.20 (s, 2H), 9.24-9.31 (m, 4H), 9.32-9.36 (m, 2H), 9.39 (dd, 2H, *J* = 8.5, 2.0 Hz), 9.54 (dd, 2H, *J* = 8.5, 1.0 Hz), 9.66 (dd, 2H, *J* = 8.5, 1.0 Hz), 9.82 (d, 2H, *J* = 8.0 Hz), 9.95 (t, 4H, *J* = 8.5 Hz), 10.29 (d, 2H, *J* = 9.0 Hz), 10.31 (d, 2H, *J* = 1.0 Hz), 10.44 (s, 2H); ¹³C NMR (THF-*d*8, 125 MHz) δ 116.72, 121.21, 125.26, 125.78, 125.90, 125.95, 126.16, 126.24, 127.06, 127.42, 127.50, 127.75, 127.94, 128.44, 129.22, 129.30, 130.13, 130.71, 131.46, 131.47, 132.58, 132.60, 134.78, 136.03, 138.25, 142.58, 143.18, 153.36; HRMS (ESI[−]) *m/z* calcd for C₆₀H₃₇O₂ (M-H⁺) 789.2794, meas 789.2814. [α]_D²⁰ = −368.5 (c 1.0, THF).



The reaction of (*R*)-**174d** (238 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na₂CO₃ (aq. 2 M, 2 mL), thiophene-3-boronic acid (205 mg, 1.60 mmol) and ethanol (2 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 1:1) gave

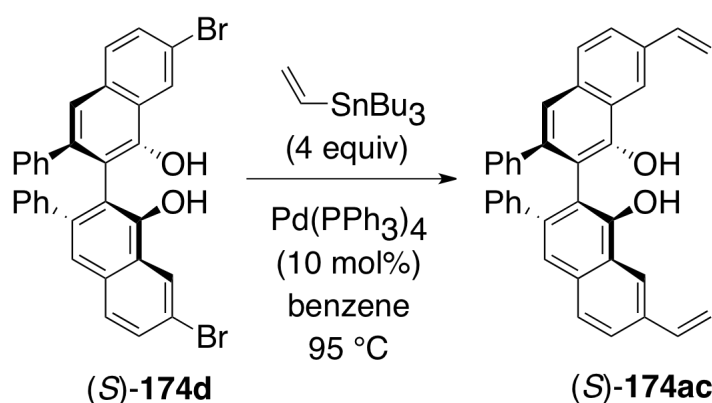
(*S*)-**174aa** as an off-white solid (160 mg, 0.266 mmol, 66%). mp >260 °C; R_f = 0.27 (1:1 CH₂Cl₂/hexanes). Spectral data for **174aa**: ¹H NMR (DMSO-*d*₆, 500 MHz) δ 6.72-6.75 (m, 4H), 6.98 (t, 4H, J = 7.5 Hz), 7.05 (t, 2H, J = 7.5 Hz), 7.70-7.74 (m, 4H), 7.84 (d, 2H, J = 8.5 Hz), 7.88 (dd, 2H, J = 8.5, 1.5 Hz), 8.00 (dd, 2H, J = 2.5, 1.5 Hz), 8.60 (s, 2H), 9.16 (s, 2H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 117.92, 118.96, 119.44, 120.93, 123.96, 124.81, 126.13, 126.18, 126.92, 127.24, 128.35, 128.67, 131.30, 132.67, 141.08, 141.25, 141.77, 151.68; HRMS (ESI–) m/z calcd for C₄₀H₂₅O₂S₂ (M-H⁺) 601.1296, meas 601.1289. $[\alpha]_D^{20}$ = +101.4 (c 1.0, THF).



The reaction of (*R*)-**174d** (238 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na₂CO₃ (aq. 2 M, 2 mL), furan-3-boronic acid (180 mg, 1.61 mmol) and ethanol (2 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 1:1) gave (*S*)-**174ab** as an off-white solid (110 mg, 0.193 mmol, 48%). mp 259-261 °C; R_f = 0.20 (1:1 CH₂Cl₂/hexanes). Spectral data for **174ab**: ¹H NMR (CDCl₃, 500 MHz) δ 5.87 (s, 2H), 6.62-6.65 (m, 4H), 6.90 (dd, 2H, J = 2.0, 1.0 Hz), 6.94-6.98 (m, 4H), 7.04-7.09 (m, 2H), 7.29 (s, 2H), 7.53 (t, 2H, J = 1.5 Hz), 7.69 (dd, 2H, J = 8.5, 2.0 Hz), 7.77 (d, 2H, J = 8.5 Hz), 7.90 (t, 2H,

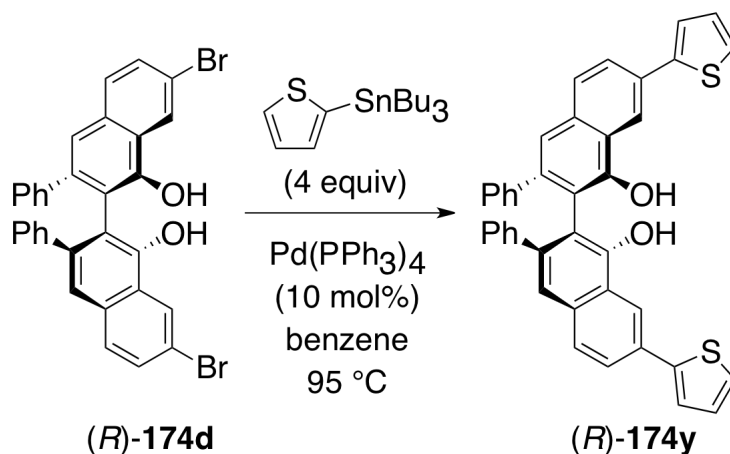
$J = 1.5$ Hz), 8.42-8.43 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 108.95, 113.19, 118.96, 121.89, 123.17, 126.04, 126.56, 126.66, 127.48, 128.31, 128.85, 129.77, 133.64, 139.05, 140.06, 140.42, 143.90, 150.29; IR (thin film) 3503br w, 1559s, 1507s, 1387s, 1163s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{40}\text{H}_{25}\text{O}_4$ ($\text{M}-\text{H}^+$) 569.1753, meas 569.1766. $[\alpha]_{\text{D}}^{20} = +105.1$ (c 1.0, CH_2Cl_2).

Stille coupling – illustrated for the synthesis of (*S*)-174ac (Procedure M)⁸²



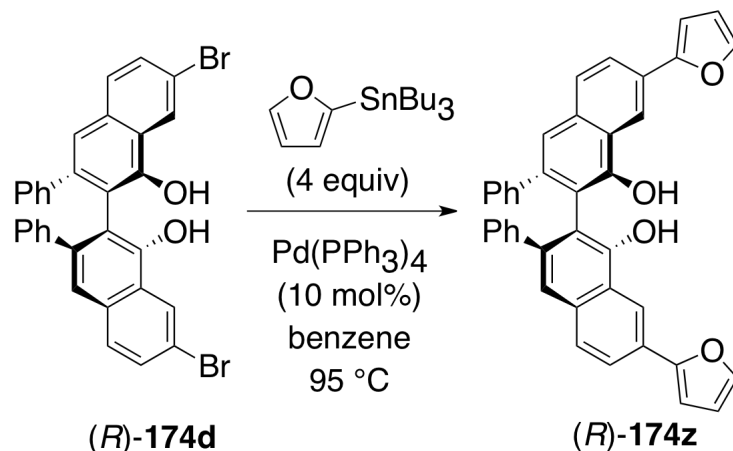
7,7'-di-vinyl VANOL 174ac: To a flame-dried 25 mL Schlenk flask were added (*S*)-**174d** (119mg, 0.20 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 0.020 mmol). The Schlenk flask was evacuated and backfill with N_2 three times. Tributylstannylethylene (234 μL , 0.80 mmol) and dry benzene (5 mL) were added to the mixture under N_2 . The Schlenk flask was sealed and mixture was stirred at 95 $^\circ\text{C}$ overnight. The mixture was cooled to room temperature, diluted with CH_2Cl_2 and filtered through a pad of Celite (eluted with CH_2Cl_2). Purification of the crude product by column chromatography on silica gel (20 mm x 250 mm, CH_2Cl_2 :hexanes 1:2) gave (*S*)-**174ac** as a white foamy solid (63 mg, 0.129 mmol, 64%). mp 113-119 $^\circ\text{C}$; $R_f = 0.28$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **174ac**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.37 (d, 2H, $J = 11.5$ Hz), 5.84 (s, 2H), 5.93 (d, 2H, $J = 17.5$ Hz), 6.61-6.63 (m, 4H), 6.92-6.98 (m, 6H),

7.04-7.08 (m, 2H), 7.27 (s, 2H), 7.69-7.74 (m, 4H), 8.26 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 113.09, 114.38, 121.24, 121.87, 122.93, 124.85, 126.66, 127.46, 128.01, 128.82, 134.24, 134.95, 136.95, 140.05, 140.70, 150.48; IR (thin film) 3511br s, 3058s, 1559s, 1497s, 1381s, 1246s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{36}\text{H}_{25}\text{O}_2$ ($\text{M}-\text{H}^+$) 489.1855, meas 489.1845. $[\alpha]_{\text{D}}^{20} = -205.2$ (c 1.0, CH_2Cl_2).

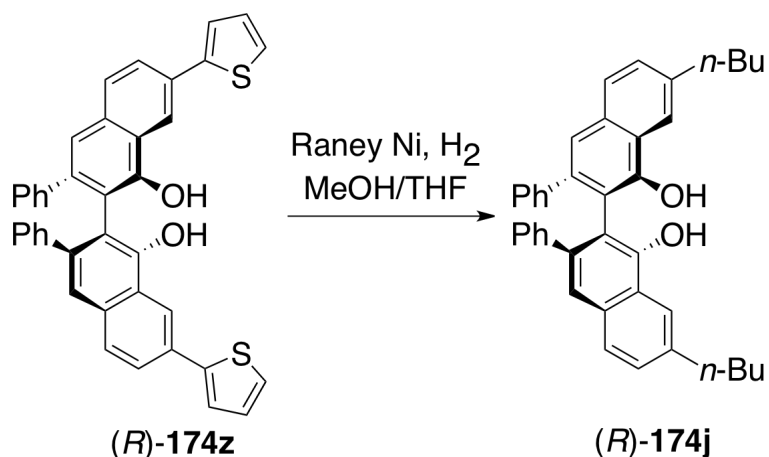


The reaction of *(R)*-**174d** (238 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), 2-(tributylstannyl)thiophene (508 mL, 1.60 mmol) and benzene (10 mL) was performed according to Procedure M. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH_2Cl_2 :hexanes 2:3) gave *(R)*-**174y** as an off-white solid (170 mg, 0.282 mmol, 71%). mp > 260 °C; $R_f = 0.20$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **174y**: ^1H NMR (THF-*d*8, 500 MHz) δ 8.57 (d, 4H, $J = 7.0$ Hz), 8.79 (t, 4H, $J = 8.0$ Hz), 8.86 (t, 2H, $J = 8.0$ Hz), 8.97-8.99 (m, 2H), 9.01 (s, 2H), 9.26 (d, 2H, $J = 5.0$ Hz), 9.41 (d, 2H, $J = 4.0$ Hz), 9.60 (d, 2H, $J = 8.5$ Hz), 9.66 (dd, 2H, $J = 3.5, 1.5$ Hz), 10.21 (s, 2H), 10.50 (s, 2H); ^{13}C NMR (THF-*d*8, 125 MHz) δ 116.69, 120.03, 121.16, 124.09, 125.44, 125.57, 125.60, 126.98, 127.84, 128.88, 129.02, 129.99, 131.85, 134.72, 142.26, 142.79, 145.79, 153.21;

IR (thin film) 3505br s, 1559s, 1456s, 1387s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{40}\text{H}_{27}\text{O}_2\text{S}_2$ ($\text{M}+\text{H}^+$) 603.1452, meas 603.1440. $[\alpha]_{\text{D}}^{20} = +30.6$ (c 1.0, THF).



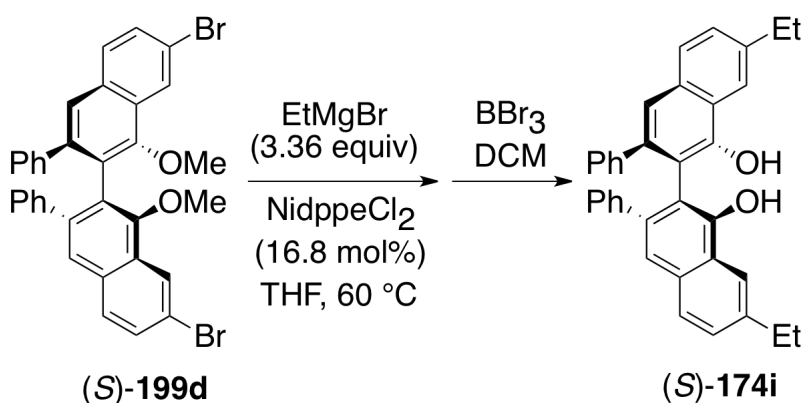
The reaction of *(R)*-**174d** (238 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), 2-(tributylstannyl)furan (504 mL, 1.60 mmol) and benzene (10 mL) was performed according to Procedure M. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH_2Cl_2 :hexanes 2:3) gave *(R)*-**174z** as an off-white solid (199 mg, 0.349 mmol, 87%). mp 185-191 $^\circ\text{C}$; $R_f = 0.20$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **174z**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.89 (s, 2H), 6.53 (dd, 2H, $J = 8.5, 2.0$ Hz), 6.64-6.67 (m, 4H), 6.83 (d, 2H, $J = 3.0$ Hz), 6.94-6.98 (m, 4H), 7.05-7.09 (m, 2H), 7.28 (s, 2H), 7.54 (d, 2H, $J = 2.0$ Hz), 7.77 (d, 2H, $J = 8.5$ Hz), 7.86 (dd, 2H, $J = 8.5, 2.0$ Hz), 8.63-8.64 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 105.83, 111.87, 113.31, 117.17, 121.90, 123.05, 123.90, 126.69, 127.47, 128.16, 128.21, 128.83, 133.73, 140.05, 140.66, 142.46, 150.57, 154.08; IR (thin film) 3509br s, 1559s, 1387s, 1223s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{40}\text{H}_{27}\text{O}_4$ ($\text{M}+\text{H}^+$) 571.1909, meas 571.1899. $[\alpha]_{\text{D}}^{20} = -1.5$ (c 1.0, CH_2Cl_2).



*7,7'-di-*n*-butyl VANOL 174j*: The following procedure was adapted from one for a related compound:¹⁴ To a 25 mL round bottom flask was added (*R*)-**174z** (193 mg, 0.32 mmol), MeOH (10 mL), THF (10 mL) and Raney-Ni (50% slurry in H₂O, 10 mL). A H₂ balloon was attached to the flask and the mixture was stirred at room temperature for 24 h. The resulting mixture was filtered through a pad of Celite (eluted with CH₂Cl₂). After removal of the solvent, the residue was partitioned between CH₂Cl₂ (10 mL) and NaHCO₃ (sat. aq. 10 mL). The aqueous layer was extracted with CH₂Cl₂ (10 mL x 2). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 1:3) gave the product (*R*)-**174j** as an off-white foamy solid (115 mg, 0.21 mmol, 65%). mp 68-72 °C; R_f = 0.26 (1:2 CH₂Cl₂/hexanes). Spectral data for **174j**: ¹H NMR (CDCl₃, 500 MHz) δ 0.96 (t, 6H, *J* = 7.5 Hz), 1.41-1.49 (m, 4H), 1.71-1.78 (m, 4H), 2.84 (t, 4H, *J* = 7.5 Hz), 5.81 (s, 2H), 6.61-6.64 (m, 4H), 6.93-6.97 (m, 4H), 7.03-7.07 (m, 2H), 7.28 (s, 2H), 7.42 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.70 (d, 2H, *J* = 8.5 Hz), 8.12 (d, 2H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 14.01, 22.53, 33.67, 36.09, 112.78, 121.14, 121.81, 122.98, 126.43, 127.40, 127.60, 128.89, 129.05, 133.07, 139.77,

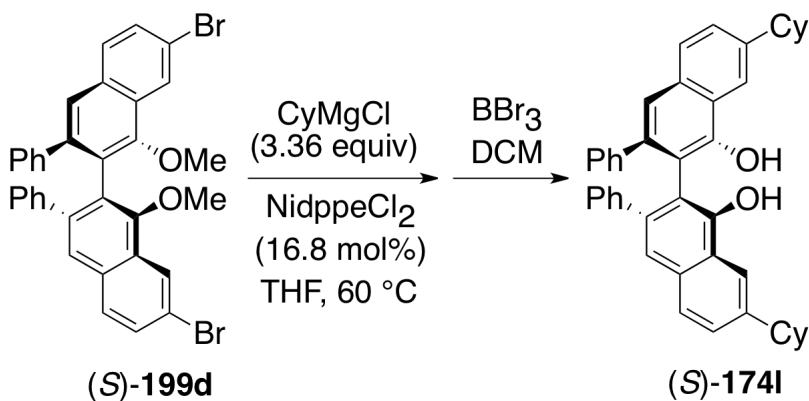
140.38, 140.54, 149.93; IR (thin film) 3515br s, 2928s, 1559s, 1456s, 1387s, 1167s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{40}\text{H}_{37}\text{O}_2$ ($\text{M}-\text{H}^+$) 549.2794, meas 549.2813. $[\alpha]_{\text{D}}^{20} = +196.3$ (c 1.0, CH_2Cl_2).

Kumada coupling – illustrated for the synthesis of 7,7'-di-ethyl VANOL 174i (Procedure N)¹⁵



To a flame-dried 25 mL round bottom flask was added (S)-199d (156 mg, 0.25 mmol), NidppeCl₂ (22 mg, 0.042 mmol) and dry THF (5 mL). To the resulting mixture was added EtMgBr (3 M in ether, 0.28 mL, 0.84 mmol) dropwise at 0 °C. The mixture was stirred at 60 °C for 24 h. After cooling to room temperature, NH₄Cl (sat. aq. 1 mL) was added to the mixture. After removal of the organic solvent, the residue was partitioned between CH₂Cl₂ (6 mL) and H₂O (3 mL). The organic layer was separated, dried over MgSO₄ filtered through Celite and concentrated to dryness. The residue was purified by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 1:3). The purified product was dissolved in CH₂Cl₂ (4 mL) and cooled to 0 °C, and then BBr₃ (1 M in CH₂Cl₂, 1.5 mL, 1.5 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred at room temperature overnight with an argon balloon

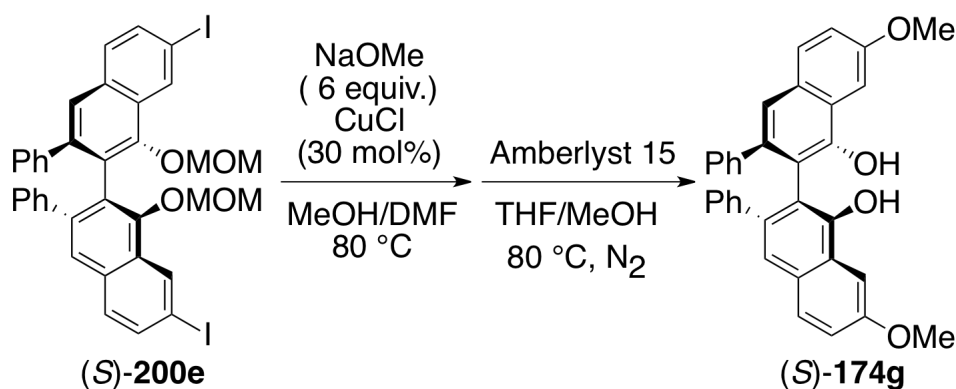
attached to the flask. The mixture was then cooled to 0 °C and H₂O (8 mL) was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 2:5) gave (*S*)-**174i** as an off-white foamy solid in 74% yield over two steps (91 mg, 0.184 mmol). mp 61-66 °C; R_f = 0.21 (1:2 CH₂Cl₂/hexanes). Spectral data for **174i**: ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (t, 6H, *J* = 7.5 Hz), 2.89 (q, 4H, *J* = 7.5 Hz), 5.82 (s, 2H), 6.62-6.65 (m, 4H), 6.94-6.97 (m, 4H), 7.03-7.08 (m, 2H), 7.29 (s, 2H), 7.44 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.71 (d, 2H, *J* = 8.5 Hz), 8.13-8.15 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.59, 29.31, 112.81, 120.46, 121.82, 123.02, 126.44, 127.40, 127.70, 128.66, 128.89, 133.09, 139.80, 140.36, 141.83, 149.96; IR (thin film) 3513br m, 2928s, 1559s 1456s, 1387s, 1167s cm⁻¹; HRMS (ESI+) *m/z* calcd for C₃₆H₃₁O₂ (M+H⁺) 495.2324, meas 495.2334. [α]_D²⁰ = -228.7 (c 1.0, CH₂Cl₂).



7,7'-di-cyclohexyl VANOL 174i: The reaction of (*S*)-**199d** (156 mg, 0.25 mmol), NidppeCl₂ (22 mg, 0.042 mmol) and CyMgCl (2 M in ether, 0.42 mL, 0.84 mmol) was performed according to Procedure N. Purification of the crude product by column chromatography on silica gel (30

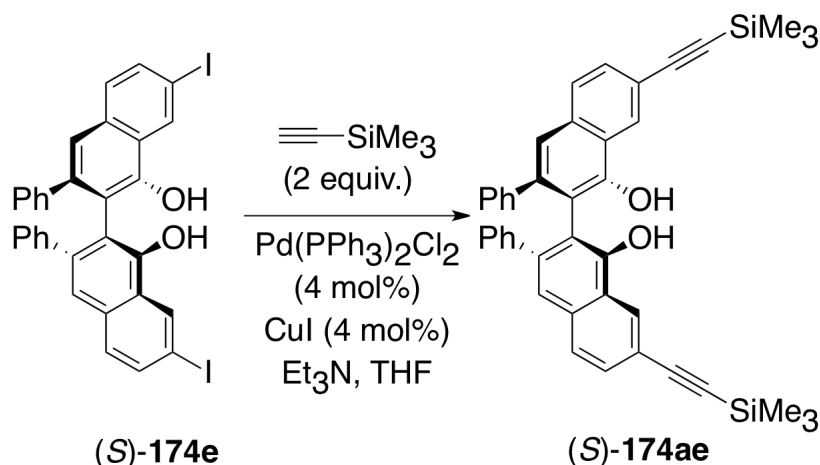
mm x 200 mm, CH₂Cl₂:hexanes 1:4) gave (*S*)-**174l** as an off-white foamy solid over in 71% yield two steps (107 mg, 0.178 mmol). mp 131-137 °C; R_f = 0.33 (1:2 CH₂Cl₂/hexanes). Spectral data for **174l**: ¹H NMR (CDCl₃, 500 MHz) δ 1.30-1.38 (m, 2H), 1.42-1.52 (m, 4H), 1.56-1.65 (m, 4H), 1.78-1.82 (m, 2H), 1.89-1.94 (m, 4H), 2.01-2.05 (m, 4H), 2.71-2.78 (m, 2H), 6.60-6.64 (m, 4H), 6.93-6.97 (m, 4H), 7.03-7.07 (m, 2H), 7.28 (s, 2H), 7.46 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.71 (d, 2H, *J* = 8.5 Hz), 8.15 (d, 2H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 26.21, 26.96, 34.43, 34.48, 44.95, 112.69, 119.46, 121.78, 122.98, 126.40, 127.41, 127.61, 127.73, 128.88, 133.25, 139.81, 140.39, 145.62, 150.06; IR (thin film) 3513br m, 2924s, 1559s, 1497s, 1387s, 1265s, 1165s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₄₄H₄₁O₂ (M-H⁺) 601.3107, meas 601.3093. [α]_D²⁰ = -156.7 (c 1.0, CH₂Cl₂).

Ullman coupling¹⁵



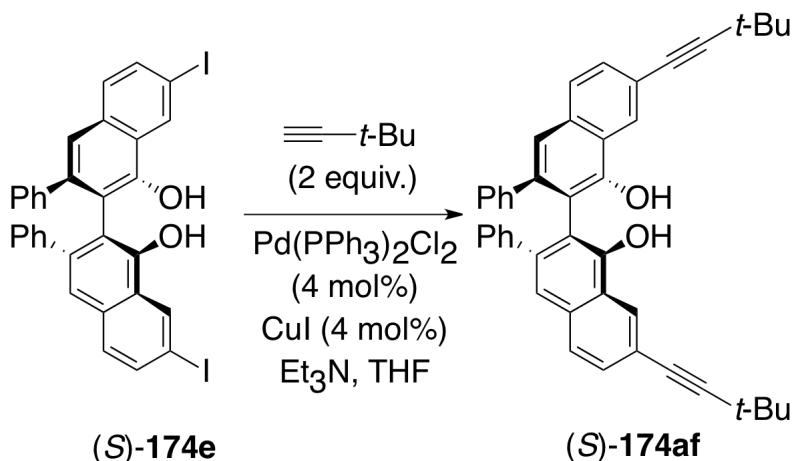
with EtOAc (30 mL x 3). The combined organic layer was washed with H₂O (50 mL x 4) and brine (50 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. The product was purified by column chromatography on silica gel (20 mm x 200 mm, EtOAc:hexanes 1:2). The purified product was dissolved in a mixture of THF and MeOH (68 mL, 1:1) and Amberlyst 15 (0.85g) was added. The mixture was stirred at 65 °C for 15 h with an argon balloon attached to the condenser. After cooling down to room temperature, the mixture was filtered through filter paper and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm x 200 mm, CH₂Cl₂) gave (*S*)-**174g** as an off-white solid in 60% yield over two steps (505 mg, 1.01 mmol). mp 178-180 °C; R_f = 0.26 (CH₂Cl₂). Spectral data for **174g**: ¹H NMR (CDCl₃, 500 MHz) δ 3.99 (s, 6H), 5.75 (s, 2H), 6.62 (dd, 4H, *J* = 8.5, 1.5 Hz), 6.95 (t, 4H, *J* = 7.5 Hz), 7.05 (t, 2H, *J* = 7.5 Hz), 7.72 (dd, 2H, *J* = 9.0, 3.0 Hz), 7.26 (s, 2H), 7.60 (d, 2H, *J* = 3.0 Hz), 7.68 (d, 2H, *J* = 9.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 55.48, 100.88, 113.38, 120.36, 121.82, 123.80, 126.40, 127.42, 128.88, 129.33, 130.08, 138.22, 140.30, 149.26, 157.76; IR (thin film) 3507br w, 2936w, 1597s, 1497s, 1392s, 1206s, 1163s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₃₄H₂₅O₄ (M-H⁺) 497.1753, meas 497.1751. [α]_D²⁰ = -206.6 (c 1.0, CH₂Cl₂).

Sonogashira coupling – illustrated for the synthesis of (*S*)-6ae** (Procedure O)^{63c}**

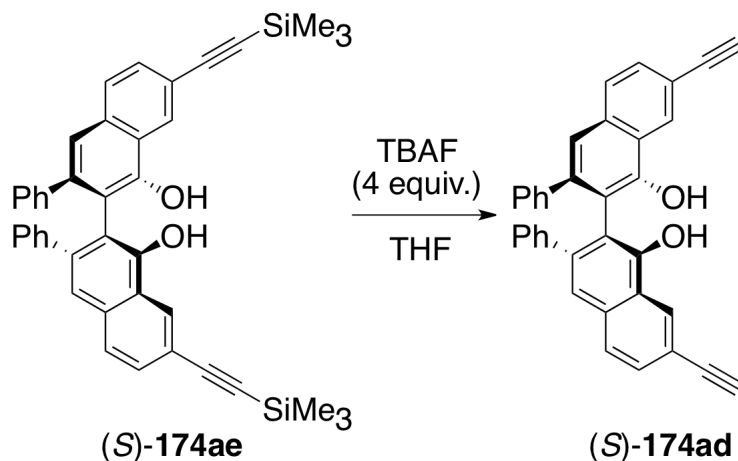


To a flame-dried 25 mL round bottom flask was added *(S)*-**174e** (345 mg, 0.50 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and THF (2mL) under N₂. Triethylamine (0.56 mL, 4 mmol) was then added to the mixture. The reaction mixture was stirred at room temperature for 5 minutes and then ethynyltrimethylsilane (0.16 mL, 1.1 mmol) was added. After stirring at room temperature for 24 h, the mixture was treated with hexanes (2 mL) and concentrated. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave *(S)*-**174ae** as an off-white solid (262 mg, 0.416 mmol, 83%). mp 267-269 °C; R_f = 0.45 (1:1 CH₂Cl₂/hexane). Spectral data for **174ae**: ¹H NMR (CDCl₃, 500 MHz) δ 0.29 (s, 18H), 5.79 (s, 2H), 6.62 (dd, 4H, *J* = 8.5, 1.5 Hz), 6.93-6.97 (m, 4H), 7.04-7.09 (m, 2H), 7.27 (s, 2H), 7.57 (dd, 2H, *J* = 8.5, 1.5 Hz), 7.68 (d, 2H, *J* = 8.5 Hz), 8.47-8.49 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 0.01, 95.07, 105.43, 113.26, 120.35, 121.88, 122.46, 126.91, 127.08, 127.52, 127.66, 128.78, 130.28, 133.97, 139.79, 141.57, 150.18; IR (thin film) 3521s, 3059m, 2959s, 2155s, 1559s, 1497m, 1387s, 1250s, 858s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 630 M⁺ (30), 315 (15), 300 (69), 239 (3). Anal

calcd for C₄₂H₃₈O₂Si₂: C, 79.95; H, 6.07. Found: C, 79.88; H, 6.22. $[\alpha]_D^{20} = -43.8$ (c 1.0, CH₂Cl₂).



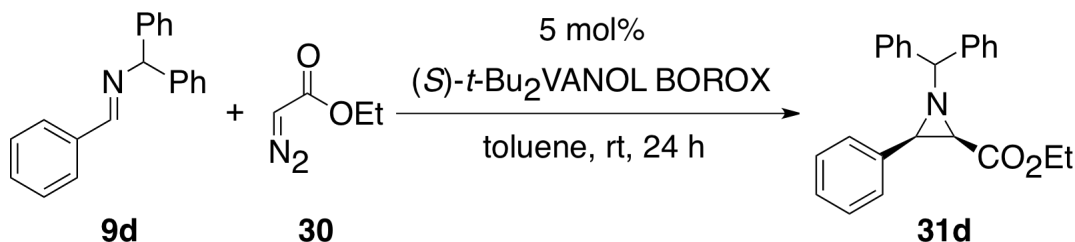
The reaction of *(S)*-**174e** (138 mg, 0.20 mmol), bis(triphenylphosphine)palladium(II) dichloride (5.6 mg, 0.0080 mmol), CuI (1.6 mg, 0.0080 mmol), triethylamine (0.23 mL, 1.6 mmol) and 3,3-dimethyl-1-butyne (54 mL, 0.44 mmol) was performed according to Procedure O. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 1:3) gave *(S)*-**174af** as an off-white solid (106 mg, 0.177 mmol, 89%). mp 175-182 °C; *R*_f = 0.41 (1:1 CH₂Cl₂/hexanes). Spectral data for **174af**: ¹H NMR (CDCl₃, 500 MHz) δ 1.37 (s, 18H), 5.79 (s, 2H), 6.60-6.63 (m, 4H), 6.92-6.96 (m, 4H), 7.04-7.08 (m, 2H), 7.25 (s, 2H), 7.52 (dd, 2H, *J* = 8.5, 1.5 Hz), 7.66 (d, 2H, *J* = 8.5 Hz), 8.38-8.39 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 28.08, 31.08, 79.43, 99.39, 113.05, 121.31, 121.81, 122.55, 125.98, 126.76, 127.45, 127.53, 128.78, 130.47, 133.46, 139.89, 140.93, 149.97; IR (thin film) 3521br s, 2987s, 1559s, 1456s, 1387s, 1279s cm⁻¹; HRMS (ESI+) *m/z* calcd for C₄₄H₃₉O₂ (M+H⁺) 599.2950, meas 599.2925. $[\alpha]_D^{20} = -76.1$ (c 1.0, CH₂Cl₂).



To a flame-dried 25 mL round bottom flask was added (*S*)-**174ae** (126 mg, 0.20 mmol) and dry THF (8 mL) under N₂. To the solution was slowly added TBAF (1 M in THF, 0.8 mL, 0.8 mmol). After stirring at room temperature for 1 h, the reaction was quenched by the addition of brine (2 mL) and ether (8 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (8 mL x 2). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 1:1) gave (*S*)-**174ad** as an off-white solid (78 mg, 0.160 mmol, 89%). mp >260 °C; R_f = 0.17 (1:1 CH₂Cl₂/hexanes). Spectral data for **174ad**: ¹H NMR (CDCl₃, 500 MHz) δ 3.17 (s, 2H), 5.83 (s, 2H), 6.58-6.61 (m, 4H), 6.94-6.98 (m, 4H), 7.06-7.10 (m, 2H), 7.27 (s, 2H), 7.59 (dd, 2H, *J* = 8.5, 1.5 Hz), 7.70 (d, 2H, *J* = 8.5 Hz), 8.53-8.54 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 77.80, 84.01, 113.23, 119.22, 121.86, 122.38, 126.91, 127.41, 127.52, 127.79, 128.75, 130.27, 134.07, 139.66, 141.73, 150.11 IR (thin film) 3505br s, 3293s, 1559s, 1497s, 1385s, 1265s cm⁻¹; HRMS (ESI⁺) *m/z* calcd for C₃₆H₂₃O₂ (M+H⁺) 487.1698, meas 487.1682. [α]_D²⁰ = -173.7 (c 1.0, CH₂Cl₂).

6.2.5 Catalytic asymmetric aziridination of benzhydryl imines with ethyl diazoacetate mediated by a catalyst prepared from 7,7'-di-*t*-butylVANOL **174m**

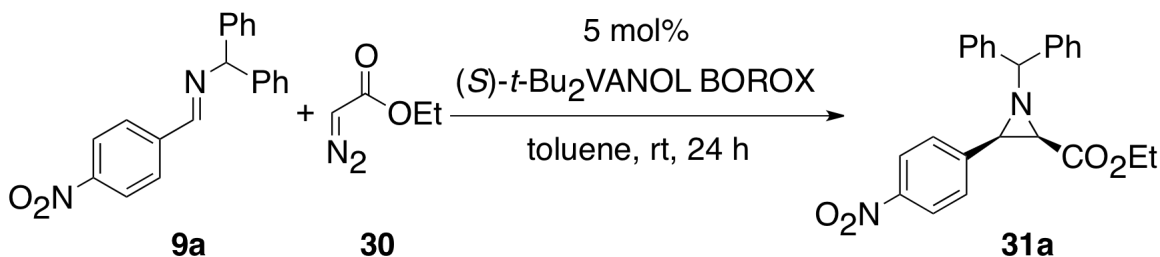
General procedure illustrated for the synthesis of *(2R,3R)*-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate (Procedure P)^{26g}



A 25 mL pear-shaped single necked Schlenk flask which had its 14/20 joint replaced by a threaded high vacuum Teflon valve was flame dried (with a stir bar in it) and cooled to room temperature under N₂ and charged with *(S)*-*t*-Bu₂VANOL **174m** (13.8 mg, 0.025 mmol) and triphenyl borate (29 mg, 0.10 mmol). The mixture was dissolved in dry toluene (1 mL). After the addition of H₂O (0.45 mL, 0.025 mmol), the Teflon valve was closed and the flask was heated at 80 °C for 1 h. Toluene was carefully removed by exposing to high vacuum (0.1 mmHg) by slightly cracking the Teflon valve. After removal of the solvent, the Teflon valve was completely opened and the flask was heated to 80 °C under high vacuum for 30 min. To the Schlenk flask containing the catalyst were added imine **31d** (136 mg, 0.50 mmol) and dry toluene (1 mL). The reaction mixture was stirred at room temperature for 5 minutes and then ethyl diazoacetate (62 μL, 0.6 mmol) was added via syringe. The Teflon valve was closed and the reaction mixture was stirred at room temperature for 24 h. The mixture was then diluted with hexanes (5 mL) and transferred to a 25 mL round bottom flask. Rotary evaporation of the solvent followed by

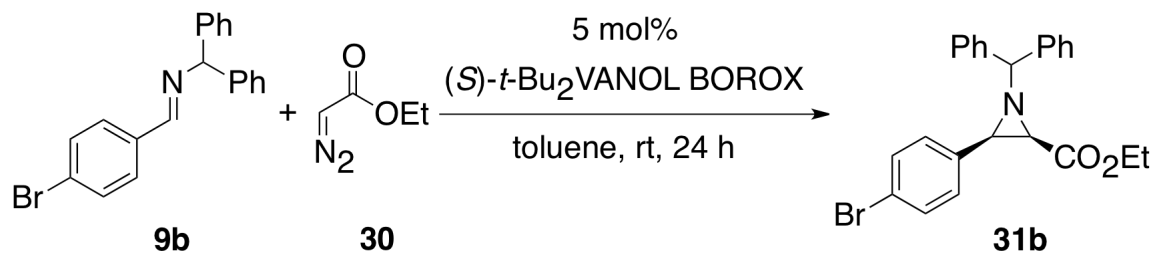
exposure to high vacuum (0.5 mm Hg) for 30 minutes gave the crude mixture as an off-white solid. The conversion was determined from the ^1H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the H on the imine carbon. The *cis/trans* ratio was determined to be >100:1 from the ^1H NMR spectrum of the crude reaction mixture by integration of the ring methine protons for each aziridine. The *cis* ($J = 6\text{-}8$ Hz) and the *trans* ($J = 1\text{-}3$ Hz) coupling constants were used to differentiate the two isomers. The yields of the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture by integration of the N-H proton of the enamine relative to the aziridine ring methine protons with the aid of the isolated yield of the *cis*-aziridine. The crude product was purified by column chromatography on silica gel (35 mm x 400 mm, EtOAc:hexanes 1:19) to afford **31d** as a white solid (146 mg, 0.41 mmol, 82%). The optical purity was determined to be 98% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 90:10 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 4.42$ min for (2*S*,3*S*)-**31d** (minor) and $R_t = 8.17$ min for (2*R*,3*R*)-**31d** (major). The reaction was repeated and stopped after a reaction time of 4 h to give an 89% yield of **31d** with 97.4% *ee*. mp 126-127 °C; $R_f = 0.13$ (1:9 EtOAc:hexanes). Spectral data for **31d**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.96 (t, 3H, $J = 7.0$ Hz), 2.65 (d, 1H, $J = 7.0$ Hz), 3.19 (d, 1H, $J = 7.0$ Hz), 3.93 (s, 1H), 3.90-3.94 (m, 2H), 7.14-7.20 (m, 2H), 7.20-7.26 (m, 5H), 7.30-7.34 (m, 2H), 7.37-7.40 (m, 2H), 7.46-7.49 (m, 2H), 7.57-7.60 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.93, 46.38, 48.03, 60.55, 77.71, 127.19, 127.21, 127.31, 127.40, 127.54, 127.75, 127.78, 128.48, 135.03, 142.38, 142.52, 167.72 (1 sp^2 C not located); IR

(thin film) 3031w, 2982w, 1738s, 1456m, 1204s cm^{-1} ; mass spectrum, m/z (% rel intensity) 357 M^+ (0.05), 190 (46), 167 (100), 117 (61). $[\alpha]_{\text{D}}^{20} = +36.2$ (c 1.0, CH_2Cl_2) on 98% *ee* (2*R*,3*R*)-**31d**.



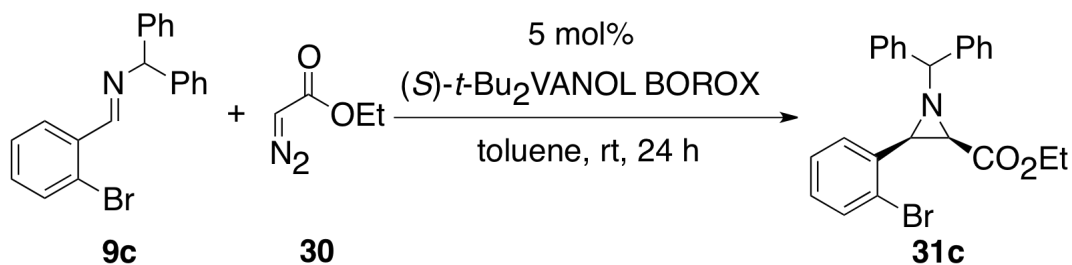
(2*R*,3*R*)-ethyl 1-benzhydryl-3-(4-nitrophenyl)aziridine-2-carboxylate **31a**:^{26g} The reaction of imine **9a** (158 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:40) to afford **31a** as an off-white solid (193 mg, 0.48 mmol, 96%). The optical purity was determined to be 98% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 90:10 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 8.01$ min for (2*S*,3*S*)-**31a** (minor) and $R_t = 9.86$ min for (2*R*,3*R*)-**31a** (major). mp 134-135 $^\circ\text{C}$; $R_f = 0.30$ (1:40 EtOAc/benzene). Spectral data for **31a**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.00 (t, 3H, $J = 7.0$ Hz), 2.78 (d, 1H, $J = 7.0$ Hz), 3.24 (d, 1H, $J = 7.0$ Hz), 3.93 (q, 2H, $J = 7.0$ Hz), 3.98 (s, 1H), 7.16-7.20 (m, 1H), 7.22-7.27 (m, 3H), 7.31-7.35 (m, 2H), 7.42-7.45 (m, 2H), 7.55-7.60 (m, 4H), 8.08-8.12 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.00, 46.91, 47.05, 60.94, 77.54, 123.05, 127.05, 127.36, 127.44, 127.68, 128.60, 128.65, 128.77, 141.82, 142.04, 142.50, 147.32, 166.95; IR (thin film)

3029w, 2982w, 1744s, 1522s, 1348s, 1202s cm^{-1} ; mass spectrum, m/z (% rel intensity) 402 M^+ (0.03), 167 (100), 165 (49), 152 (32), 89 (14). $[\alpha]_{\text{D}}^{20} = -10.9$ (c 1.0, CH_2Cl_2) on 98% *ee* (2*R*,3*R*)-**31a**.



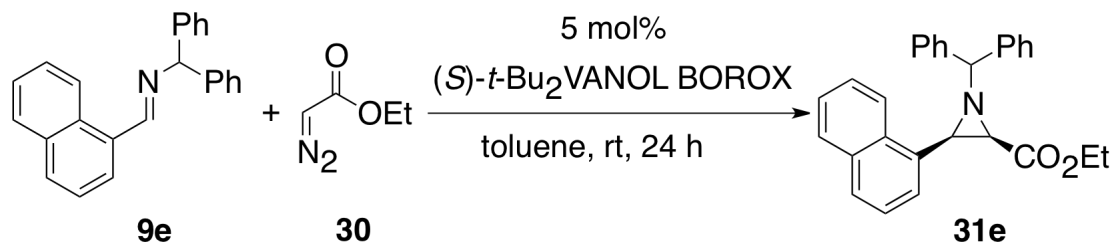
(2*R*,3*R*)-ethyl 1-benzhydryl-3-(4-bromophenyl)aziridine-2-carboxylate **31b**:^{26g} The reaction of imine **9b** (175 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (35 mm x 400 mm, EtOAc/hexanes 1:19) to afford **31b** as a white solid (196 mg, 0.45 mmol, 90%). The optical purity was determined to be 98% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 98:2 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 5.22$ min for (2*S*,3*S*)-**31b** (minor) and $R_t = 12.73$ min for (2*R*,3*R*)-**31b** (major). mp 151-152 $^\circ\text{C}$; $R_f = 0.44$ (1:40 EtOAc/benzene). Spectral data for **31b**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.01 (t, 3H, $J = 7.0$ Hz), 2.66 (d, 1H, $J = 7.0$ Hz), 3.12 (d, 1H, $J = 7.0$ Hz), 3.91-3.97 (m, 3H), 7.15-7.19 (m, 1H), 7.21-7.29 (m, 5H), 7.30-7.34 (m, 2H), 7.34-7.37 (m, 2H), 7.42-7.45 (m, 2H), 7.55-7.57 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.00, 46.47, 47.35, 60.71, 77.62, 121.35, 127.14, 127.29, 127.43, 127.50, 128.52, 128.53, 129.55, 130.90, 134.08, 142.15, 142.32, 167.42; IR (thin film) 2978w, 1734s, 1456m,

1202s, 1065m cm^{-1} ; mass spectrum, m/z (% rel intensity) 437 M^+ (0.67, ^{81}Br), 435 M^+ (0.35, ^{79}Br), 270 (23, ^{81}Br), 268 (21, ^{79}Br), 167 (100, ^{81}Br), 165 (41, ^{79}Br). $[\alpha]_{\text{D}}^{20} = +9.9$ (c 1.0, CH_2Cl_2) on 98% *ee* (2*R*,3*R*)-**31b**.



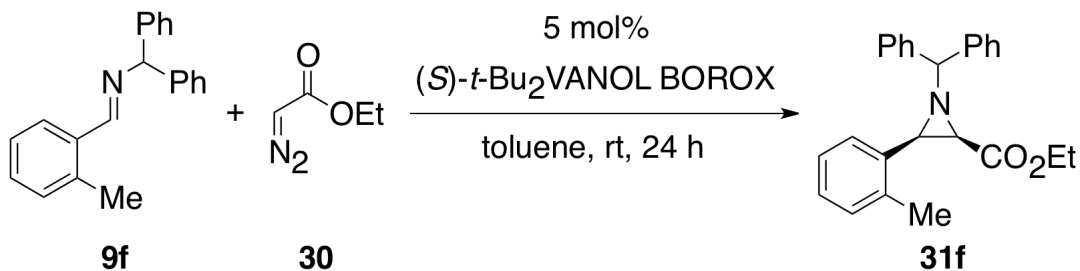
(2*R*,3*R*)-ethyl 1-benzhydryl-3-(2-bromophenyl)aziridine-2-carboxylate **31c**:^{26g} The reaction of imine **9c** (175 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* = 8:1 and the acyclic enamine products were determined to be 4% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:400) to afford **31c** as a white solid (171 mg, 0.39 mmol, 78%). The optical purity was determined to be 95% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 99.5:0.5 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: R_t = 14.66 min for (2*S*,3*S*)-**31c** (minor) and R_t = 18.68 min for (2*R*,3*R*)-**31c** (major). mp 145-146 $^{\circ}\text{C}$; R_f = 0.41 (1:40 EtOAc/benzene). Spectral data for **31c**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.95 (t, 3H, J = 7.0 Hz), 2.78 (d, 1H, J = 7.0 Hz), 3.33 (d, 1H, J = 7.0 Hz), 3.93 (q, 2H, J = 7.0 Hz), 4.00(s, 1H), 7.05 (td, 1H, J = 7.5, 1.5 Hz), 7.17-7.29 (m, 5H), 7.30-7.34 (m, 2H), 7.40 (dd, 1H, J = 7.5, 1.5 Hz), 7.47-7.50 (m, 2H), 7.56 (d, 3H, J = 8.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.89, 45.91, 48.81, 60.61, 77.59, 123.27, 126.74, 127.03, 127.21, 127.60, 127.69, 128.52, 128.58, 128.80, 130.82, 131.59, 134.45,

142.16, 142.39, 167.57; IR (thin film) 1738s, 1456s, 1200s cm^{-1} ; $[\alpha]_{\text{D}}^{20} = +21.8$ (c 1.0, CH_2Cl_2) on 95% *ee* (2*R*,3*R*)-**31c**.



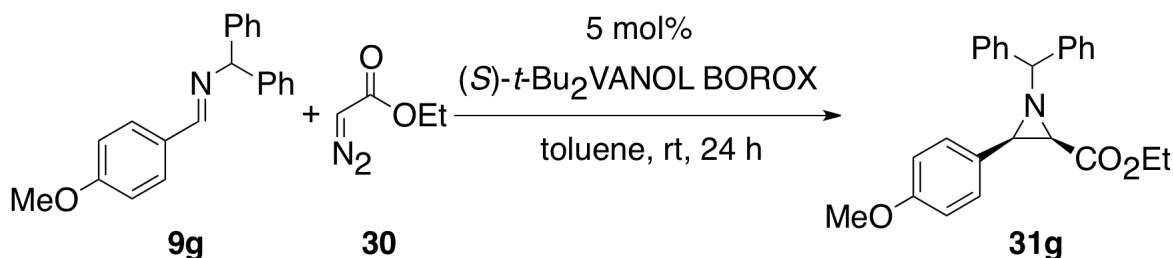
(2*R*,3*R*)-ethyl 1-benzhydryl-3-(naphthalen-1-yl)aziridine-2-carboxylate **31e**:^{26g} The reaction of imine **9e** (161 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (35 mm x 400 mm, EtOAc/hexanes 1:19) to afford **31e** as a white solid (186 mg, 0.46 mmol, 91%). The optical purity was determined to be 99% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 99:1 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 9.32$ min for (2*R*,3*R*)-**31e** (major) and $R_t = 11.52$ min for (2*S*,3*S*)-**31e** (minor). mp 152-154 $^{\circ}\text{C}$; $R_f = 0.13$ (1:9 EtOAc/hexanes). Spectral data for **31e**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.62 (t, 3H, $J = 7.0$ Hz), 2.90 (d, 1H, $J = 7.0$ Hz), 3.68-3.76 (m, 3H), 4.07 (s, 1H), 7.17-7.21 (m, 1H), 7.23-7.30 (m, 3H), 7.32-7.38 (m, 3H), 7.40-7.44 (m, 1H), 7.44-7.48 (m, 1H), 7.52-7.55 (m, 2H), 7.61-7.64 (m, 2H), 7.66 (d, 1H, $J = 7.0$ Hz), 7.68 (d, 1H, $J = 8.0$ Hz), 7.77-7.79 (m, 1H), 8.08 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.58, 46.06, 46.40, 60.38, 78.03, 122.97, 125.32, 125.41, 125.85, 126.56, 127.17, 127.19, 127.61, 127.62, 127.91, 128.52, 128.58, 130.53, 131.46, 133.08, 142.27, 142.51,

167.79 (1 sp^2 C not located); IR (thin film) 3032w, 2980w, 1738s, 1455m, 1192s cm^{-1} ; $[\alpha]_{\text{D}}^{20} = -16.1$ (c 1.0, CH_2Cl_2) on 99% *ee* (2*R*,3*R*)-**31e**.



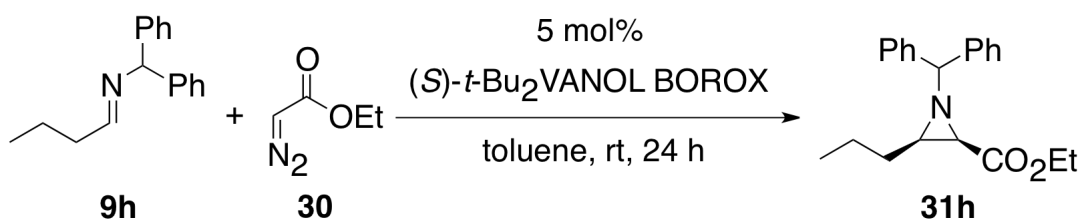
(2*R*,3*R*)-ethyl 1-benzhydryl-3-(*o*-tolyl)aziridine-2-carboxylate **31f**.^{26g} The reaction of imine **9f** (143 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:200) to afford **31f** as a white solid (171 mg, 0.46 mmol, 92%). The optical purity was determined to be 97% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 99:1 hexane/*i*PrOH, flow rate: 1.0 mL/min). Retention time: $R_t = 5.71$ min for (2*S*,3*S*)-**31f** (minor) and $R_t = 7.42$ min for (2*R*,3*R*)-**31f** (major). mp 162-163 $^\circ\text{C}$; $R_f = 0.35$ (1:40 EtOAc/benzene). Spectral data for **31f**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.88 (t, 3H, $J = 7.0$ Hz), 2.29 (s, 3H), 2.72 (d, 1H, $J = 7.0$ Hz), 3.20 (d, 1H, $J = 7.0$ Hz), 3.89 (q, 2H, $J = 7.0$ Hz), 3.94 (s, 1H), 7.00-7.03 (m, 1H), 7.06-7.12 (m, 2H), 7.16-7.20 (m, 1H), 7.21-7.29 (m, 3H), 7.30-7.34 (m, 2H), 7.49-7.54 (m, 3H), 7.58-7.61 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.82, 18.77, 45.61, 46.90, 60.43, 77.91, 125.33, 127.12, 127.13, 127.51, 127.72, 128.47, 128.49, 128.52, 129.08, 133.11, 135.99, 142.39,

142.55, 167.91 (1 sp^2 C not located); IR (thin film) 1740s, 1455s, 1196s cm^{-1} . $[\alpha]_{\text{D}}^{20} = +36.0$ (c 1.0, CH_2Cl_2) on 97% *ee* (2*R*,3*R*)-**31f**.



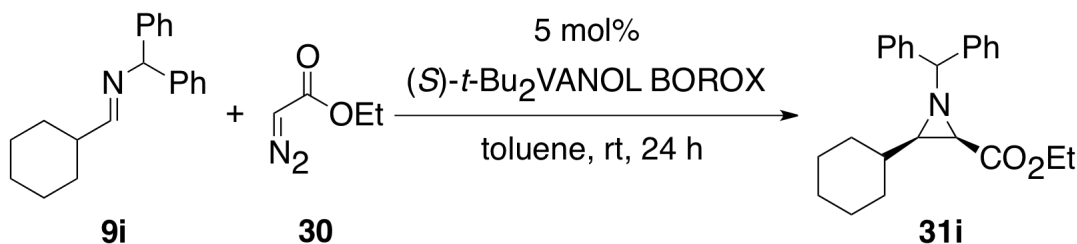
(2*R*,3*R*)-ethyl 1-benzhydryl-3-(4-methoxyphenyl)aziridine-2-carboxylate **31g**:^{26g} The reaction of imine **9g** (151 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography. The silica gel for column chromatography was pre-conditioned by preparing a slurry in a 1:9 mixture of $\text{Et}_3\text{N}:\text{CH}_2\text{Cl}_2$ which was loaded into a column (35 x 400 mm). The solvent was drained out and then the silica gel was dried by flushing with nitrogen for one hour to remove excess Et_3N . The silica gel column was then saturated with a 1:1:8 mixture of CH_2Cl_2 :ether:hexanes. The crude aziridine was loaded onto the column and then elution with the same solvent afforded **31g** as a white solid (138 mg, 0.36 mmol, 71%). The optical purity was determined to be 98% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 95:5 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 6.65$ min for (2*S*,3*S*)-**16g** (minor) and $R_t = 13.51$ min for (2*R*,3*R*)-**31g** (major). mp 134-135 $^\circ\text{C}$; $R_f = 0.21$ (1:5 EtOAc/hexanes). Spectral data for **31g**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.01 (t, 3H, $J = 7.0$ Hz), 2.61 (d, 1H, $J = 7.0$ Hz), 3.14 (d, 1H, $J = 7.0$ Hz), 3.74 (s, 3H), 3.90-3.97 (m, 2H), 3.92

(s, 1H), 6.75-6.79 (m, 2H), 7.14-7.18 (m, 1H), 7.20-7.26 (m, 3H), 7.29-7.33 (m, 4H), 7.44-7.47 (m, 2H), 7.56-7.59 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.00, 46.32, 47.73, 55.16, 60.52, 77.72, 113.23, 127.12, 127.16, 127.22, 127.35, 127.52, 128.45, 128.88, 142.41, 142.57, 158.90, 167.86 (1 sp^2 C not located); IR (thin film) 2932w, 1734s, 1518s, 1456s, 1240s, 1198s, 1032s cm^{-1} ; mass spectrum, m/z (% rel intensity) 387 M^+ (0.09), 222 (7), 221 (100), 167 (48), 166 (22), 147 (23), 146 (47), 91 (14). $[\alpha]_{\text{D}}^{20} = +23.2$ (c 1.0, CH_2Cl_2) on 98% *ee* (2*R*,3*R*)-**31h**.



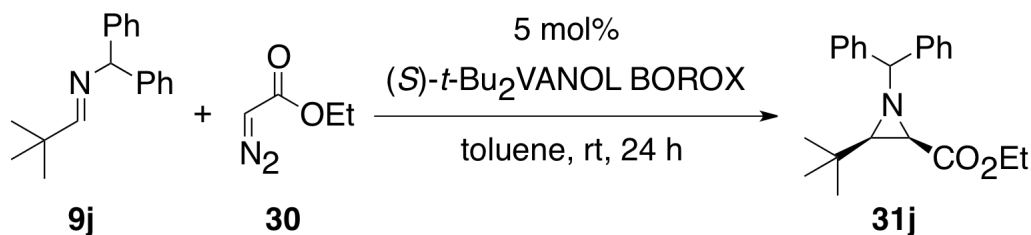
(2*R*,3*R*)-ethyl 1-benzhydryl-3-propylaziridine-2-carboxylate **31h**:^{26g} The reaction of imine **9h** (119 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:200) to afford **31h** as a white solid (125 mg, 0.39 mmol, 77%). The optical purity was determined to be 94% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 99:1 hexane/*i*PrOH, flow rate: 1.0 mL/min). Retention time: $R_t = 3.30$ min for (2*S*,3*S*)-**31h** (minor) and $R_t = 6.32$ min for (2*R*,3*R*)-**31h** (major). mp 102-103 $^\circ\text{C}$; $R_f = 0.26$ (1:40 EtOAc/benzene). Spectral data for **31h**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.73 (t, 3H, $J = 7.0$ Hz), 1.00-1.08 (m, 1H), 1.10-1.18 (m, 1H), 1.23 (t, 3H, $J = 7.0$ Hz), 1.40-1.48 (m, 1H), 1.50-1.58 (m, 1H), 2.02 (dd, 1H, $J = 6.5, 6.5$ Hz), 2.27 (d, 1H, $J = 6.5$ Hz), 3.65 (s, 1H), 4.11-4.23 (m, 2H), 7.17-7.23 (m, 2H),

7.24-7.29 (m, 4H), 7.36-7.39 (m, 2H), 7.45-7.48 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.61, 14.26, 20.31, 29.90, 43.37, 46.68, 60.67, 77.96, 126.99, 127.15, 127.35, 127.86, 128.32, 128.34, 142.46, 142.82, 169.52; IR (thin film) 2959m, 1732s, 1456m, 1196s cm^{-1} ; mass spectrum, m/z (% rel intensity) 323 M^+ (0.81), 294 (9), 206 (9), 167 (100), 156 (100), 152 (80), 128 (78). $[\alpha]_{\text{D}}^{20} = +102.2$ (c 1.0, CH_2Cl_2) on 94% *ee* (2*R*,3*R*)-**31h**.



(2*R*,3*R*)-ethyl 1-benzhydryl-3-cyclohexylaziridine-2-carboxylate **31i**.^{26g} The reaction of imine **9i** (139 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:200) to afford **31i** as a white solid (160 mg, 0.44 mmol, 88%). The optical purity was determined to be 94% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 99:1 hexane/*i*PrOH, flow rate: 1.0 mL/min). Retention time: R_t = 3.29 min for (2*S*,3*S*)-**31i** (minor) and R_t = 6.41 min for (2*R*,3*R*)-**31i** (major). mp 161-162 $^\circ\text{C}$; R_f = 0.30 (1:40 EtOAc/benzene). Spectral data for **31i**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.45-0.54 (m, 1H), 0.90-1.33 (m, 6H), 1.24 (t, 3H, J = 7.0 Hz), 1.42-1.62 (m, 4H), 1.79 (dd, 1H, J = 7.0, 2.5 Hz), 2.25 (d, 1H, J = 7.0 Hz), 3.60 (s, 1H), 4.13-4.26 (m, 2H), 7.17-7.22 (m, 2H), 7.24-7.30 (m, 4H), 7.31-7.34 (m, 2H),

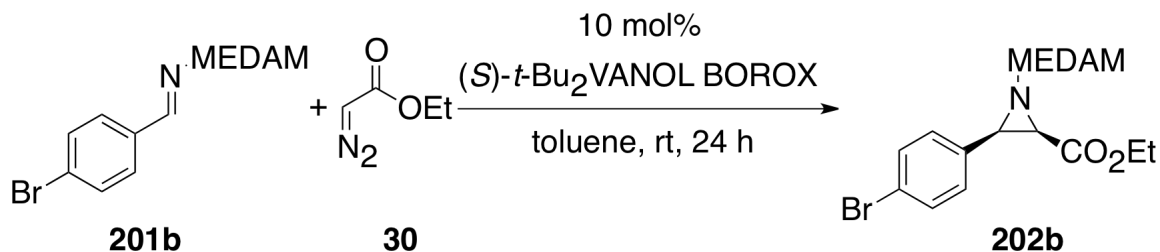
7.47-7.49 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.28, 25.36, 25.54, 26.14, 30.13, 30.73, 36.28, 43.41, 52.14, 60.67, 78.22, 126.89, 127.08, 127.49, 128.27, 128.31, 128.36, 142.36, 142.76, 169.64; IR (thin film) 2919s, 1732s, 1450m, 1190s cm^{-1} . $[\alpha]_{\text{D}}^{20} = +125.7$ (c 1.0, CH_2Cl_2) on 94% *ee* (2*R*,3*R*)-**31i**.



(2*R*,3*R*)-ethyl 1-benzhydryl-3-(tert-butyl)aziridine-2-carboxylate **31j**:^{26g} The reaction of imine **9j** (126 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.6 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:200) to afford **31j** as a white solid (150 mg, 0.45 mmol, 89%). The optical purity was determined to be 96% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 99:1 hexane/*i*PrOH, flow rate: 1.0 mL/min). Retention time: $R_t = 3.56$ min for (2*S*,3*S*)-**31j** (minor) and $R_t = 9.31$ min for (2*R*,3*R*)-**31j** (major). mp 148-149 $^\circ\text{C}$; $R_f = 0.41$ (1:40 EtOAc/benzene). Spectral data for **31j**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.69 (s, 9H), 1.28 (t, 3H, $J = 7.0$ Hz), 1.75 (d, 1H, $J = 7.0$ Hz), 2.15 (d, 1H, $J = 7.0$ Hz), 3.58 (s, 1H), 4.04-4.12 (m, 1H), 4.19-4.26 (m, 1H), 7.17-7.21 (m, 2H), 7.24-7.31 (m, 4H), 7.37-7.40 (m, 2H), 7.64-7.67 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.09, 27.40, 31.60, 43.39, 56.09, 60.58, 79.24, 126.85, 127.27, 127.37, 128.19,

128.21, 128.27, 142.63, 143.46, 169.73; IR (thin film) 2953m, 1738s, 1449m, 1194s cm^{-1} .

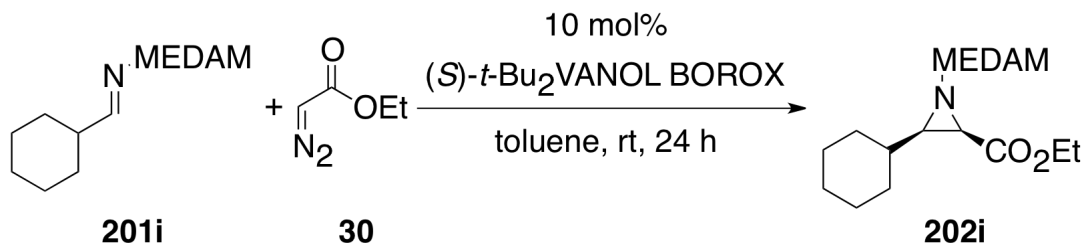
$[\alpha]_{\text{D}}^{20} = +133.2$ (c 1.0, CH_2Cl_2) on 96% *ee* (2*R*,3*R*)-**31j**.



(2*R*,3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-bromophenyl)aziridine-

-2-carboxylate **202b**:^{26j} The reaction of imine **201b** (93.2 mg, 0.20 mmol) and ethyl diazoacetate (25 μL , 0.24 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (30 mm x 250 mm, EtOAc/benzene 1:40) to afford **202b** as a white foamy solid (105 mg, 0.19 mmol, 95%). The optical purity was determined to be 99% *ee* by HPLC (Chiralcel OD-H column, 222 nm, 99:1 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 7.62$ min for (2*R*,3*R*)-**202b** (major) and $R_t = 11.58$ min for (2*S*,3*S*)-**202b** (minor). mp 147-148 $^\circ\text{C}$; $R_f = 0.21$ (1:40 EtOAc/benzene). Spectral data for **202b**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.03 (t, 3H, $J = 7.5$ Hz), 2.18 (s, 6H), 2.24 (s, 6H), 2.57 (d, 1H, $J = 6.5$ Hz), 3.04 (d, 1H, $J = 7.0$ Hz), 3.62 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H), 3.92-3.96 (m, 2H), 7.06 (s, 2H), 7.16 (s, 2H), 7.26 (dd, 2H, $J = 6.5, 2.0$ Hz), 7.35 (dd, 2H, $J = 6.5, 2.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.07, 16.18, 16.23, 46.34, 47.54, 59.54, 59.59, 60.64, 76.95, 121.22, 127.35, 127.68, 129.61, 130.68, 130.82, 134.36, 137.57, 137.76, 156.01, 156.16, 167.70 (1 sp^2 C not located); IR (thin

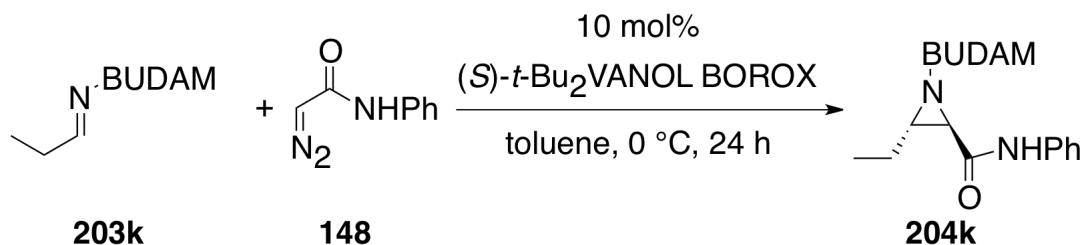
film) 2934s, 1742s, 1487s, 1221s cm^{-1} . $[\alpha]_{\text{D}}^{20} = +17.7$ (c 1.0, CH_2Cl_2) on 99% *ee* (*2R,3R*)-**202b** (HPLC).



(*2R,3R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridine-2-carboxylate

202i:^{26j} The reaction of imine **201i** (197 mg, 0.50 mmol) and ethyl diazoacetate (62 μL , 0.60 mmol) was performed according to the general procedure (Procedure P). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:40) to afford **202b** as a white foamy solid (220 mg, 0.46 mmol, 92%). The optical purity was determined to be 97% *ee* by HPLC (Chiralcel OD column, 222 nm, 99:1 hexane/*i*PrOH, flow rate: 0.7 mL/min). Retention time: $R_t = 6.61$ min for (*2R,3R*)-**202i** (major) and $R_t = 8.16$ min for (*2S,3S*)-**202i** (minor). mp 46-47 $^{\circ}\text{C}$; $R_f = 0.27$ (1:40 EtOAc/benzene). Spectral data for **202i**: ^1H NMR (CDCl_3 , 600 MHz) δ 0.48-0.55 (m, 1H), 0.81-1.11 (m, 4H), 1.24 (t, 3H, $J = 7.2$ Hz), 1.21-1.28 (m, 2H), 1.41-1.60 (m, 4H), 1.71-1.73 (m, 1H), 2.16 (d, 1H, $J = 7.2$ Hz), 2.21 (s, 6H), 2.22 (s, 6H), 3.34 (s, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 4.15-4.23 (m, 2H), 6.94 (s, 2H), 7.09 (s, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 14.34, 16.06, 16.16, 25.35, 25.53, 26.17, 30.10, 30.83, 36.35, 43.47, 52.25, 59.60, 59.65, 60.65, 77.51, 127.35, 128.54, 130.33, 130.46, 137.56, 138.11, 155.74, 156.26, 169.81; IR (thin film) 2928s, 1735s,

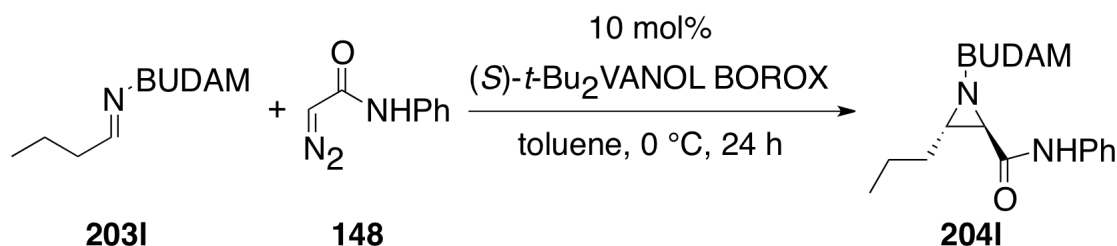
1457s, 1222s, 1182s, 1017m cm^{-1} ; mass spectrum, m/z (% rel intensity) 479 M^+ (4), 450 (15), 396 (32), 283 (100), 268 (75), 195 (29), 141 (66). $[\alpha]_{\text{D}}^{20} = +103.0$ (c 1.0, CH_2Cl_2) on 97% *ee* (2*R*,3*R*)-**202i** (HPLC).



(2*R*,3*S*)-1-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl)-3-ethyl-*N*-phenylaziridine-2-carboxamide **204k**:

^{27a} The reaction of **203k** (101 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure except that the catalyst loading was 10 mol%, temperature was 0 °C and the time was 24 h (Procedure G). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ¹H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:80) to afford **204k** as a white solid (83 mg, 0.130 mmol, 65%). The optical purity was determined to be 90% *ee* by HPLC (Regis Pirkle Covalent (R,R) Whelk O1 column, 222 nm, 98:2 hexane/*i*PrOH, flow rate: 1.0 mL/min). Retention time: $R_t = 15.73$ min for (2*S*,3*R*)-**204k** (minor) and $R_t = 25.68$ min for (2*R*,3*S*)-**204k** (major). mp 186-192 °C; $R_f = 0.27$ (1:40 EtOAc/benzene). Spectral data for **204k**: ¹H NMR (CDCl_3 , 500 MHz) δ 0.85 (t, 3H, $J = 7.5$ Hz), 1.32 (s, 18H), 1.41 (s, 18H), 1.65-1.69 (m, 2H), 2.19 (d, 1H, $J = 3.0$ Hz), 2.36 (bs, 1H), 3.60 (s, 3H), 3.65 (s, 3H), 4.27 (s, 1H), 7.06 (t, 1H, $J = 7.5$ Hz), 7.25 (s, 1H), 7.29 (t, 2H, $J = 8.0$ Hz), 7.33 (s, 2H), 7.47 (d, 2H, $J = 7.5$ Hz), 8.56 (s, 1H); ¹³C NMR (CDCl_3 , 125 MHz) δ 12.36,

19.82, 32.03, 32.13, 35.68, 35.76, 45.11, 49.05, 64.00, 64.18, 68.33, 119.16, 123.91, 125.20, 125.26, 128.93, 136.97, 137.12, 137.56, 143.24, 143.49, 158.33, 158.46, 168.85; IR (thin film) 3330w, 2963s, 1684m, 1603s 1526s, 1445s, 1414s, 1221s cm^{-1} ; mass spectrum, m/z (% rel intensity) 640 M^+ (<1), 611 (3), 518 (6), 466 (23), 451 (100), 161 (41). $[\alpha]_{\text{D}}^{20} = +52.9$ (c 1.0, EtOAc) on 90% *ee* (2*R*,3*S*)-**204k** (HPLC).



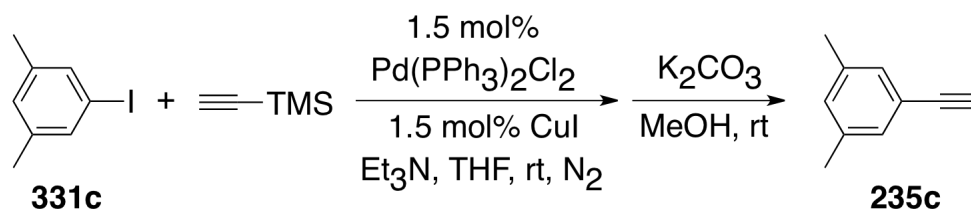
(2*R*,3*S*)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-*N*-phenyl-3-propylaziridine-2-carboxamide **204I**: The reaction of **203I** (104 mg, 0.20 mmol) and diazoacetamide **148** (45 mg, 0.28 mmol) was performed according to the general procedure except that the catalyst loading was 10 mol%, temperature was 0 °C and the time was 24 h (Procedure G). *Cis/trans* >100:1 and the acyclic enamine products were determined to be <1% from the ^1H NMR spectrum of the crude reaction mixture. The crude product was purified by column chromatography on silica gel (25 mm x 300 mm, EtOAc/benzene 1:80) to afford **204I** as a white solid (90 mg, 0.138 mmol, 69%). The optical purity was determined to be 85% *ee* by HPLC (Regis Pirkle Covalent (R,R) Whelk O1 column, 222 nm, 98:2 hexane/*i*PrOH, flow rate: 1.0 mL/min). Retention time: R_t = 15.06 min for (2*S*,3*R*)-**204I** (minor) and R_t = 25.66 min for (2*R*,3*S*)-**204I** (major). mp 174-176 °C; R_f = 0.30 (1:40 EtOAc/benzene). Spectral data for **204I**: ^1H NMR (CDCl_3 , 600 MHz) δ 0.84 (t, 3H, J = 7.2 Hz), 1.14-1.63 (m, 4H), 1.32 (s, 18H), 1.41 (s, 18H), 2.19 (d, 1H, J = 3.0 Hz), 2.37 (dd, 1H, J =

3.0 Hz), 3.60 (s, 3H), 3.65 (s, 3H), 4.25 (s, 1H), 7.05 (t, 1H, $J = 7.8$ Hz), 7.25 (s, 2H), 7.28 (t, 2H, $J = 7.8$ Hz), 7.33 (s, 2H), 7.47 (d, 2H, $J = 7.8$ Hz), 8.55 (s, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 13.84, 21.29, 28.40, 32.05, 32.13, 35.69, 35.77, 45.36, 47.33, 64.00, 64.18, 68.44, 119.16, 123.90, 125.18, 125.26, 128.93, 136.99, 137.15, 137.59, 143.25, 143.51, 158.36, 158.47, 168.82; IR (thin film) 3330w, 2961s, 1684m, 1603s, 1528s, 1445s, 1414s, 1223s cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{43}\text{H}_{63}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$) 655.4839, found 655.4835. $[\alpha]_{\text{D}}^{20} = +39.4$ (c 1.0, CH_2Cl_2) on 85% *ee* (2*R*,3*S*)-**2041** (HPLC).

6.3 Experimental for chapter four

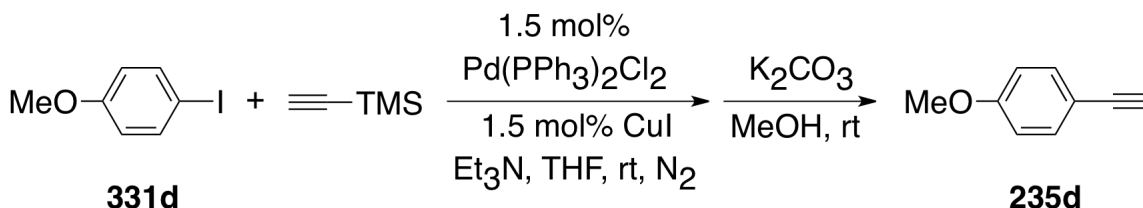
6.3.1 Preparation of alkynes

General procedure for the preparation of alkynes – illustrated for the synthesis of *1-ethynyl-3,5-dimethylbenzene 235c*⁹⁰ (Procedure Q)⁶⁴

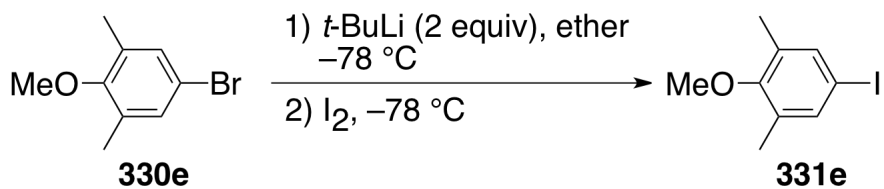


To a 1 L flame-dried flask filled was added 1-iodo-3,5-dimethylbenzene **331c** (69.6 g, 300 mmol), $\text{Pd(PPh}_3)_2\text{Cl}_2$ (3.16 g, 4.50 mol) and CuI (855 mg, 4.5 mmol), dry THF (450 mL) and Et_3N (168 mL, 1.20 mol) under argon. The reaction mixture was stirred at room temperature for 5 minutes and then trimethylsilyl acetylene (47 mL, 333 mmol) was added slowly. The reaction mixture was stirred at room temperature overnight. After removal of the solvent by rotary evaporation, the residue was treated with NaHCO_3 (sat. aq. 800 mL) and Et_2O (600 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (300 mL $\times$ 2). The combined organic layer was washed with H_2O (300 mL $\times$ 2), dried over MgSO_4 , filtered through Celite and concentrated to dryness. The crude product was roughly purified by passing through a short column (50 mm $\times$ 150 mm, neutral Al_2O_3 , hexanes as eluent) to give a yellow oil. The oil was then taken up in MeOH (900 mL) and treated with K_2CO_3 (124 g, 900 mmol). The reaction mixture was stirred at room temperature overnight. To the resulting reaction mixture was added H_2O (2.4 L) and this mixture was extracted with Et_2O (500 mL $\times$ 3). The organic layer was dried

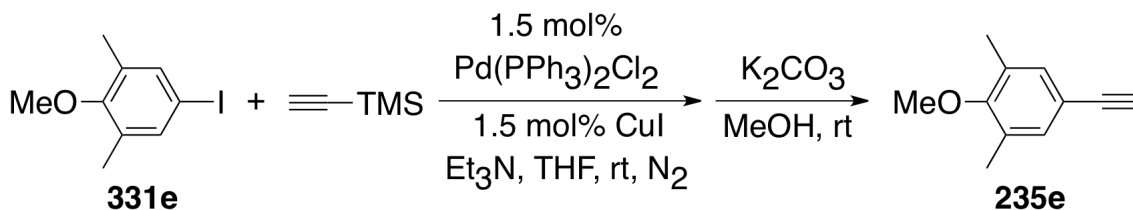
over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm $\times$ 200 mm, hexanes) gave **235c** as a yellow oil (34.2 g, 263 mmol, 88%). $R_f = 0.21$ (hexanes). Spectral data for **235c**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.28 (s, 6H), 2.99 (s, 1H), 6.97(s, 1H), 7.11 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.04, 76.34, 83.99, 121.69, 129.78, 130.67, 137.87; IR (thin film) 3295s, 2921s, 2108m, 1601s, 1456s, 1264s cm^{-1} ; mass spectrum, m/z (% rel intensity) 130 M^+ (91), 115 (100), 102 (10), 89 (12).



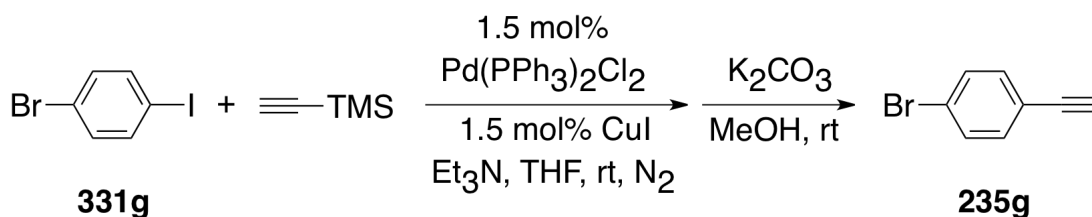
1-ethynyl-4-methoxybenzene 235d:⁹¹ The reaction of 1-iodo-4-methoxybenzene **331d** (23.4 g, 100 mmol) and trimethylsilyl acetylene (15.5 mL, 110 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm $\times$ 150 mm, CH_2Cl_2 :hexanes 1:5) gave **235d** as a colorless solid (10.9 g, 82.6 mmol, 83%). $R_f = 0.19$ (1:5 CH_2Cl_2 :hexanes). Spectral data for **235d**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.97 (s, 1H), 3.80 (s, 3H), 6.82 (dd, 2H, $J = 6.5, 2.0$ Hz), 7.41 (dd, 2H, $J = 6.5, 2.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.28, 75.73, 83.66, 113.93, 114.18, 133.59, 159.95; IR (thin film) 3289s, 2961m, 2840m, 2107m, 1507s, 1458m, 1250s, 1170s cm^{-1} ; mass spectrum, m/z (% rel intensity) 132 M^+ (100), 117 (65), 102 (11), 89 (86).



5-iodo-2-methoxy-1,3-dimethylbenzene 331e.⁶⁴ To a 1 L flame-dried flask filled with argon was added 5-bromo-2-methoxy-1,3-dimethylbenzene **330e** (21.5 g, 100 mmol) and dry Et₂O (250 mL). The mixture was stirred until the bromide was dissolved at room temperature and then the flask was submerged into a -78°C bath, followed by slow addition of *t*-BuLi (118 mL, 200 mmol, 1.7 M in hexanes) and then the solution was stirred at -78°C for 1 h. At the same time, to a flame-dried 250 mL flask iodine (27.9 g, 110 mmol) was dissolved in dry Et₂O (150 mL). The iodine solution was then cooled to -78°C and transferred to the aryllithium solution via cannula under argon. The mixture was warmed up gradually to room temperature and stir for an additional 2 h. The reaction was quenched by pouring the reaction mixture slowly into a Na₂S₂O₃ solution (aq. 5%, 200 mL) and stirred for 20 minutes. The organic layer was separated and the aqueous layer was extracted with Et₂O (100 mL $\times$ 3). the combined organic layer was washed with H₂O (100 mL $\times$ 2) and NaCl (aq. sat.), dried over MgSO₄ and filtered through Celite. Removal of the solvent by rotary evaporation afforded the crude product as a yellow oil in 100% yield. The ¹H NMR spectrum of the crude was clean, and it was used in the next step without purification. Spectral data for **331e**: ¹H NMR (CDCl₃, 500 MHz) δ 2.21 (s, 6H), 3.68 (s, 3H), 7.32 (s, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.67, 59.69, 87.55, 133.47, 137.49, 157.01.

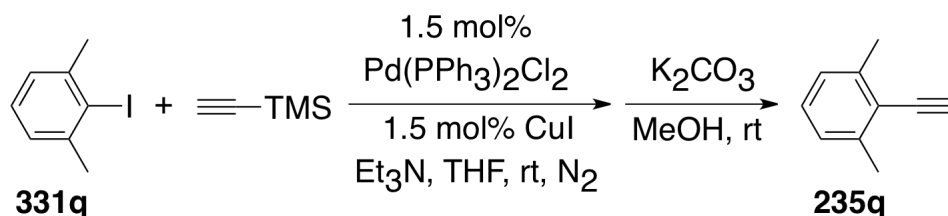


5-ethynyl-2-methoxy-1,3-dimethylbenzene **235e**:⁹¹ The reaction of 5-iodo-2-methoxy-1,3-dimethylbenzene **331e** from the above and trimethylsilyl acetylene (15.5 mL, 110 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm × 150 mm, CH₂Cl₂:hexanes 1:5) gave **235e** as a yellow oil (15.1 g, 94.4 mmol, 94%). R_f = 0.14 (1:5 CH₂Cl₂:hexanes). Spectral data for **235e**: ¹H NMR (CDCl₃, 300 MHz) δ 2.24 (s, 6H), 2.96 (s, 1H), 3.70 (s, 3H), 7.15 (s, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.89, 59.70, 75.94, 83.63, 117.26, 131.11, 132.65, 157.66; IR (thin film) 3291s, 2944s, 2107m, 1482s, 1304s, 1227s, 1140s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 160 M⁺ (100), 145 (70), 128 (6), 115 (45).

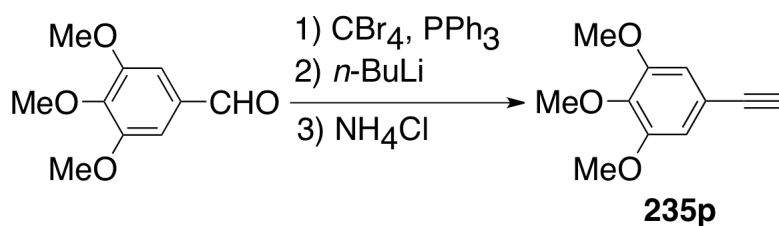


1-bromo-4-ethynylbenzene **235g**:⁹² The reaction of 1-bromo-4-iodobenzene **331g** (28.3 g, 100 mmol) and trimethylsilyl acetylene (15.5 mL, 110 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm × 200 mm, hexanes) gave **235g** as a white solid (15.9 g, 87.8 mmol, 88%). mp 63-65 °C (lit.⁹² 56-58 °C); R_f = 0.27 (hexanes). Spectral data for **235g**: ¹H NMR (CDCl₃,

500 MHz) δ 3.10 (s, 3H), 7.33 (dd, 2H, J = 7.0, 2.0 Hz), 7.44 (dd, 2H, J = 7.0, 2.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 78.32, 82.55, 121.04, 123.13, 131.60, 133.54; IR (thin film) 3270s, 1586s, 1485s, 1397s cm^{-1} .



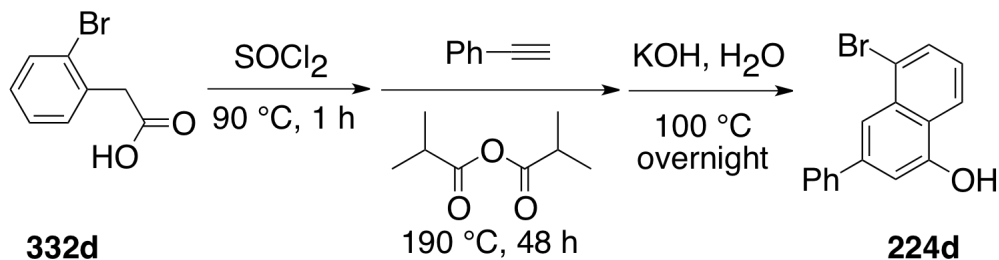
2-ethynyl-1,3-dimethylbenzene **235q**:⁹³ The reaction of 1-bromo-4-iodobenzene **331q** (13.9 g, 60 mmol) and trimethylsilyl acetylene (15.5 mL, 110 mmol) was performed according to the general procedure (Procedure Q). Vacuum distillation (85 °C at 0.5 mm Hg with a slow bleed of air through a needle) gave **235q** as a colorless oil (4.68 g, 36 mmol, 60%). R_f = 0.31 (hexanes). Spectral data for **235q**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.45 (s, 6H), 3.50 (s, 1H), 7.03 (d, 2H, J = 7.5 Hz), 7.13 (dd, 1H, J = 7.5, 1.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 20.98, 81.13, 85.33, 121.91, 126.64, 128.07, 140.93; IR (thin film) 3303s, 2920s, 2101w, 1559s, 1466s, 1379s cm^{-1} ; mass spectrum, m/z (% rel intensity) 130 M^+ (69), 115 (100), 102 (9), 89 (8)



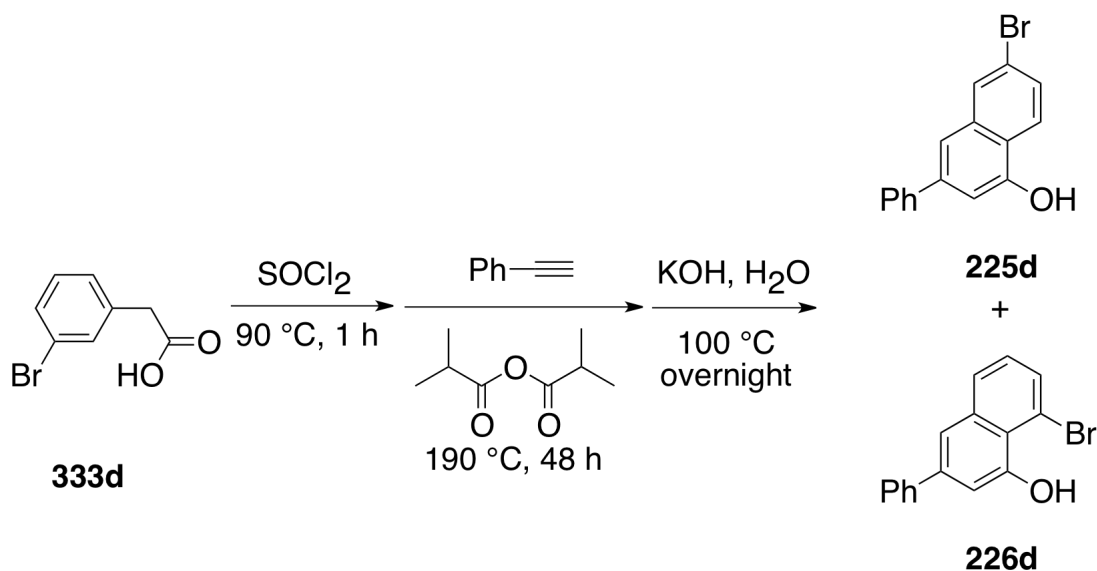
5-Ethynyl-1,2,3-trimethoxybenzene **235p**:⁸⁹ To a 1L flame-dried round bottom flask was added CBr_4 (50.8 g, 153 mmol), dry CH_2Cl_2 (200 mL) and the resulting solution was cooled to 0 °C. PPh_3 (80.2 g, 306 mmol) in dry CH_2Cl_2 (200 mL) was added dropwise to the above solution. The resulting solution was stirred at 0 °C for 15 minutes. 3,4,5-Trimethoxybenzaldehyde (20 g,

102 mmol) in dry CH_2Cl_2 (120 mL) was added dropwise. The solution was stirred at 0 °C for 15 minutes. The solvent was removed by rotary evaporation and the resulting slurry was filtered through a plug of silica gel and washed with hexanes:EtOAc (9:1, 500 mL; then 4:1, 1500 mL) until no dibromo-olefin was left by TLC. The combined organics were concentrated to dryness to give dibromo-olefin (32.2 g, 91.4 mmol), which was dissolved in dry THF (400 mL) and cooled to -78 °C. *n*-BuLi (2.5 M in hexanes, 110 mL, 274 mmol) was added dropwise and the solution stirred at -78 °C for 30 minutes. NH_4Cl (sat. aq. 100 mL) was added and the solution warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layer was washed with brine (100 mL), dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (50 mm x 280 mm, EtOAc:hexanes 1:9) gave **235p** as a white solid (15.8 g, 82.3 mmol, 81%). $R_f = 0.33$ (1:3 EtOAc/hexanes). Spectral data for **235p**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.01 (s, 1H), 3.83 (s, 6H), 3.84 (s, 3H), 6.71 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 56.11, 60.92, 76.19, 83.67, 109.32, 116.99, 153.02; IR (thin film) 3247s, 2990s, 1576s, 1456s, 1335s, 1235s, 1129s cm^{-1} ; mass spectrum, m/z (% rel intensity) 192 M^+ (100), 177 (67), 134 (25), 119 (22), 89 (15).

6.3.2 Preparation of VANOL monomer derivatives

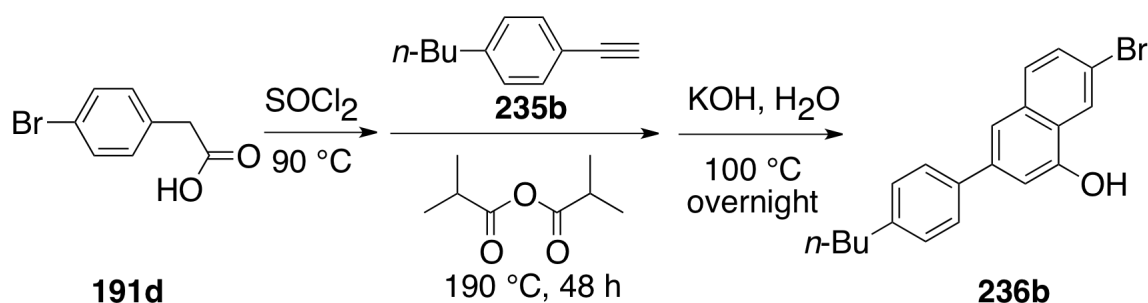


5-bromo-3-phenylnaphthalen-1-ol **224d**: The reaction of 2-bromo-phenylacetic acid **332d** (2.37 g, 11.0 mmol), SOCl_2 (2.90 mL, 39.8 mmol), phenylacetylene (1.50 mL, 13.7 mmol) and $(i\text{-PrCO})_2\text{O}$ (3.70 mL, 22.3 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:3 to 1:2 to 1:1 to 2:1) gave **224d** as a yellow solid (2.62 g, 8.76 mmol, 80%). mp $130\text{--}131\text{ }^\circ\text{C}$; $R_f = 0.31$ (CH_2Cl_2). Spectral data for **224d**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.35 (s, 1H), 7.11 (s, 1H), 7.29 (t, 1H, $J = 7.5$ Hz), 7.39 (t, 1H, $J = 7.5$ Hz), 7.48 (t, 2H, $J = 7.5$ Hz), 7.69 (d, 2H, $J = 8.0$ Hz), 7.80 (d, 1H, $J = 7.5$ Hz), 8.03 (s, 1H), 8.17 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 109.13, 118.13, 121.57, 122.95, 124.77, 125.41, 127.45, 127.79, 128.90, 131.08, 133.40, 140.22, 140.59, 151.79; IR (thin film) 3239br s, 1626m, 1595s, 1495s, 1390s, 1263m cm^{-1} ; HRMS (ESI $^-$) m/z calcd for $\text{C}_{16}\text{H}_{10}\text{OBr}$ ($\text{M}-\text{H}^+$) 296.9915, meas 296.9921.



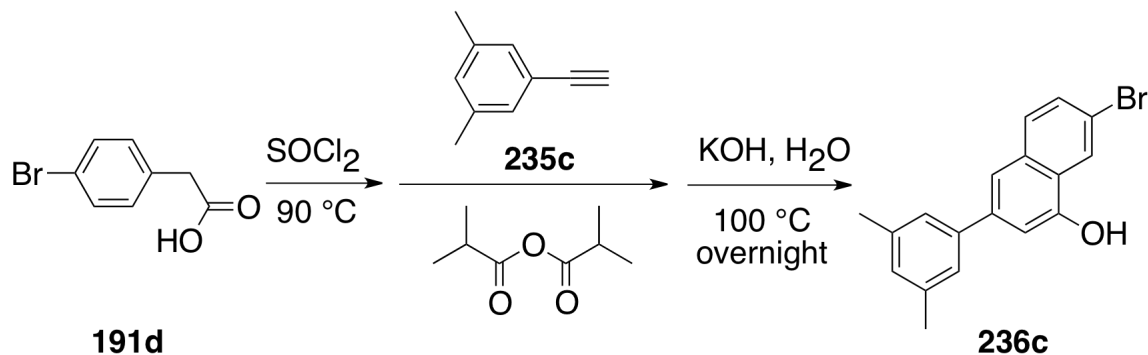
The reaction of 3-bromo-phenylacetic acid **333d** (6.45 g, 30.0 mmol), SOCl₂ (8.00 mL, 110 mmol), phenylacetylene (4.0 mL, 36 mmol) and (*i*-PrCO)₂O (10 mL, 60 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:2 to 1:1 to 1:0) gave **225d** as an off-white solid (4.19 g, 14.0 mmol, 47%). mp 144-145 °C; R_f = 0.34 (CH₂Cl₂). Purification of the crude **226d** obtained from the first column by a 2nd column chromatography on silica gel (35 mm x 300 mm, EtOAc:hexanes 1:50) gave **226d** as a yellow solid (1.71 g, 5.72 mmol, 19%). mp 53-54 °C; R_f = 0.62 (CH₂Cl₂). Spectral data for **225d**: ¹H NMR (CDCl₃, 500 MHz) δ 5.27 (s, 1H), 7.06 (d, 1H, *J* = 1.5 Hz), 7.35-7.39 (m, 1H), 7.43-7.48 (m, 2H), 7.51-7.54 (m, 2H), 7.62-7.65 (m, 2H), 7.99-8.00 (m, 1H), 8.04 (d, 1H, *J* = 9.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 108.81, 117.81, 121.25, 122.05, 123.60, 127.30, 127.77, 128.58, 128.91, 129.88, 136.14, 140.29, 140.46, 151.86; IR (thin film) 3330br s, 1576s, 1456s, 1375s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₁₆H₁₀O⁷⁹Br (M-H⁺) 296.9915, meas 296.9906.

Spectral data for **226d**: ^1H NMR (CDCl_3 , 500 MHz) δ 7.22 (t, 1H, $J = 8.0$ Hz), 7.36-7.39 (m, 2H), 7.46 (t, 2H, $J = 7.5$ Hz), 7.60 (d, 1H, $J = 7.0$ Hz), 7.63 (d, 1H, $J = 2.0$ Hz), 7.68-7.70 (m, 2H), 7.82 (d, 1H, $J = 8.5$ Hz), 8.10 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 112.59, 115.21, 118.98, 119.76, 126.36, 127.21, 127.88, 128.88, 129.60, 131.38, 137.43, 139.84, 140.22, 152.94; IR (thin film) 3482br s, 1568s, 1489s, 1368s, 1210s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{16}\text{H}_{10}\text{O}^{79}\text{Br}$ ($\text{M}-\text{H}^+$) 296.9915, meas 296.9923.

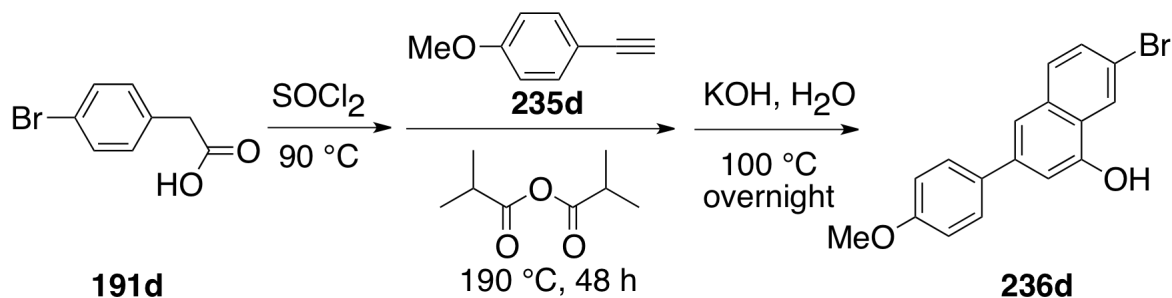


7-bromo-3-(4-butylphenyl)naphthalen-1-ol 236b: The reaction of 4-bromo-phenylacetic acid **191d** (23.7 g, 110 mmol), SOCl_2 (29 mL, 398 mmol), 1-butyl-4-ethynylbenzene **235b** (20 g, 127 mmol) and $(i\text{-PrCO})_2\text{O}$ (37 mL, 223 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:3 to 1:2 to 1:1 to 2:1) gave **236b** as a light brown solid (26.5 g, 74.6 mmol, 68%). mp 106-109 $^\circ\text{C}$; $R_f = 0.21$ (2:1 CH_2Cl_2 /hexanes). Spectral data for **236b**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.94 (t, 3H, $J = 7.5$ Hz), 1.34-1.43 (m, 2H), 1.60-1.67 (m, 2H), 2.65 (t, 2H, $J = 7.5$ Hz), 5.25 (s, 1H), 7.07 (d, 1H, $J = 1.5$ Hz), 7.25-7.28 (m, 2H), 7.53-7.57 (m, 4H), 7.69 (d, 1H, $J = 8.5$ Hz), 8.33 (d, 1H, $J = 2.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.94, 22.39, 33.58, 35.31, 109.28, 118.29, 119.10, 124.26, 124.57, 127.05, 128.98, 129.54, 130.23, 133.43,

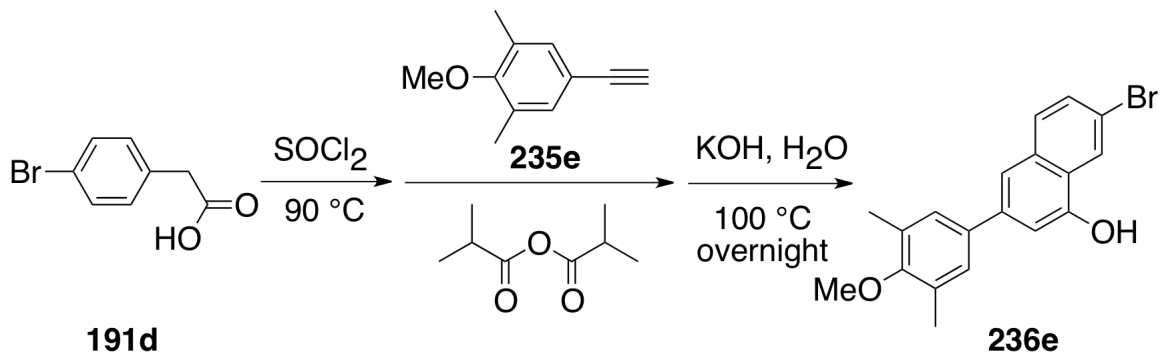
137.78, 139.42, 142.63, 150.82; IR (thin film) 3260br s, 2926s, 1589s, 1406s, 1254s cm^{-1} ; HRMS (ESI⁻) m/z calcd for $\text{C}_{20}\text{H}_{18}\text{O}^{79}\text{Br}$ ($\text{M}-\text{H}^+$) 353.0541, meas 353.0539.



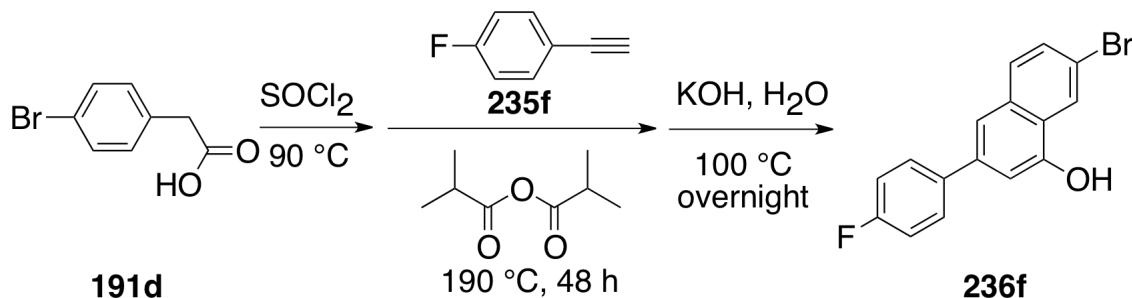
7-bromo-3-(3,5-dimethylphenyl)naphthalen-1-ol 236c: The reaction of 4-bromo-phenylacetic acid **191d** (4.30 g, 20.0 mmol), SOCl_2 (5.3 mL, 73 mmol), 1-ethynyl-3,5-dimethylbenzene **235c** (2.60 g, 20.0 mmol) and $(i\text{-PrCO})_2\text{O}$ (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:1 to 2:1 to 1:0) gave **236c** as an off-white solid (3.96 g, 12.1 mmol, 61%). mp 110-111 $^\circ\text{C}$; R_f = 0.19 (2:1 CH_2Cl_2 /hexanes). Spectral data for **236c**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.39 (s, 6H), 5.22 (s, 1H), 7.01 (s, 1H), 7.07 (d, 1H, J = 1.5 Hz), 7.26 (s, 2H), 7.55 (dd, 1H, J = 9.0, 2.0 Hz), 7.57 (s, 1H), 7.69 (d, 1H, J = 9.0 Hz), 8.33 (d, 1H, J = 2.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.40, 109.43, 118.53, 119.13, 124.25, 124.60, 125.16, 129.34, 129.55, 130.21, 133.35, 138.43, 139.67, 140.47, 150.72; IR (thin film) 3509br m, 2918w, 1587s, 1474s, 1404s, 1267s cm^{-1} ; mass spectrum, m/z (% rel intensity) 328 M^+ (91, ^{81}Br), 326 M^+ (100, ^{79}Br), 202 (42), 163 (20). Anal calcd for $\text{C}_{18}\text{H}_{15}\text{BrO}$: C, 66.07; H, 4.62. Found: C, 66.00; H, 4.42.



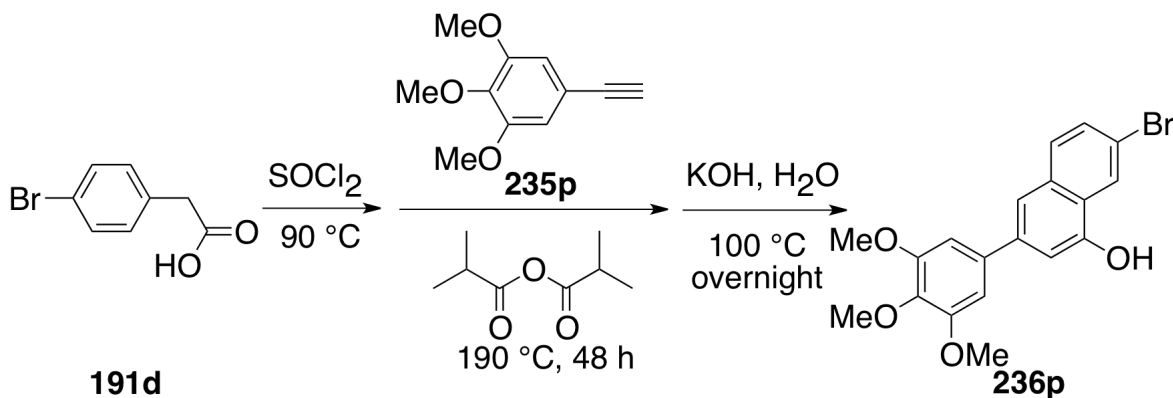
7-bromo-3-(4-methoxyphenyl)naphthalen-1-ol **236d**: The reaction of 4-bromo-phenylacetic acid **191d** (4.30 g, 20.0 mmol), SOCl_2 (5.3 mL, 73 mmol), 1-ethynyl-4-methoxybenzene **235d** (2.64 g, 20.0 mmol) and $(i\text{-PrCO})_2\text{O}$ (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:1 to 2:1 to 1:0) gave **236d** as an off-white solid (1.98 g, 6.0 mmol, 30%). mp 168-170 $^\circ\text{C}$; $R_f = 0.26$ (CH_2Cl_2). Spectral data for **236d**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.85 (s, 3H), 5.24 (s, 1H), 6.98-7.00 (m, 2H), 7.53-7.55 (m, 2H), 7.56-7.58 (m, 2H), 7.67 (d, 1H, $J = 9.0$ Hz), 8.32 (d, 1H, $J = 2.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.40, 109.13, 114.38, 117.87, 118.96, 124.24, 124.37, 128.27, 129.46, 130.25, 132.99, 133.45, 139.03, 150.82, 159.48; IR (thin film) 3395br s, 1578s, 1507s, 1402s, 1240s, 1179s cm^{-1} ; mass spectrum, m/z (% rel intensity) 330 M^+ (89, ^{81}Br), 328 M^+ (100, ^{79}Br), 315 (29, ^{81}Br), 313 (31, ^{79}Br), 285 (14), 205 (15). Anal calcd for $\text{C}_{17}\text{H}_{13}\text{BrO}_2$: C, 62.03; H, 3.98. Found: C, 61.83; H, 3.92.



7-bromo-3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **236e**: The reaction of 4-bromo-phenylacetic acid **191d** (4.30 g, 20.0 mmol), SOCl₂ (5.3 mL, 73 mmol), 5-ethynyl-2-methoxy-1,3-dimethylbenzene **235e** (3.20 g, 20.0 mmol) and (*i*-PrCO)₂O (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:1 to 2:1 to 1:0) gave **236e** as an off-white solid (3.56 g, 10.0 mmol, 50%). mp 146-148 °C; R_f = 0.22 (CH₂Cl₂). Spectral data for **236e**: ¹H NMR (CDCl₃, 500 MHz) δ 2.35 (s, 6H), 3.78 (s, 3H), 5.46 (s, 1H), 6.98 (d, 1H, *J* = 1.5 Hz), 7.27 (s, 2H), 7.51 (s, 1H), 7.54 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.67 (d, 1H, *J* = 9.0 Hz), 8.33 (d, 1H, *J* = 2.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 16.29, 59.84, 109.29, 118.15, 119.02, 124.28, 124.52, 127.72, 129.49, 130.21, 131.30, 133.38, 136.13, 139.22, 150.80, 156.79; IR (thin film) 3341br s, 2928s, 1587s, 1485s, 1402s, 1227s, 1157s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 358 M⁺ (77, ⁸¹Br), 356 M⁺ (80, ⁷⁹Br), 343 (50, ⁸¹Br), 341 (52, ⁷⁹Br), 314 (4, ⁸¹Br), 312 (5, ⁷⁹Br), 202 (28), 189 (49), 171 (34), 100 (100). Anal calcd for C₁₉H₁₇BrO₂: C, 63.88; H, 4.80. Found: C, 63.73; H, 4.72.



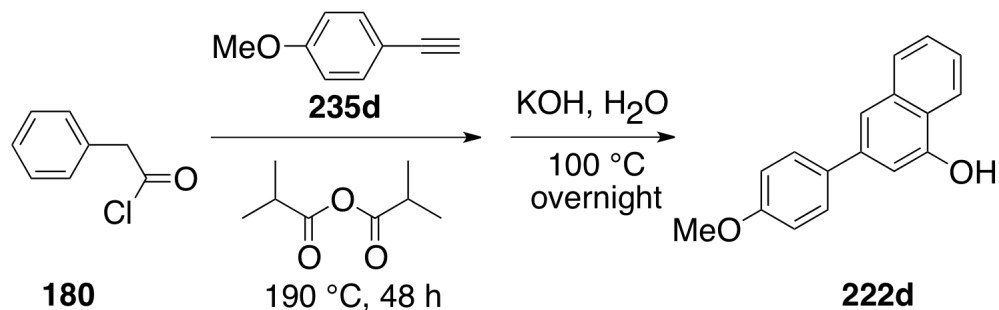
7-bromo-3-(4-fluorophenyl)naphthalen-1-ol 236f: The reaction of 4-bromo-phenylacetic acid **191d** (4.30 g, 20.0 mmol), SOCl_2 (5.3 mL, 73 mmol), 1-ethynyl-4-fluorobenzene **235f** (2.40 g, 20.0 mmol) and $(i\text{-PrCO})_2\text{O}$ (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:1 to 2:1 to 1:0) gave **236f** as an off-white solid (2.33 g, 7.35 mmol, 37%). mp 96-97 °C; $R_f = 0.30$ (CH_2Cl_2). Spectral data for **236f**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.30 (s, 1H), 7.02 (d, 1H, $J = 2.0$ Hz), 7.11-7.17 (m, 2H), 7.45-7.53 (m, 2H), 7.58 (s, 1H), 7.59-7.64 (m, 2H), 7.82-7.85 (m, 1H), 8.14-8.17 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 108.27, 115.61 ($^2J_{\text{CF}} = 21$ Hz), 118.64, 121.42, 123.47, 125.41, 127.02, 127.97, 128.83 ($^3J_{\text{CF}} = 7.9$ Hz), 134.94, 137.03 ($^4J_{\text{CF}} = 3.3$ Hz), 137.91, 151.76, 162.56 ($^1J_{\text{CF}} = 245.4$ Hz); ^{19}F NMR (CDCl_3 , 283 Hz) δ -113.30; IR (thin film) 3399br w, 1507s, 1401s, 1237s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{16}\text{H}_{12}\text{OF}$ ($\text{M}+\text{H}^+$) 239.0872, meas 239.0884.



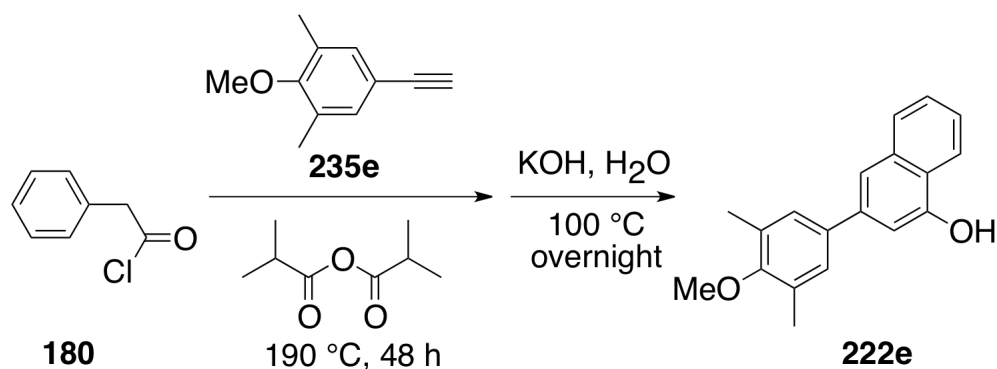
7-bromo-3-(3,4,5-trimethoxyphenyl)naphthalen-1-ol 236p: The reaction of 4-bromo-phenylacetic acid **191d** (4.30 g, 20.0 mmol), SOCl_2 (5.3 mL, 73 mmol), 5-ethynyl-1,2,3-trimethoxybenzene **235p** (3.84 g, 20.0 mmol) and $(i\text{-PrCO})_2\text{O}$ (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, EtOAc:hexanes 1:4 to 1:2) gave **236p** as a yellow solid (3.69 g, 9.49 mmol, 47%). mp 177-179 °C; R_f = 0.16 (1:2 EtOAc/hexanes). Spectral data for **236p**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.90 (s, 6H), 3.91 (s, 3H), 5.74 (s, 1H), 6.80 (s, 2H), 6.99 (d, 1H, J = 1.0 Hz), 7.50 (s, 1H), 7.56 (dd, 1H, J = 8.5, 2.0 Hz), 7.69 (d, 1H, J = 9.0 Hz), 8.36 (d, 1H, J = 2.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 56.28, 61.03, 104.71, 109.39, 118.20, 119.26, 124.38, 124.76, 129.47, 130.36, 133.28, 136.73, 139.56, 151.03, 153.53; IR (thin film) 3413br m, 2938m, 1589s, 1503s, 1406s, 1240s, 1129s cm^{-1} ; mass spectrum, m/z (% rel intensity) 390 M^+ (14, ^{81}Br), 388 M^+ (13, ^{79}Br), 375 (7, ^{81}Br), 373 (7, ^{79}Br), 236 (4, ^{81}Br), 234 (4, ^{79}Br). Anal calcd for $\text{C}_{19}\text{H}_{17}\text{BrO}_4$: C, 58.63; H, 4.40. Found: C, 58.39; H, 4.19.

Procedure R – illustrated for the synthesis of 3-(3,5-dimethylphenyl)naphthalen-1-ol 222c

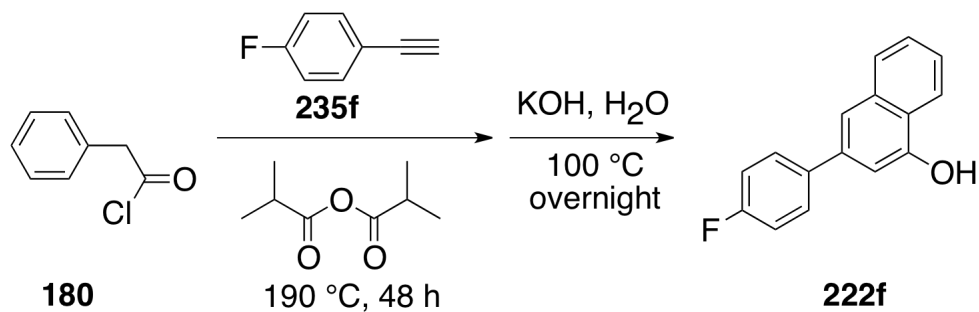
129.13, 135.00, 138.34, 139.18, 140.92, 151.59; IR (thin film) 3430br s, 2919s, 1576s, 1456s, 1400s, 1271s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{18}\text{H}_{17}\text{O}$ ($\text{M}+\text{H}^+$) 249.1279, meas 249.1268.



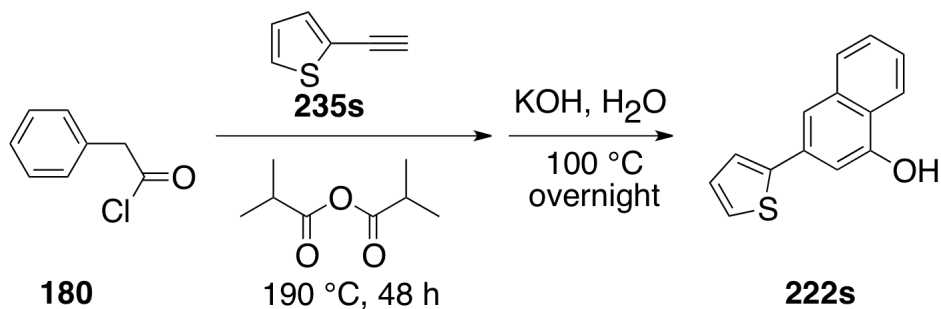
3-(4-methoxyphenyl)naphthalen-1-ol 222d: The reaction of phenylacetyl chloride **180** (2.64 mL, 20.0 mmol), 1-ethynyl-4-methoxybenzene **235d** (2.64 g, 20.0 mmol) and (*i*-PrCO)₂O (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:1 to 2:1 to 1:0) gave **222d** as a pale brown solid (2.07 g, 8.28 mmol, 41%). mp 151-152 °C; R_f = 0.19 (CH₂Cl₂). Spectral data for **222d**: ¹H NMR (CDCl₃, 500 MHz) δ 3.85 (s, 3H), 5.27 (s, 1H), 6.99 (dd, 2H, J = 9.0, 2.0 Hz), 7.05 (d, 1H, J = 1.0 Hz), 7.43-7.51 (m, 2H), 7.58-7.61 (m, 3H), 7.82 (d, 1H, J = 7.5 Hz), 8.12-8.15 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 55.39, 108.26, 114.30, 118.05, 121.40, 123.24, 125.05, 126.84, 127.88, 128.30, 133.43, 135.04, 138.51, 151.65, 159.29; IR (thin film) 3357br w, 1587s, 1456s, 1401s, 1250s, 1184s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{17}\text{H}_{13}\text{O}_2$ ($\text{M}-\text{H}^+$) 249.0916, meas 249.0921.



3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **222e**: The reaction of phenylacetyl chloride **180** (2.64 mL, 20.0 mmol), 5-ethynyl-2-methoxy-1,3-dimethylbenzene **235e** (3.20 g, 20.0 mmol) and (*i*-PrCO)₂O (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:1 to 2:1 to 1:0) gave **222e** as a light yellow solid (3.10 g, 11.1 mmol, 56%). mp 156-157 °C; *R*_f = 0.19 (CH₂Cl₂). Spectral data for **222e**: ¹H NMR (CDCl₃, 500 MHz) δ 2.36 (s, 6H), 3.77 (s, 3H), 5.33 (s, 1H), 7.02 (d, 1H, *J* = 1.5 Hz), 7.31 (s, 2H), 7.43-7.51 (m, 2H), 7.57 (s, 1H), 7.82 (d, 1H, *J* = 7.5 Hz), 8.13-8.15 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 16.29, 59.84, 108.39, 118.32, 121.44, 123.38, 125.07, 126.79, 127.75, 127.91, 131.18, 134.96, 136.54, 138.68, 151.63, 156.57; IR (thin film) 3359br s, 2942s, 1576s, 1489s, 1402s, 1230s, 1157s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₁₉H₁₇O₂ (M-H⁺) 277.1229, meas 277.1224.

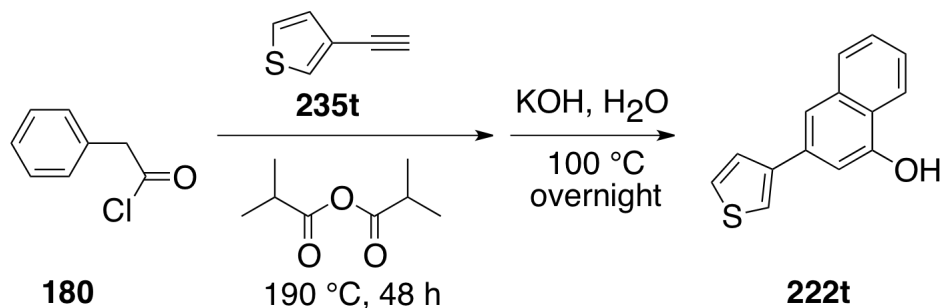


to 2:1 to 1:0) gave **222g** as an off-white solid (2.70 g, 9.03 mmol, 45%). mp 168-169 °C; R_f = 0.31 (CH_2Cl_2). Spectral data for **222g**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.36 (s, 1H), 7.01 (d, 1H, J = 1.5 Hz), 7.46-7.54 (m, 4H), 7.55-7.59 (m, 2H), 7.59 (s, 1H), 7.82-7.85 (m, 1H), 8.14-8.17 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 107.97, 118.70, 121.46, 121.70, 123.68, 125.57, 127.09, 128.03, 128.85, 131.92, 134.92, 137.64, 139.83, 151.88; IR (thin film) 3355br w, 1576s, 1493s, 1399s, 1265s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{16}\text{H}_{10}^{79}\text{BrO}$ ($\text{M}+\text{H}^+$) 296.9915, meas 296.9906.



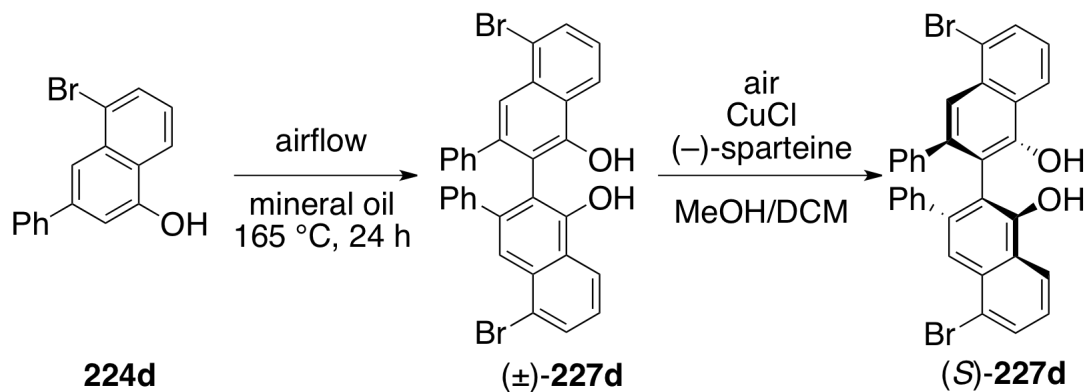
3-(thiophen-2-yl)naphthalen-1-ol 222s: The reaction of phenylacetyl chloride **180** (3.72 mL, 28.1 mmol), 2-ethynylthiophene **235s** (3.04 g, 28.1 mmol) and (*i*-PrCO)₂O (9.33 mL, 56.3 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:2 to 1:1 to 1:0) gave **222g** as a brownish pink solid (1.66 g, 7.35 mmol, 37%). mp 128-129 °C; R_f = 0.35 (CH_2Cl_2). Spectral data for **222g**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.35 (s, 1H), 7.07-7.11 (m, 2H), 7.30(dd, 1H, J = 5.0, 1.5 Hz), 7.36 (dd, 1H, J = 3.5, 1.5 Hz), 7.43-7.51 (m, 2H), 7.67 (s, 1H), 7.79-7.82 (m, 1H), 8.11-8.14 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 107.20, 117.36, 121.51, 123.42, 123.77, 125.02, 125.34, 127.14, 127.84, 128.06, 131.95, 134.91, 144.22, 151.69; IR (thin

film) 3320br s, 1599s, 1401s, 1262s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{14}\text{H}_9\text{OS}$ ($\text{M}-\text{H}^+$) 225.0374, meas 225.0377.



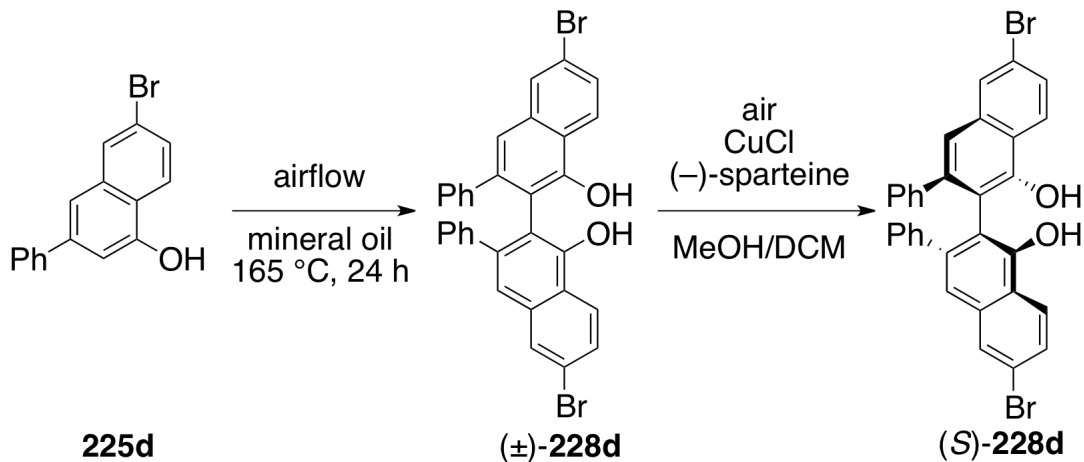
3-(thiophen-3-yl)naphthalen-1-ol 222t: The reaction of phenylacetyl chloride **180** (2.64 mL, 20.0 mmol), 3-ethynylthiophene **235t** (2.16 g, 20.0 mmol) and (*i*-PrCO)₂O (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:2 to 1:1 to 1:0) gave **222t** as a brownish pink solid (2.58 g, 11.4 mmol, 57%). mp 119-120 °C; R_f = 0.32 (CH₂Cl₂). Spectral data for **222t**: ¹H NMR (CDCl₃, 500 MHz) δ 5.34 (s, 1H), 7.06 (d, 1H, J = 1.5 Hz), 7.40 (dd, 1H, J = 5.5, 3.0 Hz), 7.45-7.51 (m, 4H), 7.65 (s, 1H), 7.82 (d, 1H, J = 7.5 Hz), 8.14 (d, 1H, J = 8.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 107.84, 117.90, 120.62, 121.43, 123.58, 125.22, 126.31, 126.38, 126.96, 127.88, 133.44, 134.99, 142.05, 151.66; IR (thin film) 3362br s, 1599s, 1507s, 1418s, 1275s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{14}\text{H}_9\text{OS}$ ($\text{M}-\text{H}^+$) 225.0374, meas 225.0382.

6.3.3 Preparation of C2-VANOL derivatives



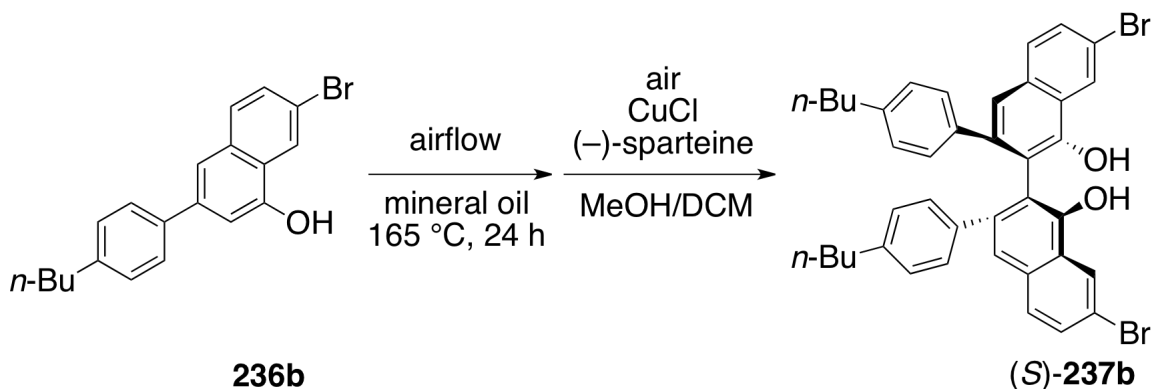
5,5'-di-bromo VANOL 227d: The synthesis of racemic **227d** was performed according to the general procedure (Procedure J) with 5-bromo-3-phenylnaphthalen-1-ol **224d** (2.50 g, 8.36 mmol). After cooling down to room temperature, CH₂Cl₂ (10 mL) and hexanes (20 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (−20 °C) and then filtered through filter paper. The yellow powder was washed with chilled CH₂Cl₂/hexanes and dried under vacuum to afford a yellow solid (1.32 g). Purification of the product remaining in the mother liquor by column chromatography on silica gel (35 mm x 250 mm, CH₂Cl₂:hexanes 2:3) gave racemic **227d** as a light yellow solid (0.26 g). The total yield is 63% (1.58 g, 2.65 mmol). After de-racemization of racemic **227d** (1.19 g, 2.00 mmol) with CuCl (337 mg, 3.40 mmol) and (−)-sparteine (1.64 g, 7.00 mmol), the crude product was purified by column chromatography on silica gel (35 mm x 250 mm, CH₂Cl₂/hexanes 2:3) to afford (*S*)-**227d** as an off-white foamy solid (534 mg, 0.90 mmol, 45%). The optical purity was determined to be >99% *ee* by HPLC analysis (Chiralcel OD-H column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 0.7 mL/min). Retention times: *R*_t = 9.68 min for (*R*)-**227d** (minor) and *R*_t = 15.00 min for (*S*)-**227d** (major). mp 234-238 °C; *R*_f =

0.22 (1:1 CH₂Cl₂/hexane). Spectral data for **227d**: ¹H NMR (CDCl₃, 500 MHz) δ 5.78 (s, 2H), 6.63-6.66 (m, 4H), 6.98-7.01 (m, 4H), 7.09-7.13 (m, 2H), 7.36-7.40 (m, 2H), 7.70 (d, 2H, *J* = 0.5 Hz), 7.86 (dd, 2H, *J* = 7.5, 1.5 Hz), 8.32-8.35 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 113.29, 121.32, 122.64, 122.70, 124.11, 126.00, 127.05, 127.65, 128.85, 131.75, 133.14, 139.68, 141.88, 150.44; IR (thin film) 3512br s, 1653s, 1558m, 1379s, 1240m cm⁻¹; HRMS (ESI⁻) *m/z* calcd for C₃₂H₁₉O₂⁷⁹Br₂ (M-H⁺) 592.9752, meas 592.9760. [α]_D²⁰ = -163.6 (c 1.0, CH₂Cl₂) on 99% *ee* (*S*)-**227d** (HPLC).



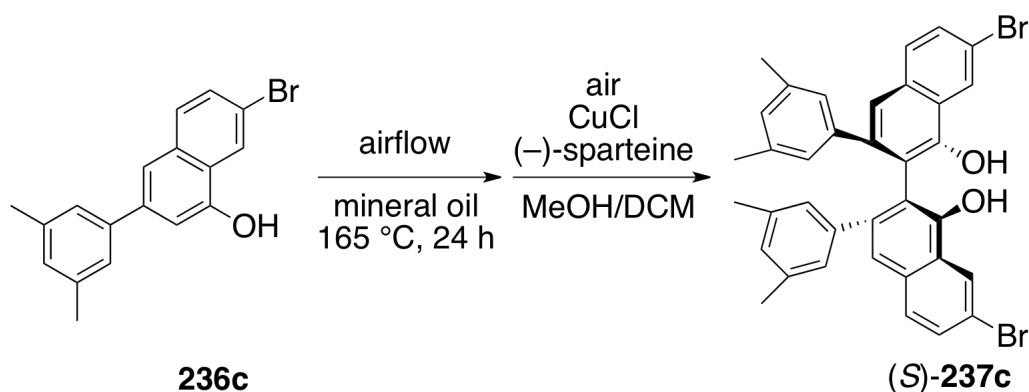
6,6'-di-bromo VANOL 228d: The synthesis of racemic **228d** was performed according to the general procedure (Procedure J) with 6-bromo-3-phenylnaphthalen-1-ol **225d** (2.39 g, 8.00 mmol). Purification by column chromatography on silica gel (35 mm × 300 mm, CH₂Cl₂/hexanes 1:2) gave racemic **228d** as an off-white solid (1.54 g, 2.58 mmol, 65% yield). After de-racemization of racemic **228d** (834 mg, 1.40 mmol) with CuCl (236 mg, 2.38 mmol) and (-)-sparteine (1.15 mg, 4.91 mmol), the crude product was purified by column chromatography on silica gel (25 mm × 200 mm, CH₂Cl₂/hexanes 1:2) to afford (*S*)-**228d** as a white solid (577 mg, 0.97 mmol, 69%). The optical purity was determined to be >99% *ee* by

CH₂Cl₂/hexanes 2:1) gave **229d** as an off-white solid (468 mg, 0.78 mmol, 98%). mp 202-206 °C; R_f = 0.29 (2:1 CH₂Cl₂/hexane). Spectral data for **229d**: ¹H NMR (CDCl₃, 500 MHz) δ 5.52 (s, 2H), 6.69-6.73 (m, 2H), 6.96-7.03 (m, 4H), 7.13-7.17 (m, 2H), 7.22-7.26 (m, 2H), 7.57-7.61 (m, 2H), 7.64-7.68 (m, 2H), 8.28-8.34 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz) δ 114.00, 116.01, 123.07, 123.95, 126.53, 126.87, 127.51, 127.55, 127.72, 127.96, 129.03, 132.08, 133.45, 139.37, 140.63, 150.04; IR (thin film) 3511br s, 1585s, 1491s, 1375s, 1265s cm⁻¹; HRMS (ESI-) m/z calcd for C₃₂H₁₉O₂⁷⁹Br₂ (M-H⁺) 592.9752, meas 592.9731. [α]_D²⁰ = -114.2 (c 1.0, CH₂Cl₂).



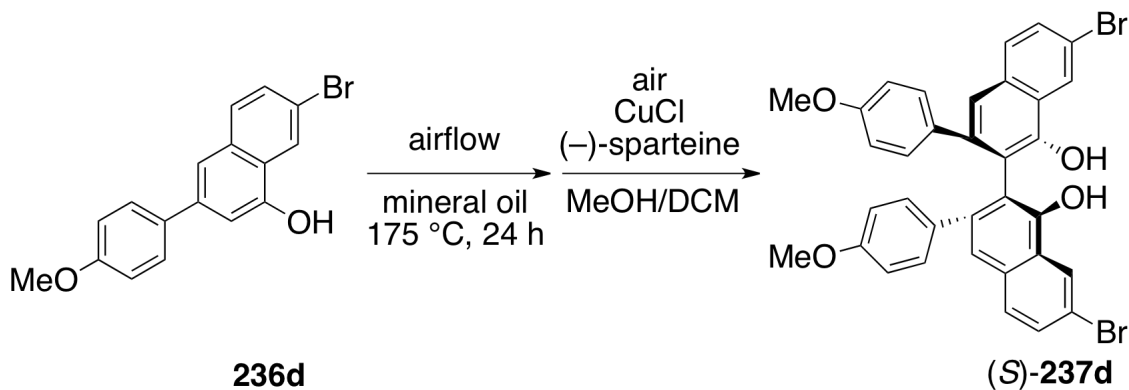
The synthesis of racemic **237b** was performed according to the general procedure (Procedure J) with 7-bromo-3-(4-butylphenyl)naphthalen-1-ol **236b** (5.09 g, 14.3 mmol). After cooling down to room temperature, CH₂Cl₂ (30 mL) and hexanes (30 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (-20 °C) and then filtered through filter paper. The yellow powder was washed with chilled CH₂Cl₂/hexanes and dried under vacuum to afford a yellow solid (2.42 g). Purification of the product remaining in the mother liquor by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂/hexanes 1:2) gave racemic **237b** as an off-white solid (1.25 g). The total yield is 72% (3.67 g, 5.18 mmol). After de-racemization of racemic **237b** (6.75 g, 9.54 mmol) with

CuCl (1.61 g, 16.3 mmol) and (–)-sparteine (7.81 g, 33.4 mmol), the crude product was purified by column chromatography on silica gel (50 mm × 250 mm, CH₂Cl₂/hexanes 1:3) to afford (*S*)-**237b** as an off-white foamy solid (5.38 g, 7.60 mmol, 80%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 23.71 min for (*S*)-**237b** (major) and *R*_t = 28.67 min for (*R*)-**237b** (minor). mp 85–88 °C; *R*_f = 0.19 (1:2 CH₂Cl₂/hexanes). Spectral data for **237b**: ¹H NMR (CDCl₃, 500 MHz) δ 0.88 (t, 6H, *J* = 7.5 Hz), 1.25–1.30 (m, 4H), 1.46–1.51 (m, 4H), 2.46 (t, 4H, *J* = 7.5 Hz), 5.68 (s, 2H), 6.52 (dd, 4H, *J* = 6.5, 2.0 Hz), 6.76 (d, 4H, *J* = 8.0 Hz), 7.29 (s, 2H), 7.59–7.65 (m, 4H), 8.46–8.48 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 13.89, 22.20, 33.45, 35.12, 113.79, 119.66, 121.74, 123.92, 125.29, 127.64, 128.57, 129.32, 130.92, 133.07, 136.94, 141.11, 141.66, 149.39; IR (thin film) 3519br s, 2928s, 2857s, 1561s, 1487s, 1375s cm^{–1}; HRMS (ESI–) *m/z* calcd for C₄₀H₃₅O₂⁷⁹Br₂ (M–H⁺) 705.1004, meas 705.0973. [α]_D²⁰ = –187.5 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**237b** (HPLC).



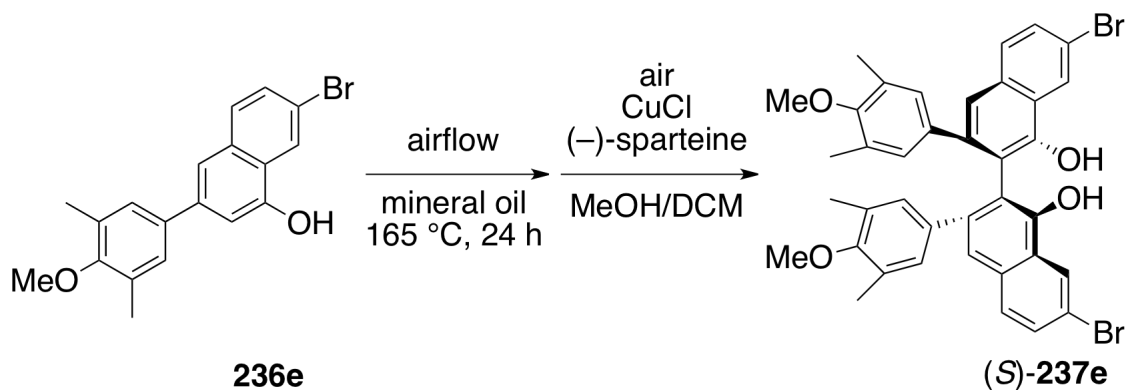
The synthesis of racemic **237c** was performed according to the general procedure (Procedure J) with 7-bromo-3-(3,5-dimethylphenyl)naphthalen-1-ol **236c** (2.62 g, 8.01 mmol). Purification by

column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:3) gave racemic **237c** as a white solid (1.62 g, 2.48 mmol, 62% yield). After de-racemization of racemic **237c** (652 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 1:3) to afford (*S*)-**237c** as an off-white foamy solid (488 mg, 0.75 mmol, 75%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 21.79 min for (*S*)-**237c** (major) and *R*_t = 24.01 min for (*R*)-**237c** (minor). mp 130-134 °C; *R*_f = 0.19 (1:2 CH₂Cl₂/hexanes). Spectral data for **237c**: ¹H NMR (CDCl₃, 500 MHz) δ 2.00 (s, 12H), 5.70 (s, 2H), 6.28 (s, 4H), 6.72 (s, 2H), 7.27 (d, 2H, *J* = 0.5 Hz), 7.60-7.62 (m, 4H), 8.48-8.49 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 21.09, 113.92, 119.66, 121.56, 123.82, 125.14, 126.68, 128.51, 129.24, 130.90, 132.95, 136.78, 139.60, 141.41, 149.50; IR (thin film) 3517br s, 2919s, 1581s, 1487s, 1373s, 1279s cm⁻¹; HRMS (ESI–) *m/z* calcd for C₃₆H₂₇O₂⁷⁹Br₂ (*M*-H⁺) 649.0378, meas 649.0355. [*α*]_D²⁰ = –171.4 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**237c** (HPLC).



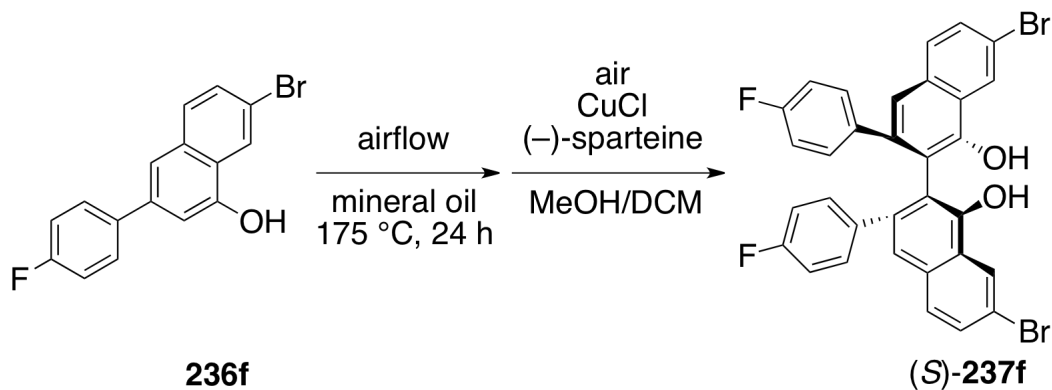
The synthesis of racemic **237d** was performed according to the general procedure (Procedure J) with 7-bromo-3-(4-methoxyphenyl)naphthalen-1-ol **236d** (1.58 g, 4.80 mmol). Purification by

column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 3:2) gave racemic **237d** as a yellow solid (654 mg, 1.00 mmol, 42% yield). After de-racemization of racemic **237d** (548 mg, 0.84 mmol) with CuCl (141 mg, 1.42 mmol) and (–)-sparteine (684 mg, 2.92 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 3:2) to afford (*S*)-**237d** as a light yellow solid (380 mg, 0.58 mmol, 69%). The optical purity was determined to be >99% *ee* by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 254 nm, flow-rate: 0.5 mL/min). Retention times: *R*_t = 4.68 min for (*R*)-**237d** (minor) and *R*_t = 6.65 min for (*S*)-**237d** (major). mp 147-150 °C; *R*_f = 0.24 (2:1 CH₂Cl₂/hexanes). Spectral data for **237d**: ¹H NMR (CDCl₃, 500 MHz) δ 3.68 (s, 6H), 5.70 (s, 2H), 6.51-6.52 (m, 4H), 6.57-6.59 (m, 4H), 7.25 (s, 2H), 7.60-7.62 (m, 4H), 8.46-8.47 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 55.17, 113.09, 113.81, 119.63, 121.71, 123.82, 125.28, 129.28, 129.85, 130.96, 132.26, 133.06, 140.70, 149.41, 158.74; IR (thin film) 3503br s, 2930m, 1514s, 1487s, 1375s, 1248s cm⁻¹; HRMS (ESI–) *m/z* calcd for C₃₄H₂₃O₄⁷⁹Br₂ (M–H⁺) 652.9963, meas 652.9937. [α]_D²⁰ = –182.6 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**237d** (HPLC).



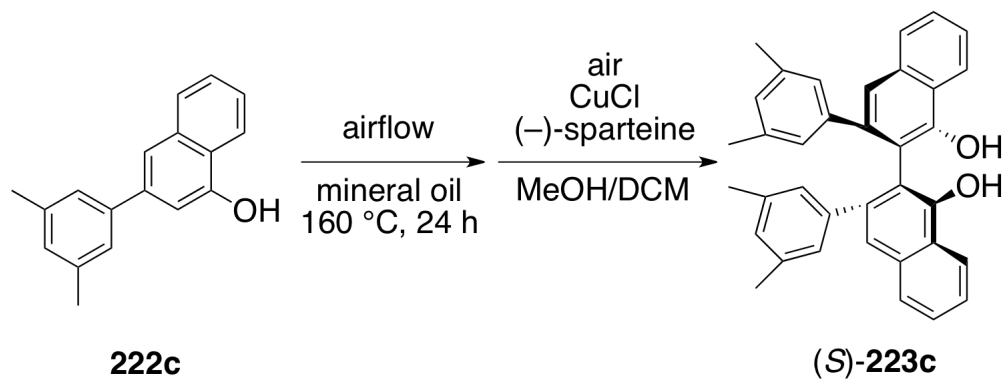
The synthesis of racemic **237e** was performed according to the general procedure (Procedure J) with 7-bromo-3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **236e** (2.50 g, 7.00 mmol).

Purification by column chromatography on silica gel (20 mm × 200 mm, CH₂Cl₂/hexanes 3:2) gave racemic **237e** as a light yellow solid (990 mg, 1.39 mmol, 40% yield). After de-racemization of racemic **237e** (712 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 3:2) to afford (*S*)-**237e** as a light yellow solid (526 mg, 0.74 mmol, 74%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 44.60 min for (*R*)-**237e** (minor) and *R*_t = 49.09 min for (*S*)-**237e** (major). mp 203-206 °C; *R*_f = 0.33 (CH₂Cl₂). Spectral data for **237e**: ¹H NMR (CDCl₃, 500 MHz) δ 1.95 (s, 12H), 3.61 (s, 6H), 5.70 (s, 2H), 6.28 (s, 4H), 7.25 (d, 2H, *J* = 0.5 Hz), 7.60-7.62 (m, 4H), 8.47-8.48 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.89, 59.70, 113.93, 119.64, 121.43, 123.75, 125.12, 129.21, 129.29, 129.68, 130.94, 132.96, 135.20, 140.85, 149.48, 156.20; IR (thin film) 3513br s, 2930s, 1577s, 1483s, 1375s, 1225s cm⁻¹; HRMS (ESI–) *m/z* calcd for C₃₈H₃₁O₄⁷⁹Br₂ (M-H⁺) 709.0589, meas 709.0590. [α]_D²⁰ = –176.4 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**237e** (HPLC).



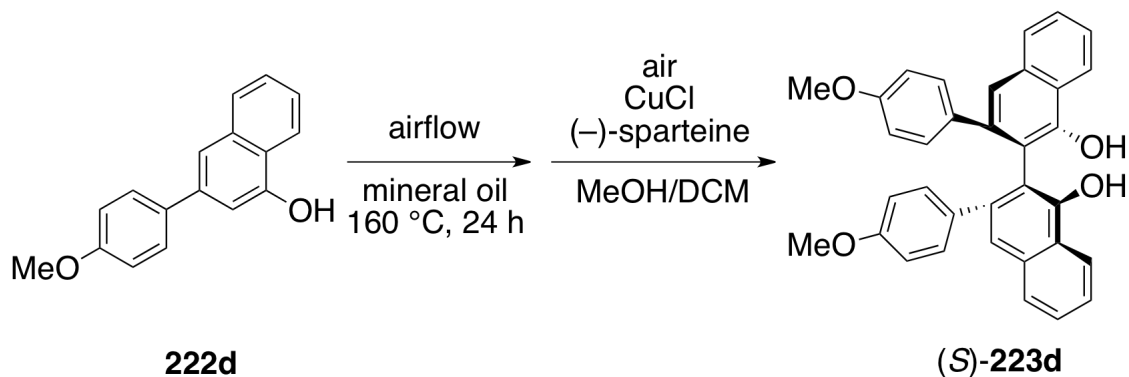
The synthesis of racemic **237f** was performed according to the general procedure (Procedure J) with 7-bromo-3-(4-fluorophenyl)naphthalen-1-ol **236f** (2.06 g, 6.50 mmol). After cooling down to room temperature, CH₂Cl₂ (30 mL) was added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (–20 °C) and then filtered through filter paper. The yellow powder was washed with chilled CH₂Cl₂/hexanes and dried under vacuum to afford a yellow solid (1.19 g). Purification of the product remaining in the mother liquor by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂/hexanes 1:1) gave racemic **237f** as a yellow solid (0.25 g). The total yield is 70% (1.44 g, 2.28 mmol). After de-racemization of racemic **237f** (632 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 2:3) to afford (*S*)-**237f** as an off-white solid (560 mg, 0.89 mmol, 89%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 29.55 min for (*R*)-**237f** (minor) and *R*_t = 35.61 min for (*S*)-**237f** (major). mp 152-158 °C; *R*_f = 0.24 (1:1 CH₂Cl₂/hexanes). Spectral data for **237f**: ¹H NMR (CDCl₃, 500 MHz) δ 5.75 (s, 2H), 6.54-6.56 (m, 4H), 6.65-6.69 (m, 4H), 7.25 (s, 2H), 7.64 (d, 4H, *J* = 1.0 Hz), 8.50 (d, 2H, *J* = 1.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 113.26, 114.58 (²*J*_{CF} = 21 Hz), 120.21, 121.99, 123.98, 125.31, 129.36, 130.34 (³*J*_{CF} = 8.1 Hz), 131.35, 133.02, 135.64 (⁴*J*_{CF} = 3.3 Hz), 139.79, 149.55, 162.06 (¹*J*_{CF} = 245.8 Hz); ¹⁹F NMR (CDCl₃, 283 MHz) δ –113.46; IR (thin film) 3517br s, 1512s, 1489s, 1375s, 1235s cm^{–1}; mass spectrum, *m/z* (% rel intensity) 634

M^+ (5, $^{81}\text{Br}^{81}\text{Br}$), 632 M^+ (10, $^{81}\text{Br}^{79}\text{Br}$), 630 M^+ (7, $^{79}\text{Br}^{79}\text{Br}$), 425 (5), 317 (21, ^{81}Br), 315 (17, ^{79}Br), 289 (12, ^{81}Br), 287 (13, ^{79}Br), 227 (65), 212 (83), 196 (100), 159 (100). Anal calcd for $\text{C}_{32}\text{H}_{18}\text{Br}_2\text{F}_2\text{O}_2$: C, 60.79; H, 2.87. Found: C, 60.99; H, 2.72. $[\alpha]_D^{20} = -152.7$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**237f** (HPLC).



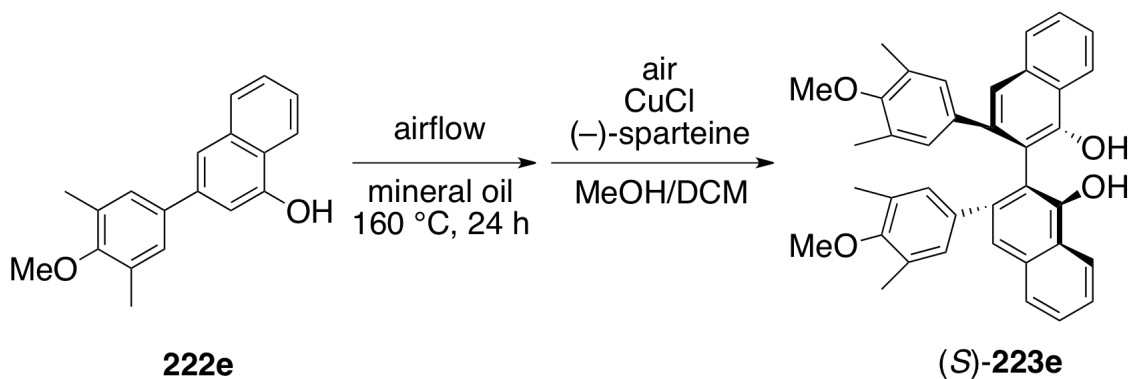
The synthesis of racemic **223c** was performed according to the general procedure (Procedure J) with 3-(3,5-dimethylphenyl)naphthalen-1-ol **222c** (992 mg, 4.00 mmol). Purification by column chromatography on silica gel (30 mm $\times$ 250 mm, CH_2Cl_2 /hexanes 1:2) gave racemic **223c** as a light yellow solid (754 mg, 1.52 mmol, 76% yield). After de-racemization of racemic **223c** (494 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (-)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (30 mm $\times$ 200 mm, CH_2Cl_2 /hexanes 1:2) to afford (*S*)-**223c** as a light yellow solid (160 mg, 0.32 mmol, 32%). The optical purity was determined to be >99% *ee* by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 254 nm, flow-rate: 0.7 mL/min). Retention times: R_t = 10.14 min for (*R*)-**223c** (minor) and R_t = 16.96 min for (*S*)-**223c** (major). mp 79-83 $^\circ\text{C}$; R_f = 0.39 (2:1 CH_2Cl_2 /hexanes). Spectral data for **223c**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.99 (s, 12H), 5.78 (s, 2H), 6.33 (d, 4H, J = 1.0 Hz), 6.70 (s, 2H), 7.31 (s, 2H), 7.50-7.55 (m, 4H), 7.74-7.77 (m, 2H), 8.31-8.34 (m, 2H);

^{13}C NMR (CDCl_3 , 125 MHz) δ 21.05, 113.06, 121.60, 122.64, 122.78, 125.46, 126.82, 127.32, 127.54, 128.19, 134.53, 136.58, 140.13, 141.00, 150.42; IR (thin film) 3513br s, 2921s, 1597s, 1497s, 1387s, 1277s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{36}\text{H}_{31}\text{O}_2$ ($\text{M}+\text{H}^+$) 495.2324, meas 495.2332. $[\alpha]_{\text{D}}^{20} = -233.9$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**223c** (HPLC).



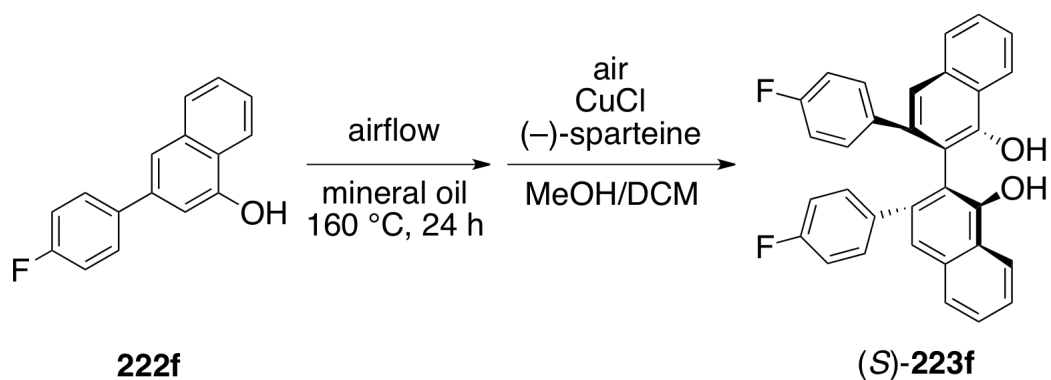
The synthesis of racemic **223d** was performed according to the general procedure (Procedure J) with 3-(4-methoxyphenyl)naphthalen-1-ol **222d** (590 mg, 2.36 mmol). Purification by column chromatography on silica gel (30 mm $\times$ 250 mm, EtOAc/hexanes 1:20 to 1:10) gave racemic **223d** as a yellow solid (362 mg, 0.73 mmol, 62% yield). After de-racemization of racemic **223d** (299 mg, 0.60 mmol) with CuCl (101 mg, 1.02 mmol) and (-)-sparteine (491 mg, 2.10 mmol), the crude product was purified by column chromatography on silica gel (35 mm $\times$ 200 mm, CH_2Cl_2 /hexanes 4:1) to afford (*S*)-**223d** as a yellow solid (50 mg, 0.10 mmol, 17%). The optical purity was determined to be >99% *ee* by HPLC analysis (Chiralpak AS column, 90:10 hexane/*i*PrOH at 254 nm, flow-rate: 0.5 mL/min). Retention times: R_t = 12.41 min for (*S*)-**223d** (major) and R_t = 22.56 min for (*R*)-**223d** (minor). mp 212-215 $^\circ\text{C}$; R_f = 0.42 (CH_2Cl_2). Spectral data for **223d**: ^1H NMR (CDCl_3 , 500 MHz) δ 3.68 (s, 6H), 5.78 (s, 2H), 6.49-6.53 (m, 4H),

6.59-6.63 (m, 4H), 7.30 (s, 2H), 7.50-7.57 (m, 4H), 7.75-7.78 (m, 2H), 8.30-8.33 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.14, 112.92, 112.93, 121.78, 122.75, 122.78, 125.43, 127.42, 127.58, 129.94, 132.83, 134.62, 140.30, 150.27, 158.46; IR (thin film) 3507br s, 2930s, 1514s, 1495s, 1383s, 1246s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{34}\text{H}_{27}\text{O}_4$ ($\text{M}+\text{H}^+$) 499.1909, meas 499.1902. $[\alpha]_{\text{D}}^{20} = -242.3$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**223d** (HPLC).



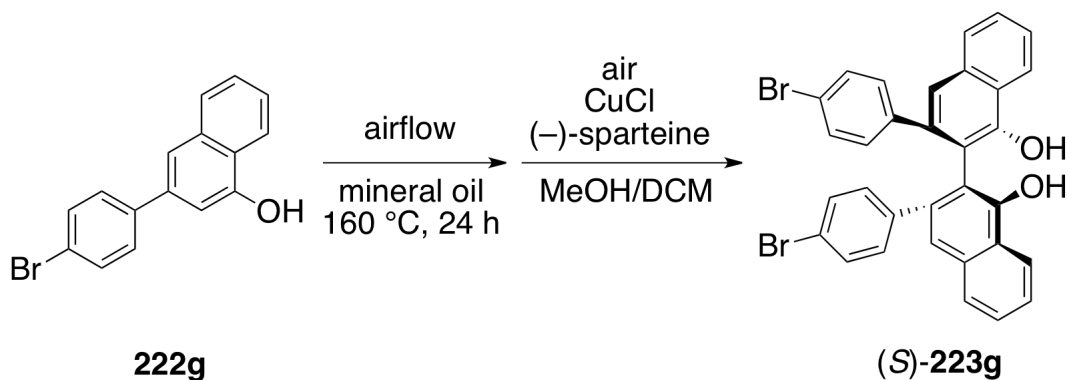
The synthesis of racemic **223e** was performed according to the general procedure (Procedure J) with 3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **222e** (1.12 g, 4.00 mmol). Purification by column chromatography on silica gel (35 mm $\times$ 250 mm, EtOAc/hexanes 1:20) gave racemic **223e** as a light yellow solid (590 mg, 1.06 mmol, 53% yield). After de-racemization of racemic **223e** (188 mg, 0.34 mmol) with CuCl (58 mg, 0.59 mmol) and (-)-sparteine (278 mg, 1.19 mmol), the crude product was purified by column chromatography on silica gel (20 mm $\times$ 200 mm, CH_2Cl_2 /hexanes 4:1) to afford (*S*)-**223e** as a yellow solid (88 mg, 0.16 mmol, 47%). The optical purity was determined to be >99% *ee* by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 254 nm, flow-rate: 0.5 mL/min). Retention times: $R_t = 24.40$ min for (*R*)-**223e** (minor) and $R_t = 27.43$ min for (*S*)-**223e** (major). mp 207-210 $^\circ\text{C}$; $R_f = 0.32$ (CH_2Cl_2). Spectral

data for **223e**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.94 (s, 12H), 3.61 (s, 6H), 5.78 (s, 2H), 6.32 (s, 4H), 7.29 (s, 2H), 7.49-7.56 (m, 4H), 7.74-7.77 (m, 2H), 8.30-8.33 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 15.85, 59.69, 113.05, 121.48, 122.62, 122.70, 125.46, 127.37, 127.51, 129.41, 129.44, 134.53, 135.73, 140.41, 150.38, 155.92; IR (thin film) 3515br s, 2930s, 1570s, 1487s, 1387s, 1225s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{36}\text{H}_{29}\text{O}_4\text{I}_2$ ($\text{M}+\text{H}^+$) 779.0155, meas 779.0159. $[\alpha]_{\text{D}}^{20} = -209.2$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**223e** (HPLC).



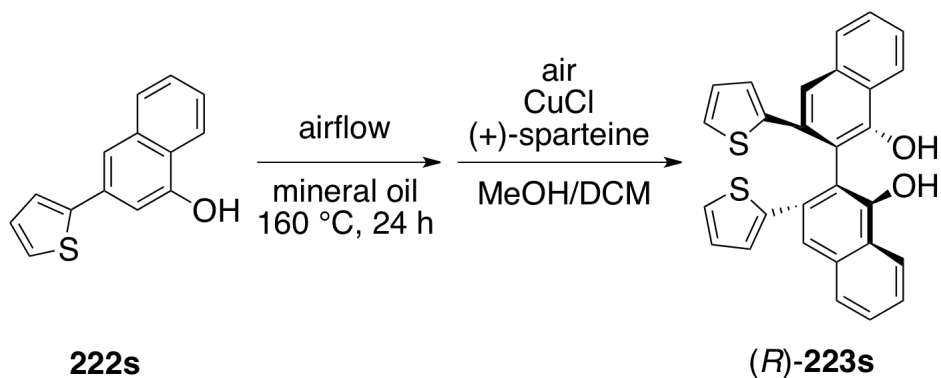
The synthesis of racemic **223f** was performed according to the general procedure (Procedure J) with 3-(4-fluorophenyl)naphthalen-1-ol **222f** (952 mg, 4.00 mmol). Purification by column chromatography on silica gel (35 mm $\times$ 200 mm, CH_2Cl_2 /hexanes 2:3) gave racemic **223f** as an off-white solid (752 mg, 1.58 mmol, 79% yield). After de-racemization of racemic **223f** (436 mg, 0.92 mmol) with CuCl (155 mg, 1.57 mmol) and (-)-sparteine (754 mg, 3.22 mmol), the crude product was purified by column chromatography on silica gel (35 mm $\times$ 200 mm, CH_2Cl_2 /hexanes 2:3) to afford (*S*)-**223f** as an off-white solid (281 mg, 0.59 mmol, 64%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: $R_t = 20.55$ min for

(*R*)-**223f** (minor) and $R_t = 24.49$ min for (*S*)-**223f** (major). mp 107-112 °C; $R_f = 0.33$ (2:1 CH₂Cl₂/hexanes). Spectral data for **223f**: ¹H NMR (CDCl₃, 500 MHz) δ 5.83 (s, 2H), 6.57-6.61 (m, 4H), 6.63-6.68 (m, 4H), 7.29 (s, 2H), 7.54-7.60 (m, 4H), 7.77-7.79 (m, 2H), 8.33-8.35 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 112.40, 114.40 (² $J_{CF} = 21.1$ Hz), 122.05, 122.78, 122.93, 125.93, 127.69, 127.77, 130.43 (³ $J_{CF} = 8.3$ Hz), 134.59, 136.16 (⁴ $J_{CF} = 3.3$ Hz), 139.41, 150.42, 161.90 (¹ $J_{CF} = 244.9$ Hz); ¹⁹F NMR (CDCl₃, 283 Hz) δ -114.15; IR (thin film) 3517br s, 3058s, 1512s, 1495s, 1385s, 1221s cm⁻¹; HRMS (ESI+) m/z calcd for C₃₂H₂₁O₂F₂ (M+H⁺) 475.1510, meas 475.1504. $[\alpha]_D^{20} = -193.6$ (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**223f** (HPLC).



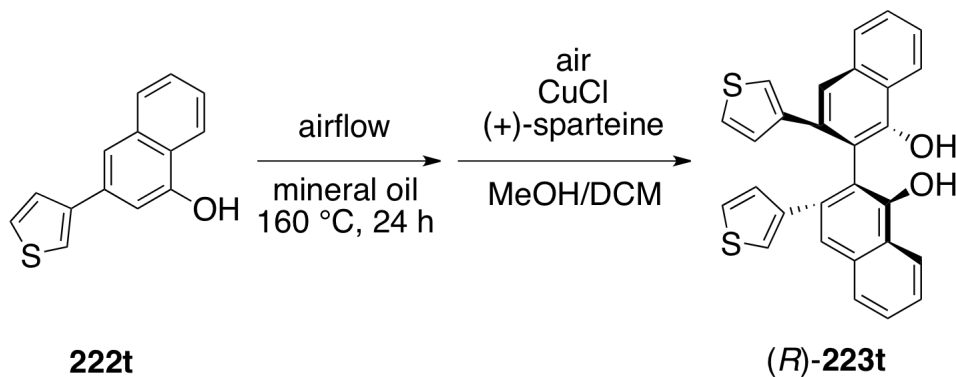
The synthesis of racemic **223g** was performed according to the general procedure (Procedure J) with 3-(4-bromophenyl)naphthalen-1-ol **222g** (1.20 g, 4.00 mmol). Purification by column chromatography on silica gel (35 mm × 250 mm, CH₂Cl₂/hexanes 1:2 to 2:3) gave racemic **223g** as an off-white solid (699 mg, 1.17 mmol, 59% yield). After de-racemization of racemic **223g** (596mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (-)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column chromatography on silica gel (35 mm × 200 mm, CH₂Cl₂/hexanes 1:2 to 2:3) to afford (*S*)-**223g** as an off-white solid (443 mg, 0.74 mmol, 74%). The optical purity was determined to be >99% *ee* by HPLC analysis (Chiralcel OD-H column,

98:2 hexane/*i*PrOH at 254 nm, flow-rate: 0.7 mL/min). Retention times: R_t = 18.72 min for (*S*)-**223g** (major) and R_t = 21.78 min for (*R*)-**223g** (minor). mp 143-148 °C; R_f = 0.33 (2:1 CH₂Cl₂/hexanes). Spectral data for **223g**: ¹H NMR (CDCl₃, 500 MHz) δ 5.82 (s, 2H), 6.48-6.51 (m, 4H), 7.08-7.11 (m, 4H), 7.29 (s, 2H), 7.55-7.61 (m, 4H), 7.78-7.80 (m, 2H), 8.32-8.35 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 112.02, 121.11, 122.12, 122.80, 123.03, 126.11, 127.76, 127.89, 130.49, 130.65, 134.58, 139.06, 139.17, 150.48; IR (thin film) 3505br s, 3052s, 1570s, 1489s, 1385s, 1221s cm⁻¹; HRMS (ESI+) m/z calcd for C₃₂H₂₁O₂⁷⁹Br₂ (M+H⁺) 594.9908, meas 594.9921. $[\alpha]_D^{20}$ = -186.8 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**223g** (HPLC).



The synthesis of racemic **223s** was performed according to the general procedure (Procedure J) with 3-(thiophen-2-yl)naphthalen-1-ol **222s** (1.70 g, 7.50 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 2:3) gave racemic **223s** as a yellow solid (757 mg, 1.68 mmol, 45% yield). After de-racemization of racemic **223s** (652 mg, 1.45 mmol) with CuCl (244 mg, 2.46 mmol) and (+)-sparteine (1.19 g, 5.09 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 1:1) to afford (*R*)-**223s** as an off-white foamy solid (476 mg, 1.06 mmol, 73%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine

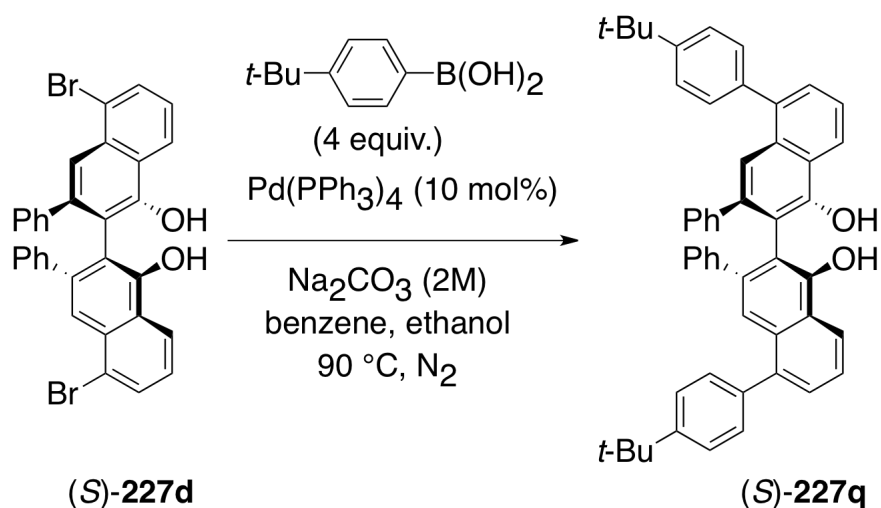
column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 30.75 min for (*R*)-**223s** (major) and R_t = 34.92 min for (*S*)-**223s** (minor). mp 157-159 °C; R_f = 0.37 (2:1 CH₂Cl₂/hexanes). Spectral data for **223s**: ¹H NMR (CDCl₃, 500 MHz) δ 5.60 (s, 2H), 6.68 (dd, 2H, J = 3.5, 1.0 Hz), 6.73 (dd, 2H, J = 5.0, 1.0 Hz), 7.50-7.54 (m, 2H), 7.56-7.61 (m, 2H), 7.76 (s, 2H), 7.86 (d, 2H, J = 8.0 Hz), 8.24-8.26 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 111.44, 121.47, 122.94, 123.29, 125.91, 126.00, 126.04, 127.03, 127.74, 127.96, 133.07, 134.80, 141.52, 151.31; IR (thin film) 3505br s, 1570s, 1491s, 1387s, 1210s cm⁻¹; HRMS (ESI-) m/z calcd for C₂₈H₁₇O₂S₂ (M-H⁺) 449.0670, meas 449.0660. $[\alpha]_D^{20}$ = +124.9 (c 1.0, CH₂Cl₂) on >99% *ee* (*R*)-**223s** (HPLC).



The synthesis of racemic **223t** was performed according to the general procedure (Procedure J) with 3-(thiophen-3-yl)naphthalen-1-ol **222t** (904 mg, 4.00 mmol). Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:1) gave racemic **223t** as a light yellow solid (534 mg, 1.19 mmol, 59% yield). After de-racemization of racemic **223t** (360 mg, 0.80 mmol) with CuCl (135 mg, 1.36 mmol) and (+)-sparteine (655 mg, 2.80 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm,

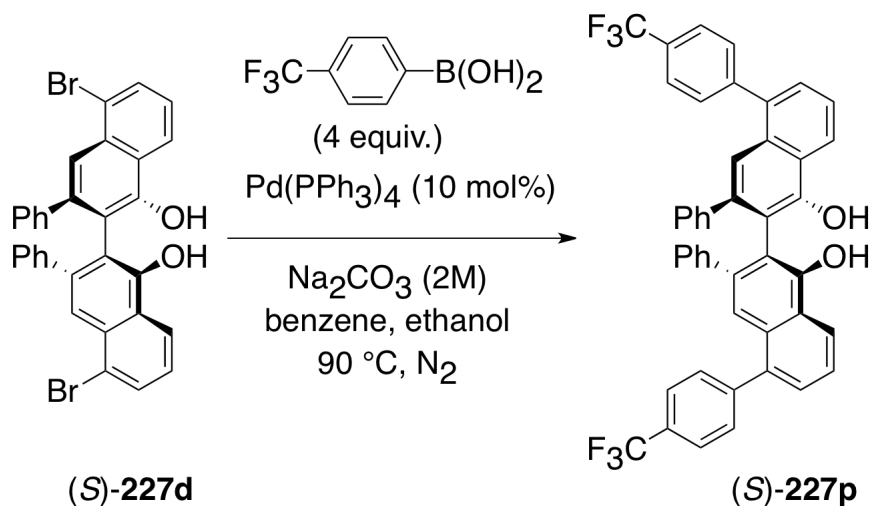
crude product by column chromatography on silica gel (30 mm x 250 mm, EtOAc/hexanes 1:80) gave **234** as a white foamy solid (148 mg, 0.33 mmol, 66%). mp 72-76 °C; R_f = 0.24 (1:10 EtOAc/hexanes). Spectral data for **234**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.76-1.88 (m, 8H), 2.68-2.77 (m, 8H), 5.19 (s, 2H), 6.54 (s, 2H), 6.58-6.61 (m, 4H), 6.98-7.03 (m, 4H), 7.05-7.09 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 22.73, 22.81, 23.23, 29.58, 115.06, 122.99, 123.22, 126.14, 127.29, 128.62, 139.31, 140.31, 140.67, 151.88; IR (thin film) 3468br s, 2930s, 1559s, 1399s, 1300s, 1229s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{32}\text{H}_{29}\text{O}_2$ ($\text{M}-\text{H}^+$) 445.2168, meas 445.2173. $[\alpha]_{\text{D}}^{20} = -143.3$ (c 1.0, CH_2Cl_2).

Suzuki coupling

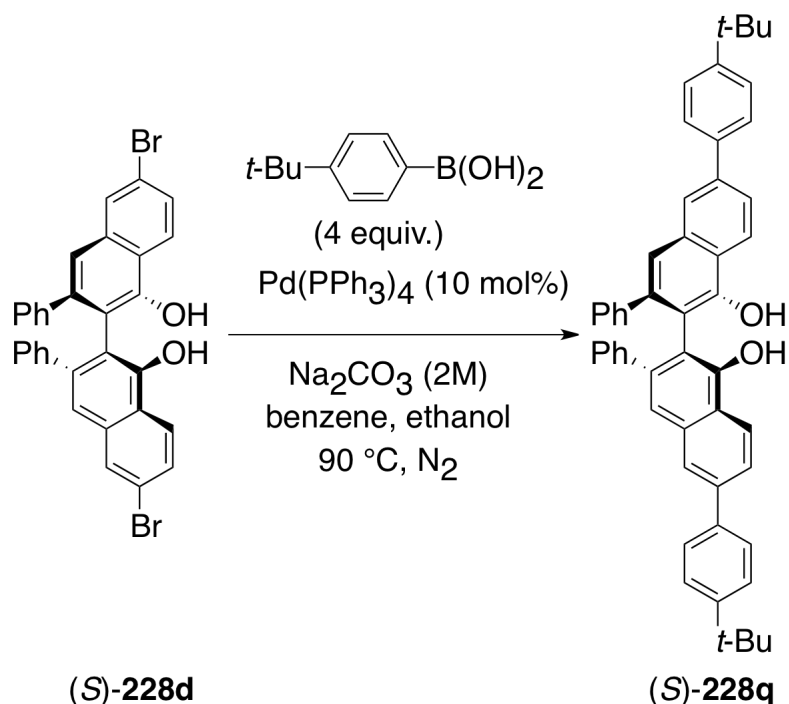


The reaction of **(S)-227d** (178 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na_2CO_3 (aq. 2 M, 1.5 mL), 4-*tert*-butylphenylboronic acid (214 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (25 mm x 250 mm, CH_2Cl_2 :hexanes 2:3)

gave (*S*)-**227q** as a white solid (179 mg, 0.255 mmol, 85%). mp >260 °C; R_f = 0.23 (1:1 CH₂Cl₂/hexane). Spectral data for **227q**: ¹H NMR (CDCl₃, 500 MHz) δ 1.35 (s, 18H), 5.90 (s, 2H), 6.55-6.58 (m, 4H), 6.91-6.95 (m, 4H), 7.01-7.06 (m, 2H), 7.39-7.47 (m, 10H), 7.52 (dd, 2H, J = 7.0, 1.5 Hz), 7.58-7.62 (m, 2H), 8.38-8.41 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 31.37, 34.56, 112.54, 120.21, 122.07, 123.31, 125.26, 125.27, 126.43, 127.37, 128.81, 128.99, 129.60, 132.78, 137.40, 140.07, 140.43, 150.10, 150.47 (1 sp² C not located); IR (thin film) 3520s, 2963s, 1576m, 1483m, 1383s, 1238m cm⁻¹; HRMS (ESI-) m/z calcd for C₅₂H₄₅O₂ (M-H⁺) 701.3420, meas 701.3439. $[\alpha]_D^{20}$ = -106.2 (c 1.0, CH₂Cl₂).

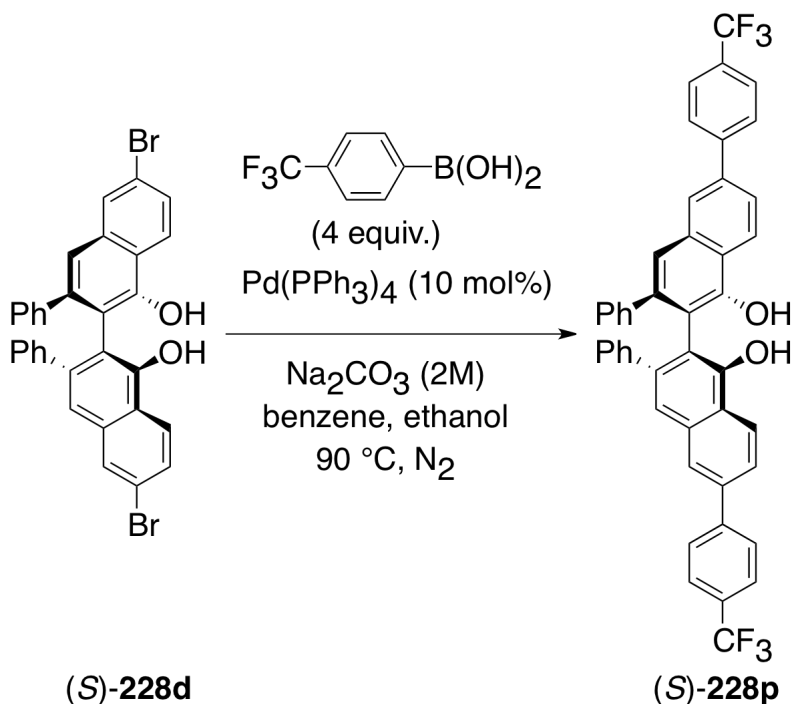


2H), 6.54-6.57 (m, 4H), 6.92-6.96 (m, 4H), 7.04-7.08 (m, 2H), 7.29 (s, 2H), 7.51 (dd, 2H, $J = 7.5$, 1.5 Hz), 7.59 (d, 4H, $J = 8.0$ Hz), 7.61-7.65 (m, 2H), 7.69 (d, 4H, $J = 8.0$ Hz), 8.44-8.47 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 112.79, 119.61, 123.08, 123.12, 124.34 (q, $^1J_{\text{CF}} = 255.63$ Hz), 125.29 (q, $^3J_{\text{CF}} = 3.9$ Hz), 126.74, 127.52, 128.82, 128.90, 129.54 (q, $^2J_{\text{CF}} = 31.9$ Hz), 130.29, 132.43, 138.59, 140.10, 141.06, 144.13, 150.63 (1 sp^2 C not located); ^{19}F NMR (CDCl_3 , 283 Hz) δ -60.81; IR (thin film) 3522br s, 1576s, 1485s, 1385s, 1325s, 1240s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{46}\text{H}_{27}\text{O}_2\text{F}_6$ (M-H^+) 725.1915, meas 725.1891. $[\alpha]_{\text{D}}^{20} = -110.4$ (c 1.0, CH_2Cl_2).



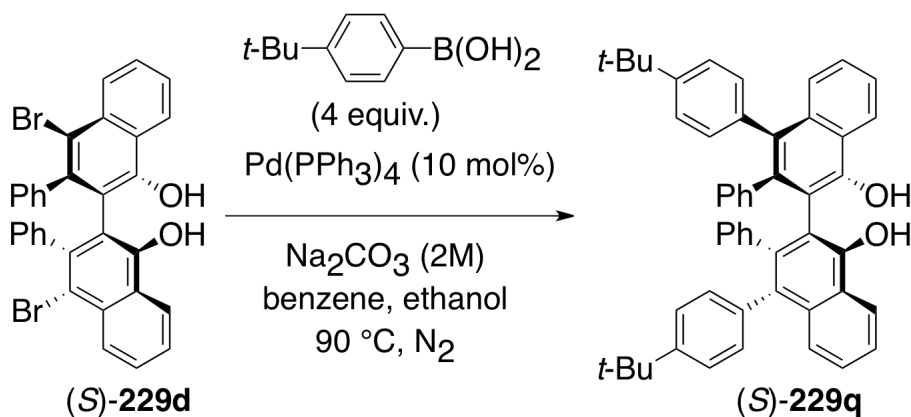
The reaction of (S)-**228d** (178 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na_2CO_3 (aq. 2 M, 1.5 mL), 4-*tert*-butylphenylboronic acid (214 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (20 mm x 200 mm, CH_2Cl_2 :hexanes 1:2) gave (S)-**228q** as a white solid (110 mg, 0.157 mmol, 53%). mp >260 °C; $R_f = 0.26$ (1:1

CH₂Cl₂/hexanes). Spectral data for **228q**: ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 18H), 5.85 (s, 2H), 6.68 (dd, 4H, *J* = 8.0, 1.5 Hz), 6.99 (t, 4H, *J* = 8.0 Hz), 7.09 (t, 2H, *J* = 7.5 Hz), 7.37 (s, 2H), 7.52-7.54 (m, 4H), 7.67-7.70 (m, 4H), 7.82 (dd, 2H, *J* = 9.0, 2.0 Hz), 7.96 (d, 2H, *J* = 1.5 Hz), 8.40 (d, 2H, *J* = 8.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 31.38, 34.61, 112.64, 121.88, 122.29, 123.36, 125.27, 125.38, 125.89, 126.66, 127.06, 127.50, 128.90, 134.97, 137.92, 140.09, 140.23, 141.13, 150.39, 150.72; IR (thin film) 3521br s, 3031w, 2963s, 1570s, 1489s, 1383s, 1227s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₅₂H₄₅O₂ (M-H⁺) 701.3420, meas 701.3394. [α]_D²⁰ = -235.9 (c 1.0, CH₂Cl₂).



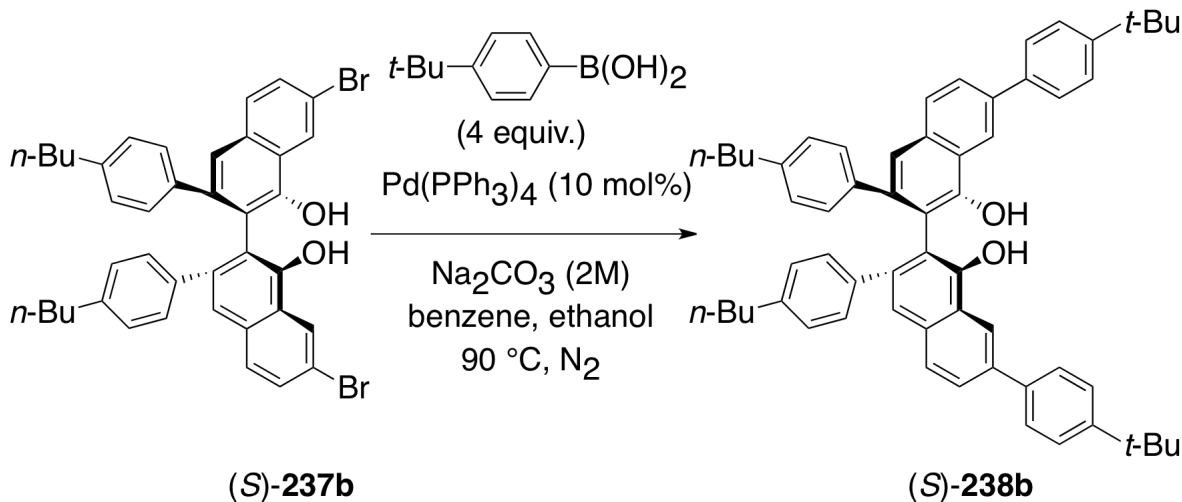
The reaction of (*S*)-**228d** (238 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na₂CO₃ (aq. 2 M, 2 mL), 4-(trifluoromethyl)phenylboronic acid (304 mg, 1.60 mmol) and ethanol (2 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 1:2)

gave (*S*)-**228p** as a white solid (146 mg, 0.201 mmol, 50%). mp >260 °C; R_f = 0.27 (1:1 CH₂Cl₂/hexanes). Spectral data for **228p**: ¹H NMR (CDCl₃, 500 MHz) δ 5.89 (s, 2H), 6.64-6.68 (m, 4H), 6.98-7.01 (m, 4H), 7.08-7.12 (m, 2H), 7.38 (s, 2H), 7.75 (d, 4H, J = 8.0 Hz), 7.79 (dd, 2H, J = 9.0, 1.5 Hz), 7.83 (d, 4H, J = 8.0 Hz), 7.98 (d, 2H, J = 1.5 Hz), 8.44 (d, 2H, J = 9.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 113.22, 122.35, 122.39, 124.27 (q, $^1J_{CF}$ = 270.4 Hz), 123.81, 125.07, 125.86 (q, $^3J_{CF}$ = 3.9 Hz), 126.09, 126.84, 127.56, 127.69, 128.85, 129.67 (q, $^2J_{CF}$ = 32.5 Hz), 134.80, 138.78, 139.90, 141.47, 144.33 (q, $^4J_{CF}$ = 1.3 Hz), 150.38; ¹⁹F NMR (CDCl₃, 283 Hz) δ -60.76; IR (thin film) 3521br s, 1561s, 1489s, 1385s, 1325s, 1225s cm⁻¹; HRMS (ESI-) m/z calcd for C₄₆H₂₇O₂F₆ (M-H⁺) 725.1915, meas 725.1890. $[\alpha]_D^{20}$ = -231.4 (c 1.0, CH₂Cl₂).



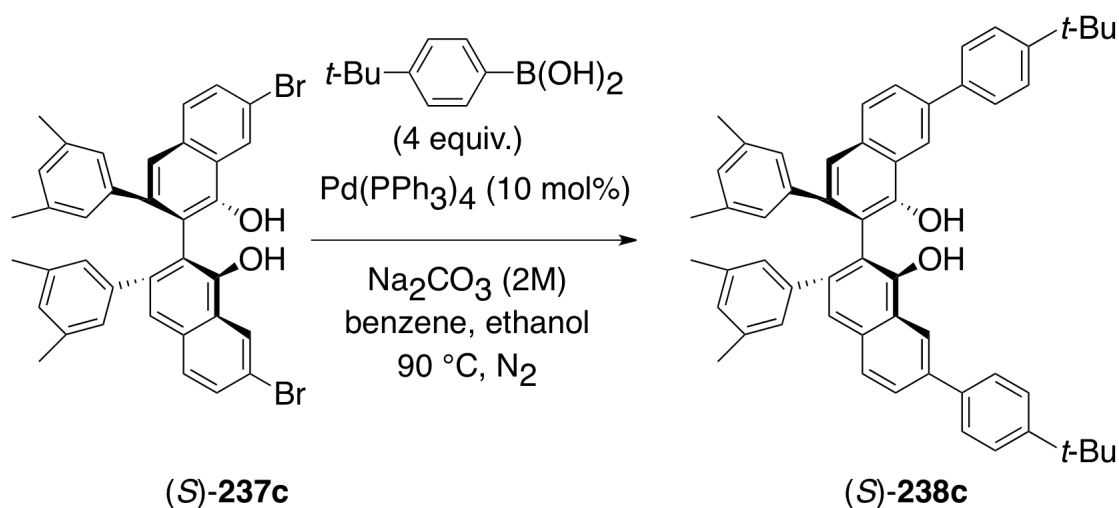
The reaction of (*S*)-**229d** (178 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na₂CO₃ (aq. 2 M, 1.5 mL), 4-*tert*-butylphenylboronic acid (214 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (25 mm x 300 mm, CH₂Cl₂:hexanes 1:3) gave (*S*)-**229q** as a white solid (125 mg, 0.178 mmol, 59%). mp >260 °C; R_f = 0.25 (1:1

CH₂Cl₂/hexane). Spectral data for **229q**: ¹H NMR (CDCl₃, 500 MHz) δ 1.21 (s, 18H), 5.80 (s, 2H), 5.92 (bs, 2H), 6.58 (dd, 2H, *J* = 8.0, 2.0 Hz), 6.62 (bs, 2H), 6.79 (s, 4H), 6.90 (s, 2H), 6.96-6.99 (m, 4H), 7.21 (dd, 2H, *J* = 8.0, 2.0 Hz), 7.40-7.44 (m, 2H), 7.51-7.56 (m, 4H), 8.41 (d, 2H, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 31.29, 34.32, 113.72, 122.62, 122.91, 123.72, 124.61, 125.29, 125.67, 126.92, 127.05, 130.75, 131.60, 132.56, 134.08, 135.83, 138.58, 139.22, 148.89, 149.56; IR (thin film) 3519br s, 2961s, 1576s, 1456s, 1373s, 1210s cm⁻¹; HRMS (ESI-) *m/z* calcd for C₅₂H₄₅O₂ (M-H⁺) 701.3420, meas 701.3401. [α]_D²⁰ = -1.9 (c 1.0, CH₂Cl₂).



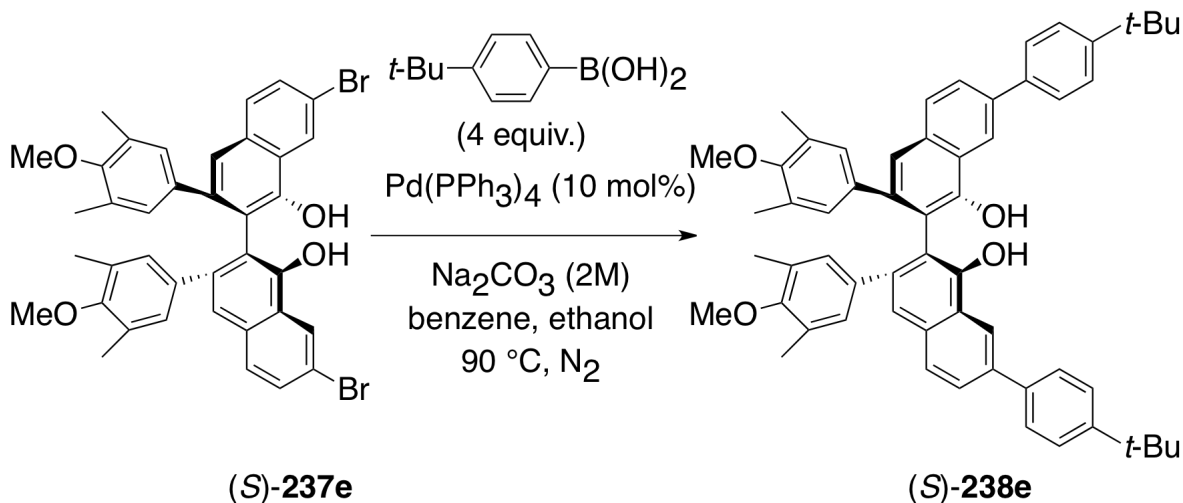
The reaction of **(S)-237b** (284 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na₂CO₃ (aq. 2 M, 4 mL), 4-*tert*-butylphenylboronic acid (285 mg, 1.60 mmol) and ethanol (2 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 2:5) gave **(S)-238b** as an off-white solid (162 mg, 0.199 mmol, 50%). mp >260 °C; *R*_f = 0.22 (1:2 CH₂Cl₂/hexanes). Spectral data for **238b**: ¹H NMR (CDCl₃, 500 MHz) δ 0.89 (t, 6H, *J* = 7.5 Hz), 1.27-1.32 (m, 4H), 1.39 (s, 18H), 1.49-1.52 (m, 4H), 2.47 (t, 2H, *J* = 7.5 Hz), 5.84 (s, 2H), 6.58

(dd, 4H, $J = 6.5, 2.0$ Hz), 6.78 (d, 4H, $J = 8.0$ Hz), 7.36 (d, 2H, $J = 1.0$ Hz), 7.52 (dd, 4H, $J = 6.5, 2.0$ Hz), 7.74 (dd, 4H, $J = 6.5, 2.0$ Hz), 7.83-7.84 (m, 4H), 8.54 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.91, 22.24, 31.40, 33.52, 34.59, 35.15, 113.30, 120.48, 121.61, 123.18, 125.84, 126.98, 127.08, 127.57, 128.14, 128.69, 133.69, 137.53, 138.09, 138.18, 140.60, 141.26, 150.48, 150.49; IR (thin film) 3499br s, 2957s, 1559s, 1456s, 1388s, 1267s cm^{-1} ; HRMS (ESI $^-$) m/z calcd for $\text{C}_{60}\text{H}_{61}\text{O}_2$ ($\text{M}-\text{H}^+$) 813.4672, meas 813.4709. $[\alpha]_{\text{D}}^{20} = -31.7$ (c 1.0, CH_2Cl_2).



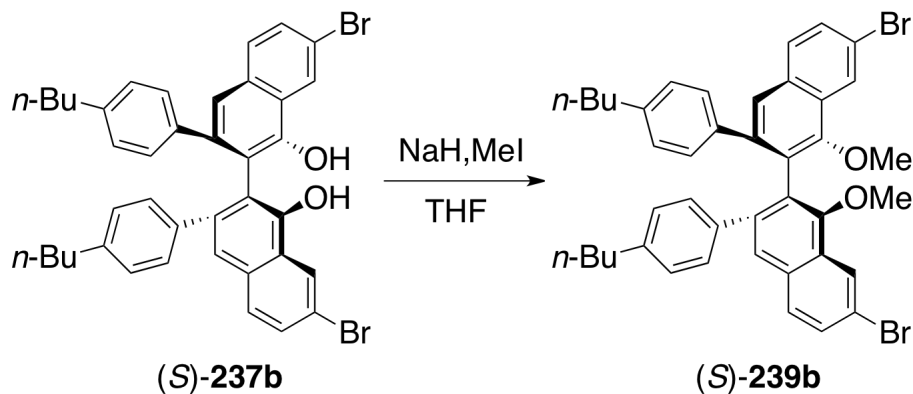
The reaction of **(S)-237c** (261 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na_2CO_3 (aq. 2 M, 4 mL), 4-*tert*-butylphenylboronic acid (285 mg, 1.60 mmol) and ethanol (2 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH_2Cl_2 :hexanes 2:5) gave **(S)-238c** as an off-white solid (145 mg, 0.191 mmol, 48%). mp 170-185 °C; $R_f = 0.19$ (1:2 CH_2Cl_2 /hexanes). Spectral data for **238c**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.38 (s, 18H), 2.01 (s, 12H), 5.82 (s, 2H), 6.36 (d, 4H, $J = 0.5$ Hz), 6.71 (s, 2H), 7.33 (d, 2H, $J = 0.5$ Hz), 7.52 (dd, 4H, $J = 6.5, 2.0$ Hz), 7.75 (dd, 4H, $J = 7.0, 2.0$ Hz), 7.82-7.83 (m, 4H), 8.55 (d, 2H, $J = 0.5$ Hz); ^{13}C

NMR (CDCl₃, 125 MHz) δ 21.10, 31.39, 34.59, 113.41, 120.24, 121.36, 123.07, 125.84, 126.82, 126.86, 127.03, 128.06, 128.22, 133.58, 136.62, 137.95, 138.12, 140.17, 140.90, 150.49, 150.65; IR (thin film) 3519br s, 2961s, 1597s, 1495s, 1387s, 1267s cm⁻¹; HRMS (ESI-) m/z calcd for C₅₆H₅₃O₂ (M-H⁺) 757.4046, meas 757.4055. $[\alpha]_D^{20} = -6.2$ (c 1.0, CH₂Cl₂).



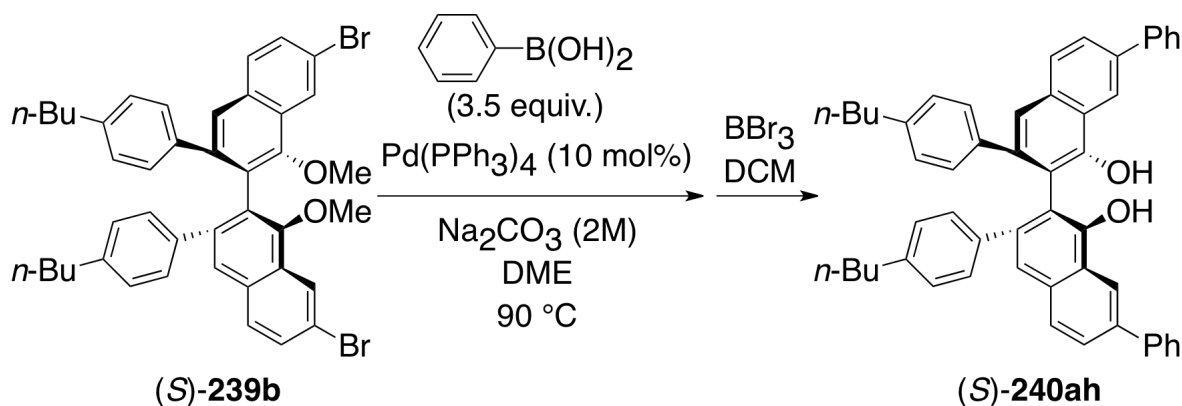
The reaction of (*S*)-**237e** (214 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na₂CO₃ (aq. 2 M, 1.5 mL), 4-*tert*-butylphenylboronic acid (214 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 200 mm, CH₂Cl₂:hexanes 3:2) gave (*S*)-**238e** as an off-white solid (63 mg, 0.077 mmol, 26%). mp 172-178 °C; R_f = 0.40 (CH₂Cl₂). Spectral data for **238e**: ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 18H), 1.96 (s, 12H), 3.62 (s, 6H), 5.84 (s, 2H), 6.36 (s, 4H), 7.32 (s, 2H), 7.53 (dd, 4H, J = 6.5, 2.0 Hz), 7.76 (dd, 4H, J = 6.5, 2.0 Hz), 7.82-7.83 (m, 4H), 8.55-8.56 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.89, 31.39, 34.59, 59.90, 113.44, 120.22, 121.26, 123.02, 125.85, 126.91, 127.03, 128.04, 129.42, 129.49, 133.60, 135.79, 137.96, 138.12, 140.34, 150.50, 150.64, 155.9; IR (thin film) 3519br s,

2959s, 1559s, 1489s, 1389s, 1223s cm^{-1} ; HRMS (ESI⁻) m/z calcd for $\text{C}_{58}\text{H}_{57}\text{O}_4$ ($\text{M}-\text{H}^+$) 817.4257, meas 817.4262. $[\alpha]_{\text{D}}^{20} = -40.8$ (c 1.0, CH_2Cl_2).



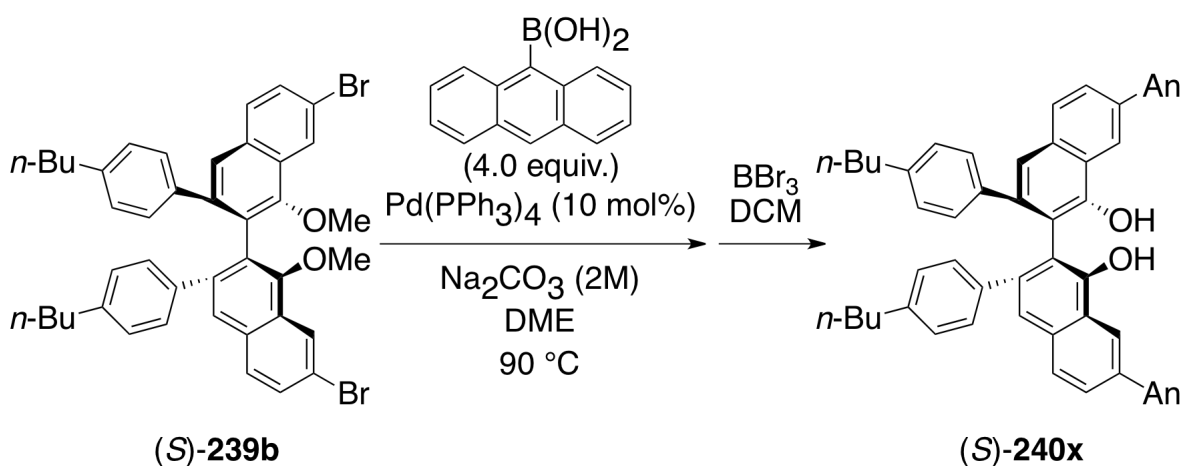
To a flame-dried 250 mL round bottom flask was added (*S*)-**237b** (1.42 g, 2.00 mmol) and dry THF (15 mL). The resulting mixture was cooled to 0 °C and NaH (176 mg, 60% in mineral oil, 4.40 mmol) was added. The mixture was stirred at 0 °C for 15 minutes and MeI (0.8 mL, 12.8 mmol) was added. The mixture was warmed up to room temperature and stirred for additional 24 h. NH_4Cl (sat. aq. 4 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The residue was extracted with CH_2Cl_2 (5 mL $\times$ 3). The combined organic layer was washed with $\text{Na}_2\text{S}_2\text{O}_3$ (sat. aq. 5 mL $\times$ 2), brine (5 mL), and dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm $\times$ 320 mm, CH_2Cl_2 :hexanes 1:4) gave (*S*)-**239b** as a white foamy solid (1.30 g, 1.76 mmol, 88%). mp 75-77 °C; $R_f = 0.29$ (1:2 CH_2Cl_2 /hexanes). Spectral data for **239b**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.91 (t, 6H, $J = 7.5$ Hz), 1.28-1.33 (m, 4H), 1.49-1.53 (m, 4H), 2.45-2.49 (m, 4H), 3.63 (s, 6H), 6.63 (dd, 4H, $J = 6.5, 2.0$ Hz), 6.74 (d, 4H, $J = 8.0$ Hz), 7.50 (s, 2H), 7.57 (dd, 2H, $J = 8.5, 2.0$ Hz), 7.71 (d, 2H, $J = 8.5$ Hz), 8.33 (d, 2H, $J =$

2.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.91, 22.24, 33.58, 35.10, 61.14, 120.02, 124.84, 125.25, 126.37, 127.64, 128.10, 128.72, 129.82, 129.90, 132.99, 137.66, 140.65, 141.17, 153.39; IR (thin film) 2955s, 2928s, 2857s, 1561s, 1480s, 1352s, 1105s cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{42}\text{H}_{41}\text{O}_2^{79}\text{Br}_2$ ($\text{M}+\text{H}^+$) 735.1473, found 735.1495. $[\alpha]_{\text{D}}^{20} = -85.4$ (c 1.0, CH_2Cl_2).



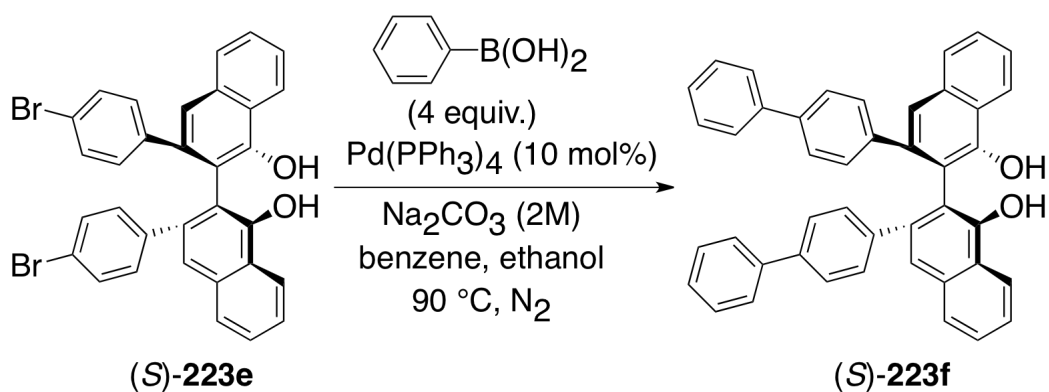
To a flame-dried 25 mL round bottom flask were added (*S*)-**239b** (184 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol) and DME (1.7 mL) under argon. To the stirred mixture were added phenylboronic acid (107 mg, 0.88 mmol) and Na_2CO_3 (aq. 2 M, 0.7 mL). The mixture was stirred at 90 $^\circ\text{C}$ for 14 h with an argon balloon attached. After cooling down to room temperature, the mixture was filtered through a pad of Celite and washed with CH_2Cl_2 . After removal of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with NH_4Cl (sat. aq. 5 mL) and brine (5 mL). The organic layer was separated, dried over MgSO_4 , filtered through Celite and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 mm x 250 mm, CH_2Cl_2 :hexanes 1:2). The purified and concentrated product was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 $^\circ\text{C}$, BBr_3 (1 M in CH_2Cl_2 , 1.5 mL, 1.5 mmol) was added dropwise to the mixture at 0 $^\circ\text{C}$. The mixture was stirred at room

temperature overnight with an argon balloon attached to the flask. The mixture was then cooled to 0 °C and H₂O (8 mL) was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (5 mL×3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm x 260 mm, CH₂Cl₂:hexanes 1:2) gave (*S*)-**240ah** as a light yellow solid in 74% isolated yield over two steps (130 mg, 0.185 mmol). mp 225-226 °C; R_f = 0.26 (1:1 CH₂Cl₂/hexanes). Spectral data for **240ah**: ¹H NMR (CDCl₃, 500 MHz) δ 0.89 (t, 6H, *J* = 7.5 Hz), 1.27-1.32 (m, 4H), 1.47-1.54 (m, 4H), 2.47 (t, 4H, *J* = 7.5 Hz), 5.84 (s, 2H), 6.59 (d, 4H, *J* = 8.0 Hz), 6.78 (d, 4H, *J* = 8.0 Hz), 7.36-7.40 (m, 4H), 7.48-7.52 (m, 4H), 7.78-7.88 (m, 8H), 8.55 (d, 2H, *J* = 0.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 13.90, 22.23, 33.51, 35.15, 113.36, 120.75, 121.63, 123.15, 127.02, 127.41, 127.44, 127.59, 128.24, 128.69, 128.89, 133.81, 137.46, 138.25, 140.78, 141.10, 141.33, 150.53; IR (thin film) 3503br s, 2928s, 1559s, 1489s, 1387s, 1215s cm⁻¹; HRMS (ESI⁻) *m/z* calculated for C₅₂H₄₅O₂ (M-H⁺) 701.3420, found 701.3411. [α]_D²⁰ = -86.8 (c 1.0, CH₂Cl₂).



To a flame-dried 25 mL round bottom flask were added (*S*)-**239b** (184 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol) and DME (1.7 mL) under argon. To the stirred mixture were added anthracene-9-boronic acid (195 mg, 0.88 mmol) and Na₂CO₃ (aq. 2 M, 0.7 mL). The mixture was stirred at 90 °C for 14 h with an argon balloon attached. After cooling down to room temperature, the mixture was filtered through a pad of Celite and washed with CH₂Cl₂. After removal of the solvent, the residue was dissolved in CH₂Cl₂ (20 mL) and washed with NH₄Cl (sat. aq. 5 mL) and brine (5 mL). The organic layer was separated, dried over MgSO₄, filtered through Celite and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 mm x 250 mm, CH₂Cl₂:hexanes 1:2). The purified and concentrated product was dissolved in CH₂Cl₂ (4 mL) and cooled to 0 °C, BBr₃ (1 M in CH₂Cl₂, 1.5 mL, 1.5 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred at rt overnight with an argon balloon attached to the flask. The mixture was then cooled to 0 °C and H₂O (8 mL) was added dropwise. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (5 mL×3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (20 mm x 260 mm, CH₂Cl₂:hexanes 1:2) gave (*S*)-**240x** as a light yellow solid in 53% isolated yield over two steps (120 mg, 0.133 mmol). mp 170-172 °C; R_f = 0.15 (1:2 CH₂Cl₂/hexane). Spectral data for **240x**: ¹H NMR (CDCl₃, 500 MHz) δ 0.96 (t, 6H, *J* = 7.5 Hz), 1.35-1.40 (m, 4H), 1.56-1.62 (m, 4H), 2.57 (t, 4H, *J* = 7.5 Hz), 5.87 (s, 2H), 6.69 (d, 4H, *J* = 8.0 Hz), 6.89 (d, 4H, *J* = 8.0 Hz), 7.30-7.34 (m, 2H), 7.40-7.50 (m, 8H), 7.61 (dd, 2H, *J* = 8.5, 2.0 Hz), 7.72 (d, 2H, *J* = 8.5 Hz), 7.82 (d, 2H, *J* = 8.5 Hz), 7.98 (d, 2H, *J* = 8.5 Hz),

8.04-8.09 (m, 4H), 8.42 (d, 2H, $J = 1.0$ Hz), 8.53 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.97, 22.34, 33.63, 35.26, 113.59, 121.84, 122.91, 125.10, 125.14, 125.17, 125.44, 125.51, 126.76, 126.95, 127.64, 127.69, 128.35, 128.47, 128.82, 130.42, 130.53, 131.07, 131.45, 131.49, 133.94, 136.03, 136.94, 137.63, 141.11, 141.41, 150.54 (1 sp^2 C not located); IR (thin film) 3520br s, 3052m, 2928s, 1559s, 1456s, 1387s cm^{-1} ; HRMS (ESI $^-$) m/z calculated for $\text{C}_{68}\text{H}_{53}\text{O}_2$ ($\text{M}-\text{H}^+$) 901.4046, found 901.4084. $[\alpha]_{\text{D}}^{20} = -497.9$ (c 1.0, CH_2Cl_2).

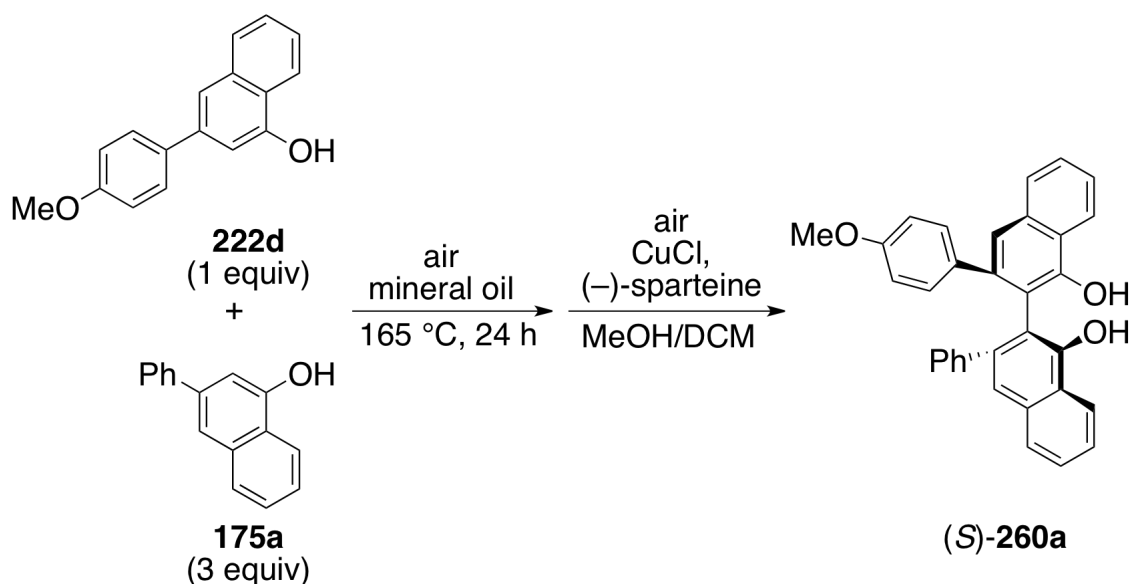


The reaction of (*S*)-**223e** (179 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol), benzene (3 mL), Na_2CO_3 (aq. 2 M, 1.5 mL), phenylboronic acid (146 mg, 1.20 mmol) and ethanol (1.5 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (20 mm x 200 mm, CH_2Cl_2 :hexanes 2:3) gave (*S*)-**223f** as a white solid (125 mg, 0.212 mmol, 71%). mp 154-159 °C; $R_f = 0.29$ (2:1 CH_2Cl_2 /hexanes). Spectral data for **223f**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.90 (s, 2H), 6.70-6.74 (m, 4H), 7.20-7.24 (m, 4H), 7.27-7.32 (m, 2H), 7.36-7.40 (m, 6H), 7.49-7.52 (m, 4H), 7.55-7.60 (m, 4H), 7.78-7.81 (m, 2H), 8.36-8.39 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 112.66, 122.07, 122.84, 123.01, 125.76, 126.11, 126.90, 127.23, 127.60, 127.75, 128.72, 129.34, 134.66, 139.24, 139.26, 140.21,

140.63, 150.41; IR (thin film) 3511br s, 3056s, 1570s, 1487s, 1383s, 1221s cm^{-1} ; HRMS (ESI+) m/z calcd for $\text{C}_{44}\text{H}_{31}\text{O}_2$ ($\text{M}+\text{H}^+$) 591.2324, meas 591.2335. $[\alpha]_{\text{D}}^{20} = -167.3$ (c 1.0, CH_2Cl_2).

6.3.4 Preparation of *CI*-VANOL derivatives

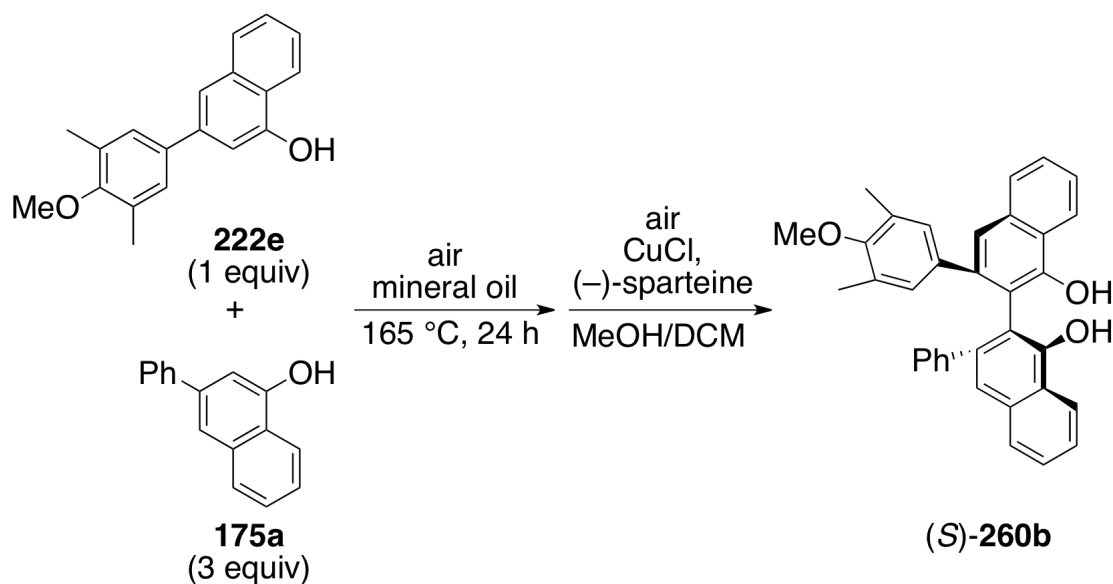
Procedure R



Oxidative phenol-coupling:^{13g,73} To a 250 mL flame-dried three neck round bottom flask equipped with a cooling condenser was added 3-(4-methoxyphenyl)naphthalen-1-ol **222d** (1.00 g, 4.00 mmol), 3-phenylnaphthalen-1-ol **175a** (2.64 g, 12.0 mmol) and mineral oil (24 mL). Airflow was introduced from one side neck via a needle located one inch above the mixture. The airflow rate is about one bubble per second. The mixture was stirred at 165 °C for 24 h. Purification of the crude product by column chromatography on silica gel (1st column, 35 mm x 250 mm, CH_2Cl_2 :hexanes 1:1; 2nd column, 35 mm x 250 mm, EtOAc:hexanes, 1:20) gave racemic **260a** as a light yellow solid (980 mg, 2.09 mmol, 52%).

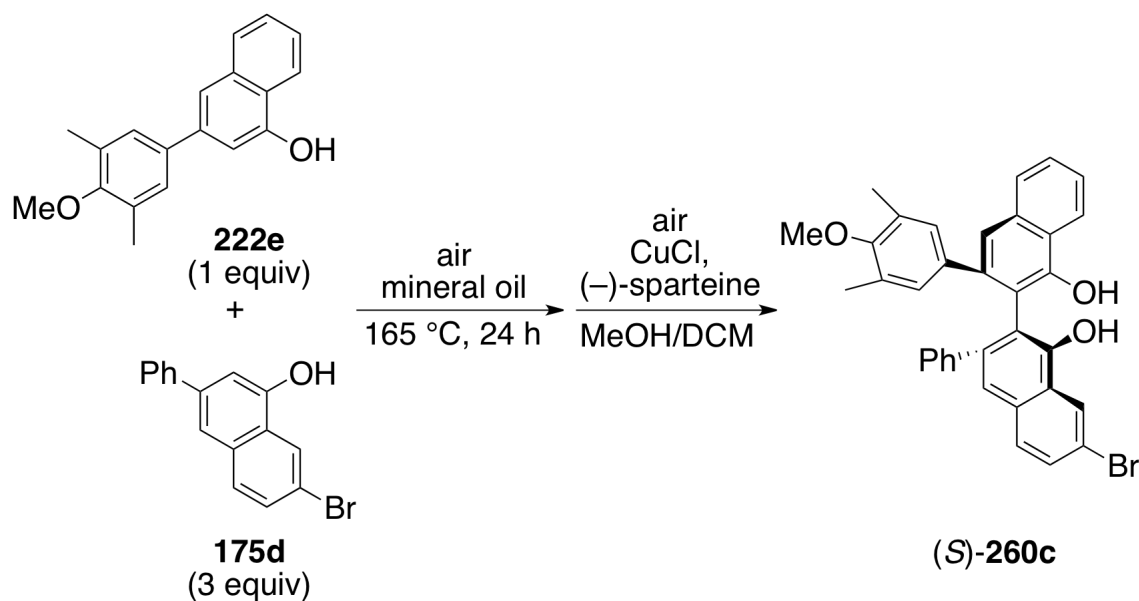
De-racemization:^{13c} To a 100 mL round bottom flask was added (–)-sparteine (819 mg, 3.50 mmol), CuCl (168 mg, 1.70 mmol) and MeOH (30 mL) under an atmosphere of air. The reaction mixture was sonicated in a water bath for 60 minutes with exposure to air. The flask was then sealed with a septum and purged with argon, which was introduced by a needle under the surface for 60 minutes. At the same time, to a 500 mL flame-dried round bottom flask was added racemic **260a** (468 mg, 1.00 mmol) and CH₂Cl₂ (120 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 **260a** 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 NaHCO₃ (sat. aq. 13 mL), H₂O (50 mL) and most of the organic solvent was removed under reduced pressure. The residue was then extracted with CH₂Cl₂ (50 mL × 3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (25 mm × 200 mm, EtOAc:hexanes 1:20) gave the product (*S*)-**260a** as an off-white foamy solid (82 mg, 0.175 mmol, 18%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 28.22 min for (*R*)-**260a** (minor) and *R*_t = 31.71 min for (*S*)-**260a** (major). mp 112-117 °C; *R*_f = 0.15 (2:1 CH₂Cl₂/hexanes). Spectral data for **260a**: ¹H NMR (CDCl₃, 500 MHz) δ 3.69 (s, 3H), 5.78 (s, 1H), 5.81 (s, 1H), 6.49-6.52 (m, 2H), 6.55-6.58 (m, 2H), 6.67 (dd, 2H, *J* = 8.5, 1.5 Hz), 6.94-6.98 (m, 2H), 7.05 (t, 1H, *J* = 7.5 Hz), 7.28 (s, 1H), 7.34

(s, 1H), 7.50-7.59 (m, 4H), 7.74-7.80 (m, 2H), 8.31-8.35 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 55.39, 112.97, 113.09, 113.19, 121.99, 122.31, 122.97, 123.02, 123.04, 123.16, 125.70, 125.89, 126.84, 127.67, 127.69, 127.74, 127.82, 127.93, 129.08, 130.23, 133.02, 134.82, 134.88, 140.45, 140.52, 140.94, 150.55, 158.71 (1 sp^2 C not located); IR (thin film) 3507br s, 3054m, 2930m, 1570s, 1493s, 1383s, 1246s cm^{-1} ; HRMS (ESI $^-$) m/z calculated for $\text{C}_{33}\text{H}_{23}\text{O}_3$ ($\text{M}-\text{H}^+$) 467.1647, found 467.1638. $[\alpha]_{\text{D}}^{20} = -244.2$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**260a** (HPLC).

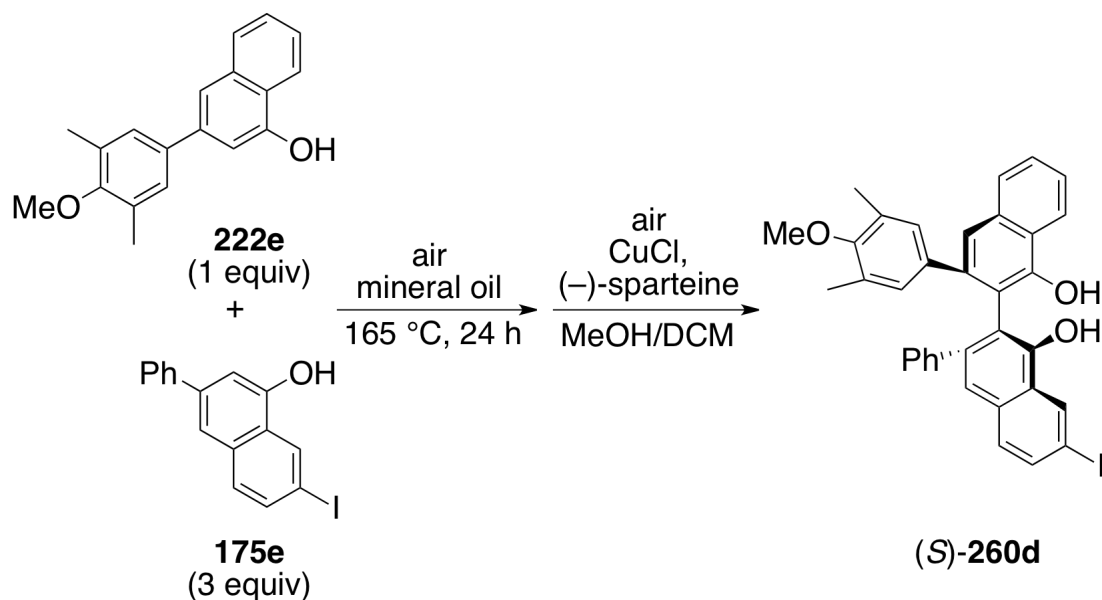


The synthesis of racemic **260b** was performed according to the general procedure (Procedure R) with 3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **222e** (1.11 g, 4 mmol) and 3-phenyl-1-naphthol **175a** (2.64 g, 12 mmol). Purification by column chromatography on silica gel (1st column, silica gel, 35 mm x 250 mm, CH_2Cl_2 :hexanes 1:1; 2nd column, silica gel, 35 mm x 250 mm, EtOAc:hexanes 1:20) gave racemic **260b** as a light yellow solid (998 mg, 2.01 mmol, 50%). After de-racemization of racemic **260b** (496 mg, 1.00 mmol) with CuCl (168 mg, 1.70 mmol) and (–)-sparteine (819 mg, 3.50 mmol), the crude product was purified by column

chromatography on silica gel (25 mm × 180 mm column, CH₂Cl₂:hexanes 2:1) to afford (*S*)-**260b** as a light yellow solid (142 mg, 0.29 mmol, 29%). The optical purity was determined to be >99% ee by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 24.21 min for (*R*)-**260b** (minor) and *R*_t = 26.81 min for (*S*)-**260b** (major). mp 71-76 °C; *R*_f = 0.14 (2:1 CH₂Cl₂/hexanes). Spectral data for **260b**: ¹H NMR (CDCl₃, 500 MHz) δ 1.92 (s, 6H), 3.61 (s, 3H), 5.80 (s, 1H), 5.83 (s, 1H), 6.20 (s, 2H), 6.64-6.60 (m, 2H), 6.94-6.98 (m, 2H), 7.04-7.08 (m, 1H), 7.28 (s, 1H), 7.32 (s, 1H), 7.51-7.58 (m, 4H), 7.74-7.78 (m, 2H), 8.32-8.35 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.73, 59.71, 112.79, 112.91, 121.48, 121.88, 122.66, 122.76, 122.80, 125.49, 125.62, 126.49, 127.26, 127.42, 127.46, 127.56, 127.59, 128.93, 129.46, 129.47, 134.52, 134.57, 135.54, 140.18, 140.46, 140.60, 150.24, 150.36, 155.83 (1 sp² C not located); IR (thin film) 3510br s, 2930s, 1570s, 1491s, 1385s, 1225s cm⁻¹; HRMS (ESI⁻) *m/z* calculated for C₁₇H₁₃O₂ (M-H⁺) 495.1960, found 495.1952. [α]_D²⁰ = -225.0 (c 1.0, CH₂Cl₂) on >99% ee (*S*)-**260b** (HPLC).

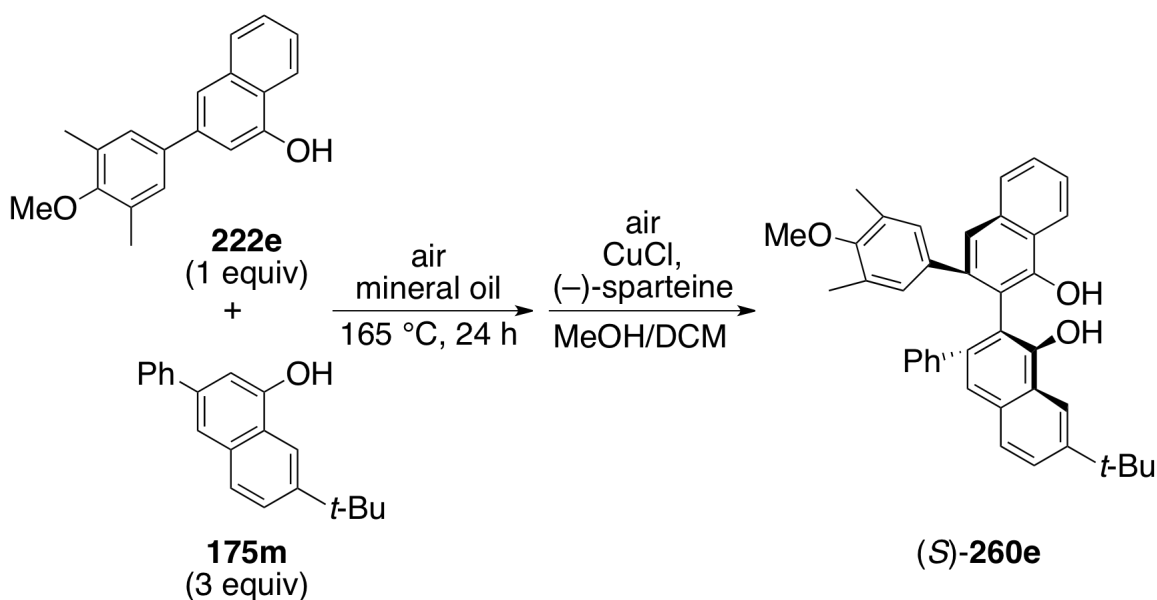


The synthesis of racemic **260c** was performed according to the general procedure (Procedure R) with 3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **222e** (1.11 g, 4 mmol) and 7-bromo-3-phenyl-1-naphthol **175d** (3.59 g, 12 mmol). Purification by column chromatography on silica gel (1st column, silica gel, 35 mm x 250 mm, CH₂Cl₂:hexanes 1:2; 2nd column, silica gel, 35 mm x 250 mm, EtOAc:hexanes 1:20) gave racemic **260c** as a light yellow solid (537 mg, 0.93 mmol, 23%). After de-racemization of racemic **260c** (463 mg, 0.805 mmol) with CuCl (136 mg, 1.37 mmol) and (–)-sparteine (660 mg, 2.82 mmol), the crude product was purified by column chromatography on silica gel (30 mm x 200 mm column, CH₂Cl₂:hexanes 2:1) to afford (*S*)-**260c** as an off-white solid (272 mg, 0.47 mmol, 59%). The optical purity was determined to be >99% ee by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 28.98 min for (*R*)-**260c** (minor) and *R*_t = 32.42 min for (*S*)-**260c** (major). mp 124-128 °C; *R*_f = 0.26 (2:1 CH₂Cl₂/hexanes). Spectral data for **260c**: ¹H NMR (CDCl₃, 500 MHz) δ 1.94 (s, 6H), 3.61 (s, 3H), 5.75 (s, 1H), 5.82 (s, 1H), 6.18 (s, 2H), 6.62-6.65 (m, 2H), 6.94-6.98 (m, 2H), 7.05-7.09 (m, 1H), 7.27 (s, 1H), 7.28 (s, 1H), 7.51-7.57 (m, 2H), 7.59-7.63 (m, 2H), 7.74-7.77 (m, 1H), 8.31-8.34 (m, 1H), 8.49-8.50 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.77, 59.72, 112.55, 114.13, 119.69, 121.61, 121.64, 122.72, 122.79, 123.85, 125.18, 125.60, 126.72, 127.35, 127.57, 127.62, 128.85, 129.24, 129.43, 129.56, 130.86, 132.87, 134.65, 135.41, 139.82, 140.29, 141.21, 149.53, 150.19, 155.93; IR (thin film) 3509br s, 3054m, 2932m, 1570s, 1487s, 1375s, 1224s cm⁻¹; HRMS (ESI+) *m/z* calculated for C₃₅H₂₈O₃⁷⁹Br (M-H⁺) 575.1222, found 575.1233. [*α*]_D²⁰ = –234.9 (c 1.0, CH₂Cl₂) on >99% ee (*S*)-**260c** (HPLC).



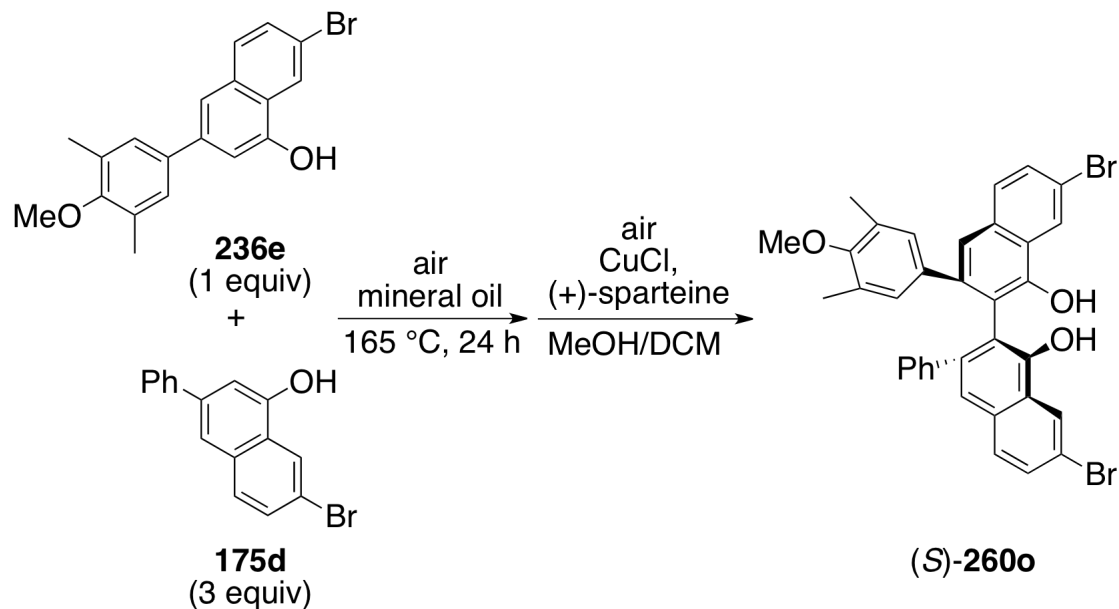
The synthesis of racemic **260d** was performed according to the general procedure (Procedure R) with 3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **222e** (1.11 g, 4 mmol) and 7-iodo-3-phenyl-1-naphthol **175m** (4.15 g, 12 mmol). Purification by column chromatography on silica gel (1st column, silica gel, 35 mm x 250 mm, CH₂Cl₂:hexanes 1:2; 2nd column, silica gel, 35 mm x 250 mm, EtOAc:hexanes 1:20) gave racemic **260d** as a light yellow solid (590 mg, 0.95 mmol, 24%). After de-racemization of racemic **260d** (450 mg, 0.723 mmol) with CuCl (122 mg, 1.23 mmol) and (-)-sparteine (593 mg, 2.53 mmol), the crude product was purified by column chromatography on silica gel (30 mm x 200 mm column, CH₂Cl₂:hexanes 2:1) to afford (*S*)-**260d** as a light yellow (183 mg, 0.29 mmol, 41%). The optical purity was determined to be >99% ee by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 30.86 min (minor) for (*R*)-**260d** and *R*_t = 34.17 min for (*S*)-**260d** (major). mp 128-132 °C; *R*_f = 0.26 (2:1 CH₂Cl₂/hexanes). Spectral data for **260d**: ¹H NMR (CDCl₃, 500 MHz) δ 1.94 (s, 6H), 3.61 (s, 3H), 5.74 (s, 1H), 5.80 (s, 1H), 6.18 (s,

2H), 6.63 (dd, 2H, $J = 8.0, 1.0$ Hz), 6.96 (t, 2H, $J = 8.0$ Hz), 7.05-7.09 (m, 1H), 7.26 (s, 1H), 7.28 (s, 1H), 7.49 (d, 1H, $J = 8.5$ Hz), 7.52-7.57 (m, 2H), 7.74-7.79 (m, 2H), 8.31-8.34 (m, 1H), 8.72-8.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 15.78, 59.72, 91.08, 112.52, 113.98, 121.66, 122.73, 122.79, 124.27, 125.60, 126.73, 127.35, 127.57, 127.62, 128.84, 129.12, 129.42, 129.57, 131.76, 133.14, 134.65, 135.41, 136.03, 139.82, 140.30, 141.42, 149.29, 150.19, 155.94 (1 sp^2 C not located); IR (thin film) 3507br s, 2932m, 1570s, 1485s, 1373s, 1225s cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{35}\text{H}_{28}\text{O}_3\text{I}$ ($\text{M}+\text{H}^+$) 623.1083, found 623.1067. $[\alpha]_{\text{D}}^{20} = -223.8$ (c 1.0, CH_2Cl_2) on >99% *ee* (*S*)-**260d** (HPLC).



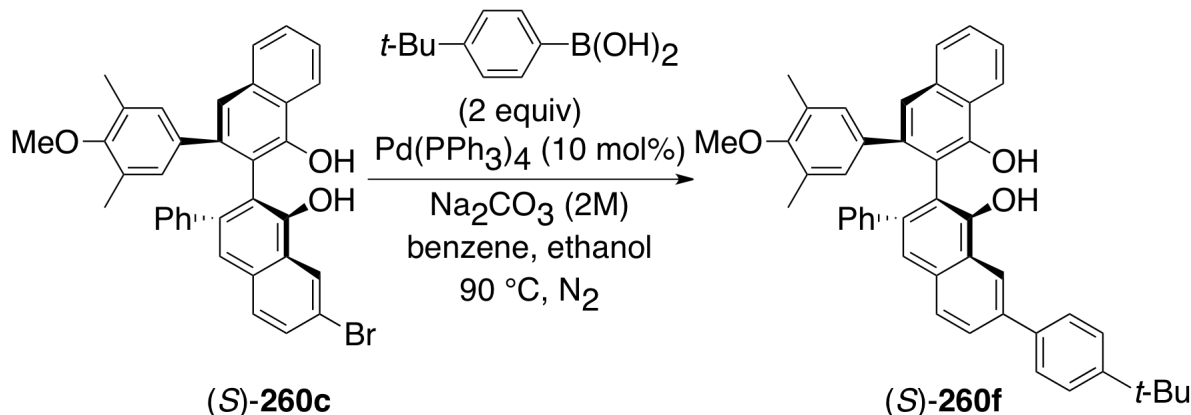
The synthesis of racemic **260e** was performed according to the general procedure (Procedure R) with 3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **222e** (1.11 g, 4 mmol) and 7-(*tert*-butyl)-3-phenylnaphthalen-1-ol **175m** (3.31 g, 12 mmol). Purification by column chromatography on silica gel (1st column, silica gel, 35 mm x 250 mm, CH_2Cl_2 :hexanes 1:2; 2nd column, silica gel, 35 mm x 300 mm, EtOAc:hexanes 1:20) gave racemic **260e** as a light yellow

solid (290 mg, 0.53 mmol, 13%). After de-racemization of racemic **260e** (127 mg, 0.23 mmol) with CuCl (39 mg, 0.39 mmol) and (–)-sparteine (188 mg, 0.80 mmol), the crude product was purified by column chromatography on silica gel (20 mm × 200 mm column, CH₂Cl₂:hexanes 2:1) to afford (*S*)-**260e** as an off-white solid (80 mg, 0.145 mmol, 63%). The optical purity was determined to be >99% ee by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 15.47 min for (*R*)-**260e** (minor) and *R*_t = 17.08 min for (*S*)-**260e** (major). mp 125-130 °C; *R*_f = 0.33 (2:1 CH₂Cl₂/hexanes). Spectral data for **260e**: ¹H NMR (CDCl₃, 500 MHz) δ 1.47 (s, 9H), 1.94, (s, 6H), 3.62 (s, 3H), 5.76 (s, 1H), 5.83 (s, 1H), 6.23 (s, 2H), 6.63-6.66 (m, 2H), 6.95 (t, 2H, *J* = 7.5 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 7.29 (d, 2H, *J* = 2.0 Hz), 7.51-7.56 (m, 2H), 7.65 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.72 (d, 1H, *J* = 8.5 Hz), 7.74-7.77 (m, 1H), 8.27 (d, 1H, *J* = 1.5 Hz), 8.32-8.35 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 15.76, 31.35, 35.20, 59.71, 112.70, 113.13, 117.56, 121.50, 121.54, 122.66, 122.81, 125.46, 126.37, 127.28, 127.36, 127.40, 127.61, 128.94, 129.48, 129.50, 132.82, 134.59, 135.67, 139.86, 140.41, 140.57, 148.62, 150.26, 150.29, 155.91 (2 sp² C not located); IR (thin film) 3517br s, 2959s, 1597s, 1487s, 1387s, 1225s cm⁻¹; HRMS (ESI+) *m/z* calculated for C₃₉H₃₇O₃ (M+H⁺) 553.2743, found 553.2740. [α]_D²⁰ = –214.8 (c 1.0, CH₂Cl₂) on >99% ee (*S*)-**260e** (HPLC).



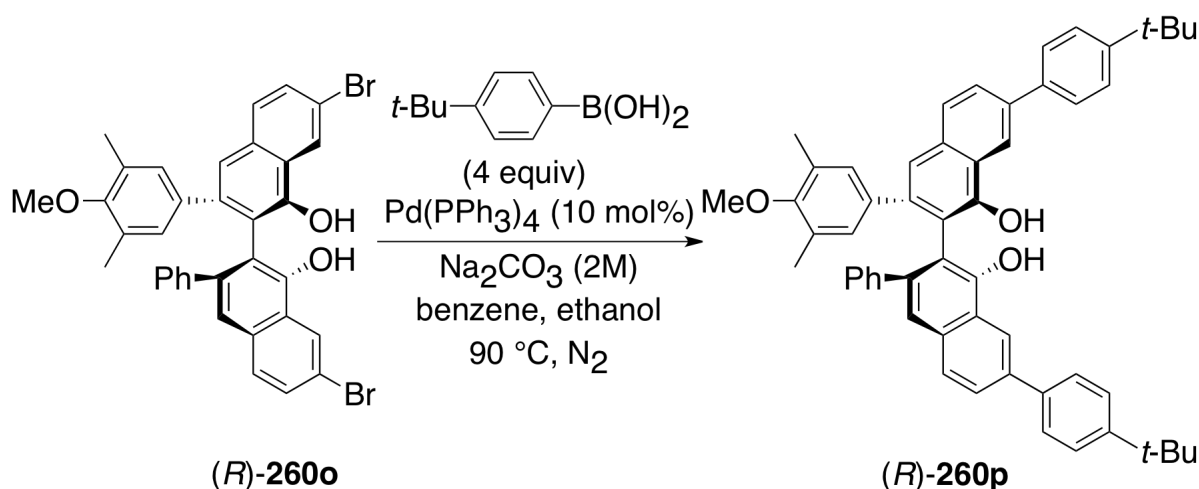
The synthesis of racemic **260o** was performed according to the general procedure (Procedure R) with 7-bromo-3-(4-methoxy-3,5-dimethylphenyl)naphthalen-1-ol **236e** (1.29 g, 3.60 mmol) and 7-bromo-3-phenyl-1-naphthol **175d** (3.23 g, 10.8 mmol). Purification by column chromatography on silica gel (1st column, silica gel, 35 mm x 250 mm, CH₂Cl₂:hexanes 2:5; 2nd column, silica gel, 35 mm x 250 mm, EtOAc:hexanes 1:20) gave racemic **260o** as a light yellow solid (1.19 g, 1.82 mmol, 51%). After de-racemization of racemic **260o** (785 mg, 1.20 mmol) with CuCl (202 mg, 2.04 mmol) and (+)-sparteine (983 mg, 4.20 mmol), the crude product was purified by column chromatography on silica gel (30 mm x 200 mm column, CH₂Cl₂:hexanes 1:1) to afford (*R*)-**260o** as a light yellow solid (770 mg, 1.18 mmol, 98%). The optical purity was determined to be >99% ee by HPLC analysis (Pirkle D-Phenylglycine column, 98:2 hexane/*i*PrOH at 254 nm, flow-rate: 1.0 mL/min). Retention times: *R*_t = 40.65 min for (*R*)-**260o** (major) and *R*_t = 45.82 min for (*S*)-**260o** (minor). mp 127-133 °C; *R*_f = 0.35 (2:1 CH₂Cl₂/hexanes). Spectral data for **260o**: ¹H NMR (CDCl₃, 500 MHz) δ 1.93 (s, 6H), 3.61 (s, 3H), 5.77 (s, 1H), 5.80 (s, 1H), 6.16

(s, 2H), 6.59-6.61 (m, 2H), 6.94-6.98 (m, 2H), 7.06-7.10 (m, 1H), 7.23 (s, 1H), 7.26 (s, 1H), 7.59-7.64 (m, 4H), 8.49 (d, 2H, $J = 1.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 15.76, 59.72, 113.73, 113.77, 119.67, 119.82, 121.39, 121.75, 123.81, 123.85, 125.16, 125.26, 126.82, 127.38, 128.78, 129.25, 129.27, 129.34, 129.67, 130.95, 131.00, 132.91, 132.98, 135.02, 139.64, 140.87, 141.02, 149.38, 149.48, 156.07; IR (thin film) 3509br s, 2926s, 1561s, 1485s, 1375s, 1225s cm^{-1} ; HRMS (ESI $^-$) m/z calcd for $\text{C}_{35}\text{H}_{25}\text{O}_3^{79}\text{Br}_2$ ($\text{M}-\text{H}^+$) 651.0170, meas 651.0153. $[\alpha]_{\text{D}}^{20} = +160.8$ (c 1.0, CH_2Cl_2) on >99% *ee* (*R*)-**260o** (HPLC).



The reaction of (*S*)-**260c** (115 mg, 0.20 mmol), tetrakis(triphenylphosphine)palladium (11.6 mg, 0.013 mmol), benzene (2 mL), Na_2CO_3 (aq. 2 M, 0.4 mL), 4-*tert*-butylphenylboronic acid (54 mg, 0.30 mmol) and ethanol (1 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (20 mm x 200 mm, CH_2Cl_2 :hexanes 3:2) gave (*S*)-**260f** as an off-white solid (73 mg, 0.116 mmol, 58%). mp 156-161 °C; $R_f = 0.38$ (2:1 CH_2Cl_2 /hexanes). Spectral data for **260f**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.39 (s, 9H), 1.94 (s, 6H), 3.61 (s, 3H), 5.83 (s, 1H), 5.86 (s, 1H), 6.23 (s, 2H), 6.66-6.69 (dm, 2H), 6.95-6.99 (m, 2H), 7.05-7.09 (m, 1H), 7.29 (s, 1H), 7.33 (d, 1H, $J = 0.5$ Hz), 7.51-7.56 (m, 4H), 7.74-7.78 (m, 3H),

7.83-7.84 (m, 2H), 8.33-8.36 (m, 1H), 8.55-8.56 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 15.77, 31.39, 34.59, 59.71, 112.99, 113.18, 120.25, 121.50, 121.62, 122.78, 122.80, 123.14, 125.49, 125.86, 126.50, 126.99, 127.04, 127.29, 127.43, 127.60, 128.09, 128.93, 129.48, 129.50, 133.57, 134.60, 135.58, 138.06, 138.11, 140.25, 140.51, 150.28, 150.53, 150.61, 155.90 (1 sp^2 C not located); IR (thin film) 3519br s, 2959s, 1570s, 1491s, 1387s, 1225s cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{45}\text{H}_{41}\text{O}_3$ ($\text{M}+\text{H}^+$) 629.3056, found 629.3069. $[\alpha]_{\text{D}}^{20} = -219.2$ (c 1.0, CH_2Cl_2)

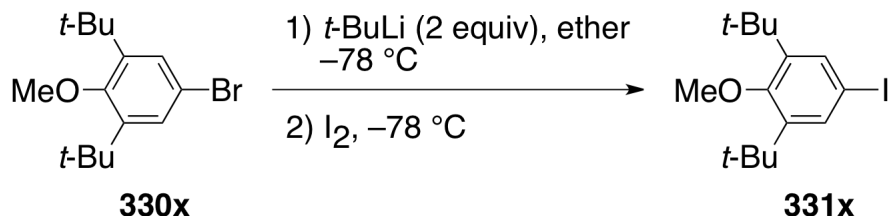


The reaction of (*R*)-**260o** (262 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol), benzene (4 mL), Na_2CO_3 (aq. 2 M, 2 mL), 4-*tert*-butylphenylboronic acid (285 mg, 1.60 mmol) and ethanol (2 mL) was performed according to Procedure K. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH_2Cl_2 :hexanes 1:2) gave (*R*)-**260o** as an off-white solid (133 mg, 0.175 mmol, 44%). mp 158-164 °C; R_f = 0.37 (1:1 CH_2Cl_2 /hexanes). Spectral data for **260o**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.40 (s, 18H), 1.95 (s, 6H), 3.63 (s, 3H), 5.89 (s, 1H), 5.92 (s, 1H), 6.26 (s, 2H), 6.69-6.71 (m, 2H), 6.97-7.01 (m, 2H), 7.06-7.10 (m, 1H), 7.31 (s, 1H), 7.35 (s, 1H), 7.52-7.56 (m, 4H), 7.74-7.79 (m, 4H), 7.81-7.87 (m,

4H), 8.57-8.59 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 15.76, 31.38, 34.58, 59.71, 113.21, 113.31, 120.26, 120.42, 121.24, 121.62, 123.07, 123.13, 125.85, 126.51, 126.97, 127.03, 127.05, 127.31, 128.09, 128.11, 128.93, 129.46, 129.51, 133.57, 133.61, 135.60, 138.05, 138.07, 138.08, 138.11, 140.23, 140.37, 140.50, 150.46, 150.50, 150.51, 150.61, 155.87 (2 sp^2 C not located); IR (thin film) 3513br s, 2959s, 1559s, 1458s, 1387s, 1265s cm^{-1} ; HRMS (ESI-) m/z calcd for $\text{C}_{55}\text{H}_{51}\text{O}_3$ ($\text{M}-\text{H}^+$) 759.3838, meas 759.3824. $[\alpha]_{\text{D}}^{20} = +5.7$ (c 1.0, CH_2Cl_2).

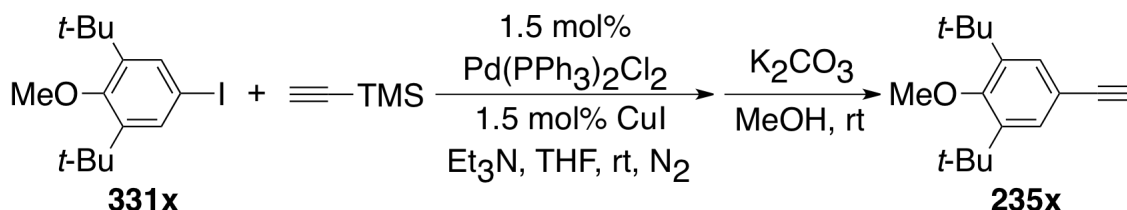
6.4 Experimental for chapter five

6.4.1 Preparation of aryl alkyne **331x**



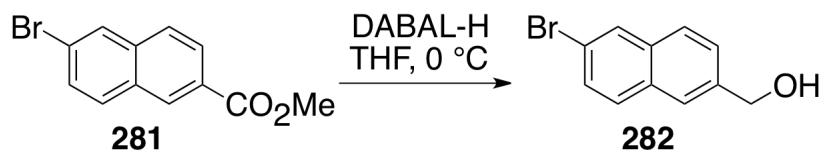
1,3-di-tert-butyl-5-iodo-2-methoxybenzene 331x: To a 1 L flame-dried flask filled with argon was added 5-bromo-1,3-di-*tert*-butyl-2-methoxybenzene **330x** (34.6 g, 100 mmol) and dry Et₂O (250 mL). The mixture was stirred until the bromide was dissolved at room temperature and then the flask was submerged into a -78 °C bath, followed by slow addition of *t*-BuLi (118 mL, 200 mmol, 1.7 M in hexanes) and then the solution was stirred at -78 °C for 1 h. At the same time, to a flame-dried 250 mL flask iodine (27.9 g, 110 mmol) was dissolved in dry Et₂O (150 mL). The iodine solution was then cooled to -78 °C and transferred to the aryllithium solution via cannula under argon. The mixture was warmed up gradually to room temperature and stir for an additional 2 h. The reaction was quenched by pouring the reaction mixture slowly into a Na₂S₂O₃ solution (aq. 5%, 200 mL) and stirred for 20 minutes. The organic layer was separated and the aqueous layer was extracted with Et₂O (100 mL × 3). the combined organic layer was washed with H₂O (100 mL × 2) and NaCl (aq. sat.), dried over MgSO₄ and filtered through Celite. Removal of the solvent by rotary evaporation afforded the crude product as a yellow liquid in 100% yield. The ¹H NMR spectrum of the crude was clean, and it was used in the next step without purification. Spectral data for **331x**: ¹H NMR (CDCl₃, 500 MHz) δ 1.38 (s, 18H),

3.65 (s, 3H), 7.48 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 31.87, 35.76, 64.39, 88.13, 135.68, 146.42, 159.66.



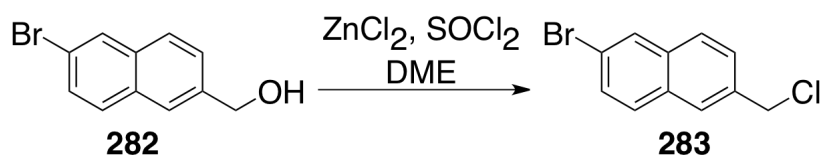
1,3-di-tert-butyl-5-ethynyl-2-methoxybenzene **235x**:¹¹² The reaction of 1,3-di-*tert*-butyl-5-iodo-2-methoxybenzene **331x** from the above and trimethylsilyl acetylene (15.5 mL, 110 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm × 200 mm, hexanes) gave **235x** as a colorless solid (22.1 g, 90.6 mmol, 91%). R_f = 0.16 (hexanes). Spectral data for **235x**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.40 (s, 18H), 2.98 (s, 1H), 3.66 (s, 3H), 7.37 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 31.90, 35.72, 64.37, 75.49, 84.52, 116.24, 130.60, 144.04, 160.47.

6.4.2 Preparation of aryl acetic acids



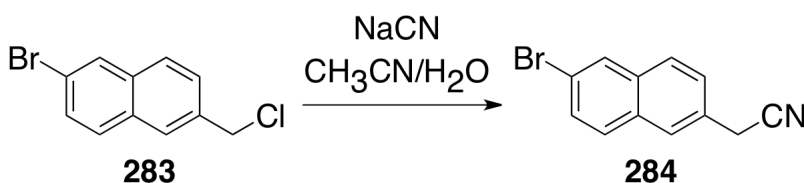
(6-bromonaphthalen-2-yl)methanol **282**:⁹⁹ To a flame-dried round bottom flask was added methyl 6-bromo-2-naphthoate **281** (31.8 g, 120 mmol) and dry THF (300 mL) under argon. The solution was cooled to 0 °C and DIBAL-H (1 M in heptane, 252 mL, 252 mmol) was added dropwise to the mixture. The mixture was warmed up to room temperature and stirred overnight.

The resulting mixture was poured slowly into HCl (4N aq. 200 mL) at 0 °C. The mixture was stirred for 30 min and the organic layer was separated. The organic layer was washed with HCl (4N aq. 48 mL), NaHCO₃ (5% aq. 240 mL), and brine (240 mL). The organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. EtOAc (20 mL) and hexanes (160 mL) were added to the product. Filtration by filter paper and drying under vacuum gave **282** as a white solid (27.0 g, 114 mmol, 95%). mp 150-151 °C (lit.⁹⁹ 152-153 °C). Spectral data for **282**: ¹H NMR (CDCl₃, 500 MHz) δ 1.75 (t, 1H, *J* = 0.5 Hz), 4.83 (d, 2H, *J* = 5.5 Hz), 7.48 (dd, 1H *J* = 8.5, 1.5 Hz), 7.53 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.68 (d, 1H, *J* = 8.5 Hz), 7.73 (d, 1H, *J* = 8.5 Hz), 7.77 (s, 1H), 7.98 (d, 1H, *J* = 2.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 65.25, 119.83, 125.28, 126.16, 127.42, 129.52, 129.59, 129.78, 131.80, 133.98, 138.85; IR (thin film) 3276s, 1591s, 1269s, 1129s, 1013s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 238 M⁺ (32, ⁸¹Br), 236 M⁺ (35, ⁷⁹Br), 209 (9, ⁸¹Br), 207 (12, ⁷⁹Br), 157 (7), 139 (20), 128 (100).



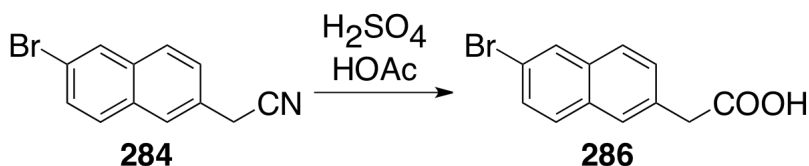
2-bromo-6-(chloromethyl)naphthalene **283**:⁹⁹ To a 250 mL round bottom flask was added (6-bromonaphthalen-2-yl)methanol **282** (1.90, 8.00 mmol), ZnCl₂ (27.2 mg, 0.20 mmol) and DME (20 mL). The reaction mixture was cooled to 0 °C and SOCl₂ (1.17 mL, 16 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 3 h, and then room temperature overnight. The solvent was removed by rotary evaporation. Hexanes (25 mL) was added to the crude product. Filtration by filter paper and drying under vacuum gave **283** as a white solid (2.00

g, 7.80 mmol, 98%). mp 118-119 °C (lit.⁹⁹ 130-131 °C). Spectral data for **283**: ¹H NMR (CDCl₃, 500 MHz) δ 4.71 (s, 2H), 7.51 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.55 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.68 (d, 1H, *J* = 8.5 Hz), 7.74 (d, 1H, *J* = 8.5 Hz), 7.78 (s, 1H), 7.99 (d, 1H, *J* = 2.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 46.27, 120.54, 127.32, 127.43, 127.79, 129.59, 129.82, 129.90, 131.59, 134.13, 135.35; IR (thin film) 1576s, 1456s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 256 M⁺ (23, ⁸¹Br), 254 M⁺ (18, ⁷⁹Br), 221 (66, ⁸¹Br), 219 (69, ⁷⁹Br), 139 (64), 111 (22).

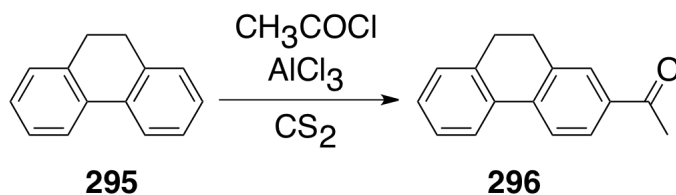


2-(6-bromonaphthalen-2-yl)acetonitrile **284**:⁹⁹ To a 500 mL round bottom flask was added 2-bromo-6-(chloromethyl)naphthalene **283** (27.1 g, 106 mmol), NaCN (6.76 g, 138 mmol), CH₃CN (275 ml) and H₂O (33 mL). The mixture was refluxed overnight. After cooling to room temperature, H₂O (240 mL) was added to the flask. The organic solvent was removed by rotary evaporation and H₂O (320 mL) was added. CH₂Cl₂ (500 ml) was added to the mixture. The organic layer was separated, dried over MgSO₄, filtered through Celite and concentrated to dryness. The crude product was washed with CH₂Cl₂/hexanes (1:25). Filtration by filter paper and drying under vacuum gave **284** as a light yellow solid (25.6 g, 104 mmol, 98%). mp 117-118 °C (lit.⁹⁹ 118-119 °C). Spectral data for **284**: ¹H NMR (CDCl₃, 500 MHz) δ 3.88 (s, 2H), 7.39 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.58 (dd, 1H, *J* = 9.0, 2.0 Hz), 7.69 (d, 1H, *J* = 9.0 Hz), 7.76 (d, 1H, *J* = 9.0 Hz), 7.79 (s, 1H), 7.99 (d, 1H, *J* = 1.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 23.82, 117.50,

120.58, 126.53, 126.84, 127.78, 128.16, 129.35, 129.84, 130.26, 131.77, 133.77; IR (thin film) 1558s, 1456s cm^{-1} .

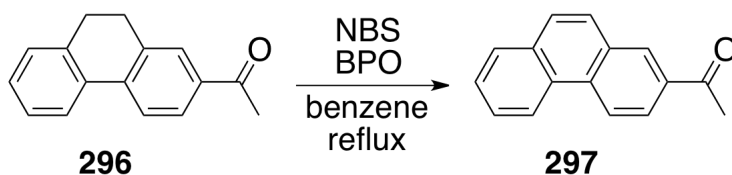


2-(6-bromonaphthalen-2-yl)acetic acid **286**:⁹⁹ To a 500 mL round bottom flask was added 2-(6-bromonaphthalen-2-yl)acetonitrile **284** (21.1 g, 86 mmol), H_2O (85 mL), acetic acid (115 mL) and H_2SO_4 (80 mL). The mixture was stirred at 110 °C for 24 h. After cooling to room temperature, the mixture was poured into ice H_2O (750 mL). The crude product was filtered by filter paper and washed with H_2O (200 mL). The solid was dissolved in acetone, dried over MgSO_4 , filtered through Celite and concentrated to dryness. Drying under vacuum gave **286** as a tan solid (22.7 g, 86 mmol, 100%). mp 177-179 °C (lit.⁹⁹ 178-180 °C). Spectral data for **286**: ^1H NMR (DMSO- d_6 , 500 MHz) δ 3.74 (s, 2H), 7.47 (dd, 1H, $J = 8.5, 1.5$ Hz), 7.61 (dd, 1H, $J = 8.5, 2.0$ Hz), 7.80 (s, 1H), 7.85 (dd, 2H, $J = 9.0, 6.0$ Hz), 8.17 (d, 1H, $J = 2.0$ Hz), 12.39 (s, 1H); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ 40.66, 118.70, 126.85, 127.72, 129.01, 129.15, 129.32, 129.68, 131.40, 132.98, 133.49, 172.43.



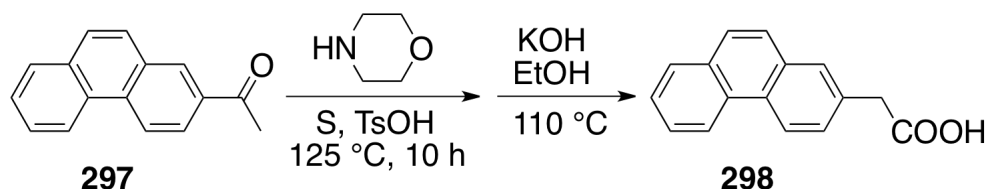
1-(9,10-dihydrophenanthren-2-yl)ethanone **296**:¹⁰⁰ The following procedure was adapted from one for a related compound:⁷⁴ A solution of 9,10-dihydrophenanthrene (10.5 g, 58.2 mmol) and

acetyl chloride (4.14 mL, 58.2 mmol) in CS₂ (60 mL) was added dropwise to a mixture of AlCl₃ (8.54 g, 64.0 mmol) in CS₂ (40 mL) at 0 °C. After stirring at 0 °C for 2 h, the mixture was refluxed overnight. CS₂ was then removed by rotary evaporation. Ice H₂O (90 mL) and H₂SO₄ (9 mL) was added to the residue. The mixture was extracted with CH₂Cl₂ (60 mL x 3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (60 mm x 250 mm, CH₂Cl₂/hexanes 1:1 to 3:1) gave **296** as a white solid upon storing at the refrigerator (10.8 g, 48.6 mmol, 84%). mp 54-57 °C; R_f = 0.21 (1:1 CH₂Cl₂/hexanes). Spectral data for **296**: ¹H NMR (CDCl₃, 500 MHz) δ 2.60-2.94 (m, 4H), 7.24-7.30 (m, 2H), 7.32 (td, 1H, *J* = 8.0, 1.5 Hz), 7.76-7.83 (m, 3H), 7.87 (dd, 1H, *J* = 8.0, 2.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 26.60, 28.77, 28.90, 123.75, 124.37, 127.14, 127.24, 128.03, 128.32, 128.57, 133.42, 135.77, 137.50, 137.98, 139.15, 197.81; IR (thin film) 1684s, 1559s, 1456s cm⁻¹; mass spectrum, *m/z* (% rel intensity) 222 M⁺ (87), 207 (100), 178 (92), 152 (39), 96 (22).



1-(phenanthren-2-yl)ethanone **297**:¹⁰¹ The following procedure was adapted from one for a related compound:¹⁵ To a 250 mL round bottom flask was added 1-(9,10-dihydrophenanthren-2-yl)ethanone **296** (222 mg, 1.00 mmol), *N*-bromosuccinimide (187 mg, 1.05 mmol), benzoyl peroxide (24 mg, 0.10 mmol) and benzene (50 mL). The mixture was refluxed overnight. After cooling to room temperature, the mixture was filtered through a pad of

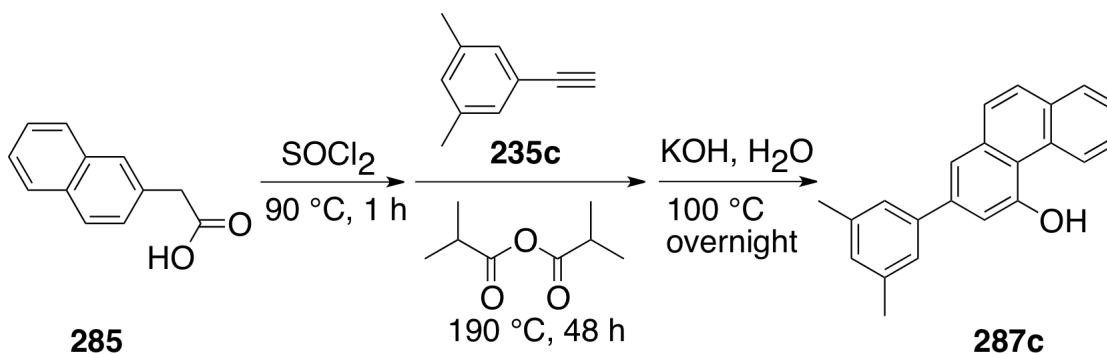
Al₂O₃ (neutral) and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:1 to 2:1) gave **297** as a white solid (154 mg, 0.70 mmol, 70%). mp 141-143 °C; R_f = 0.20 (2:1 CH₂Cl₂/hexanes). Spectral data for **297**: ¹H NMR (CDCl₃, 500 MHz) δ 2.73 (s, 3H), 7.63-7.70 (m, 2H), 7.78-7.79 (m, 2H), 7.88-7.91 (m, 1H), 8.17 (dd, 1H, *J* = 8.0, 2.0 Hz), 8.45 (d, 1H, *J* = 2.0 Hz), 8.66-8.71 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 26.74, 123.11, 123.29, 125.12, 127.00, 127.28, 127.75, 127.89, 128.69, 129.65, 129.81, 131.41, 132.96, 133.40, 134.87, 197.95; mass spectrum, *m/z* (% rel intensity) 220 M⁺ (60), 205 (100), 177 (68), 151 (26), 111 (15).



2-phenanthreneacetic acid **298**:¹⁰² The following procedure was adapted from one for a related compound:⁷⁷ To a 1 L round bottom flask was added 1-(phenanthren-2-yl)ethanone **297** (11.5 g, 52 mmol), morpholine (15.7 mL, 180 mmol), sulfur (3.36 g, 105 mmol) and *p*-toluene sulfonic acid monohydrate (0.4 g, 2 mmol). The mixture was stirred at 125 °C for 10 h. After cooling down to room temperature, alcoholic KOH (3M, 87 mL) was added and the mixture was stirred at 110 °C overnight. After cooling down to room temperature, H₂O (75 mL) was added to the mixture. The mixture was acidified with 6N HCl to pH 2. CH₂Cl₂ (150 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (60 mL x 2). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica

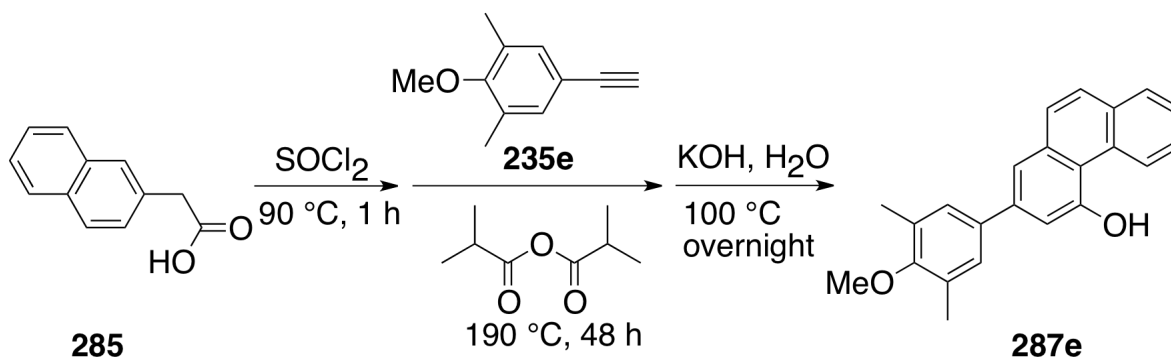
gel (60 mm x 250 mm column, CH₂Cl₂/hexanes 1:1, then CH₂Cl₂, and then acetone/hexanes 1:2 as eluent) gave **298** as a yellow solid (10.6 g, 44.9 mmol, 86%). mp 191-193 °C; R_f = 0.35 (1:1 acetone/hexanes). Spectral data for **298**: ¹H NMR (DMSO-d₆, 500 MHz) δ 3.80 (s, 2H), 7.58-7.64 (m, 2H), 7.65-7.70 (m, 1H), 7.79 (d, 1H, *J* = 9.0 Hz), 7.83 (d, 1H, *J* = 8.5 Hz), 7.85 (d, 1H, *J* = 1.5 Hz), 7.97 (dd, 1H, *J* = 8.0, 1.5 Hz), 8.76 (d, 1H, *J* = 8.5 Hz), 8.79 (d, 1H, *J* = 8.5 Hz), 12.4 (s, 1H); ¹³C NMR (DMSO-d₆, 125 MHz) δ 40.59, 122.83, 122.90, 126.58, 126.65, 126.86, 126.96, 128.42, 128.45, 128.53, 128.75, 129.64, 131.44, 131.54, 133.67, 172.70; mass spectrum, *m/z* (% rel intensity) 236 M⁺ (63), 191 (100), 189 (43), 165 (11).

6.4.3 Preparation of monomers



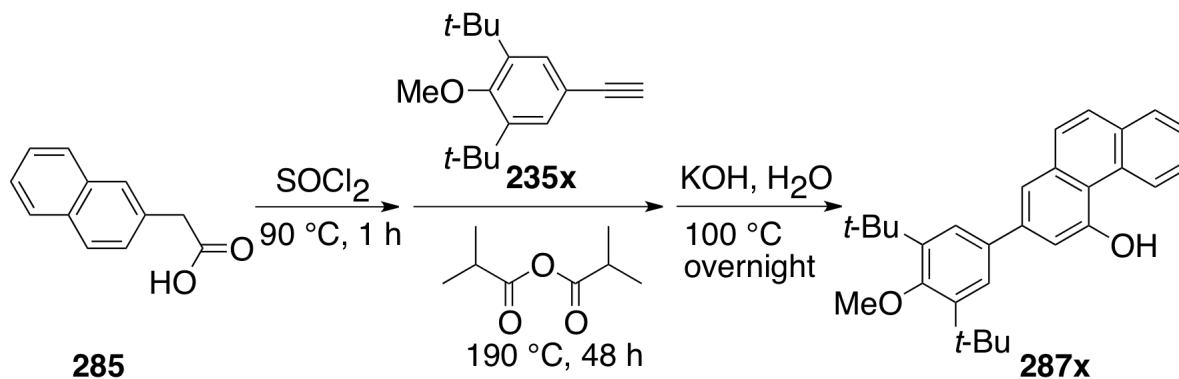
2-(3,5-dimethylphenyl)phenanthren-4-ol **287c**: The reaction of 2-naphthaleneacetic acid **285** (11.2 g, 60.0 mmol), SOCl₂ (16 mL, 219 mmol), 1-ethynyl-3,5-dimethylbenzene **235c** (8.58 g, 66.0 mmol) and (*i*-PrCO)₂O (20 mL, 120 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:3 to 1:1 to 2:1) gave **287c** as a yellow solid (10.1 g,

33.8 mmol, 56%). mp 140-142 °C; R_f = 0.18 (1:1 CH₂Cl₂/hexane). Spectral data for **287c**: ¹H NMR (CDCl₃, 500 MHz) δ 2.41 (s, 6H), 5.64 (s, 2H), 7.03 (s, 1H), 7.20 (d, 1H, J = 1.5 Hz), 7.34 (s, 2H), 7.55-5.59 (m, 1H), 7.63-7.66 (m, 1H), 7.70 (d, 1H, J = 1.5 Hz), 7.73 (s, 2H), 7.87 (dd, 1H, J = 8.0, 1.0 Hz), 9.61 (d, 1H, J = 9.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 21.44, 112.35, 118.45, 119.88, 125.15, 125.93, 126.62, 127.27, 128.24, 128.32, 128.41, 129.29, 130.19, 132.57, 135.26, 138.42, 139.46, 140.08, 154.49; IR (thin film) 3517s, 2921m, 1597s, 1458s, 1279m, 1229s cm⁻¹; HRMS (ESI-) m/z calculated for C₂₂H₁₇O (M-H⁺) 297.1279, found 297.1281.



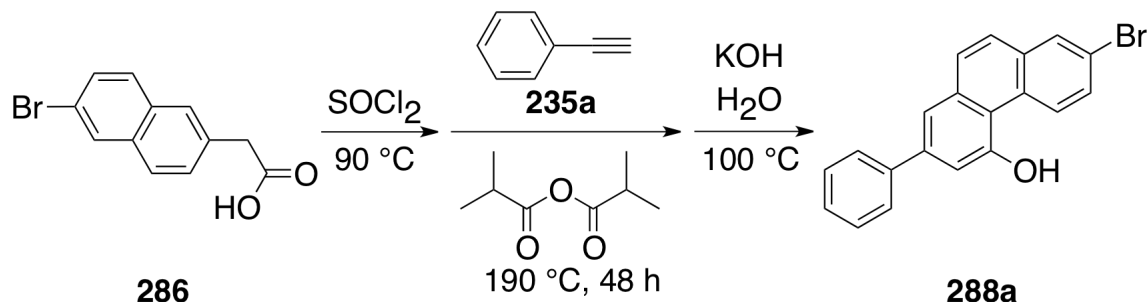
2-(4-methoxy-3,5-dimethylphenyl)phenanthren-4-ol **287e**: The reaction of 2-naphthaleneacetic acid **285** (7.44 g, 40.0 mmol), SOCl₂ (10.5 mL, 144 mmol), 5-ethynyl-2-methoxy-1,3-dimethylbenzene **235e** (6.4 g, 40.0 mmol) and (*i*-PrCO)₂O (13.3 mL, 80.0 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:1 to 2:1 to 1:0) gave **287e** as an off-white solid (4.64 g, 14.1 mmol, 35%). mp 164-165 °C; R_f = 0.31 (CH₂Cl₂). Spectral data for **287e**: ¹H NMR (CDCl₃, 500 MHz) δ 2.38 (s, 6H), 3.79 (s, 3H), 5.76 (s, 1H), 7.15 (d, 1H, J = 1.5 Hz), 7.36 (s, 2H), 7.54-7.58 (m, 1H), 7.62-7.66 (m, 2H), 7.72 (d, 2H, J = 1.0 Hz), 7.86 (dd, 1H, J = 8.0, 1.5 Hz), 9.61 (dd, 1H, J = 8.5, 0.5 Hz); ¹³C NMR (CDCl₃,

125 MHz) δ 16.31, 59.85, 112.22, 118.32, 119.55, 125.87, 126.60, 127.25, 127.71, 128.23, 128.30, 128.41, 130.25, 131.28, 132.55, 135.26, 135.76, 139.02, 154.60, 156.77; IR (thin film) 3341br s, 2934s, 1487s, 1381s, 1265s, 1226s, 1159s cm^{-1} ; HRMS (ESI⁻) m/z calculated for $\text{C}_{23}\text{H}_{19}\text{O}_2$ ($\text{M}-\text{H}^+$) 327.1385, found 327.1391.

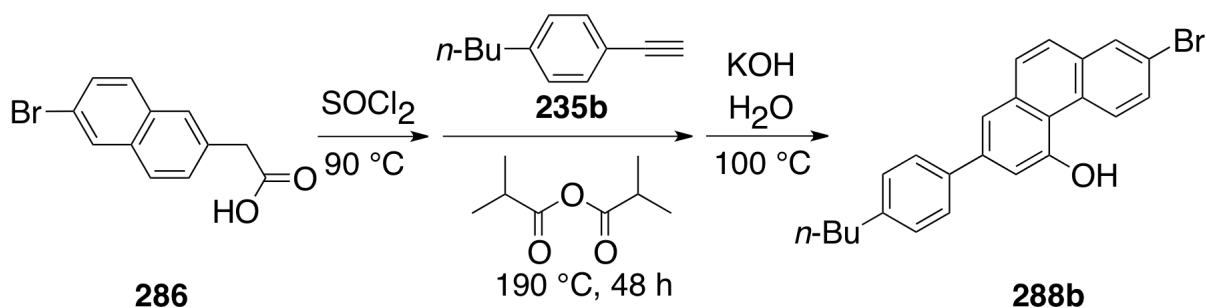


2-(3,5-di-tert-butyl-4-methoxyphenyl)phenanthren-4-ol **287x**: The reaction of 2-naphthaleneacetic acid **285** (4.84 g, 26.0 mmol), SOCl_2 (6.8 mL, 93 mmol), 1,3-di-tert-butyl-5-ethynyl-2-methoxybenzene **235x** (7.03 g, 28.8 mmol) and $(i\text{-PrCO})_2\text{O}$ (8.7 mL, 52.5 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:3 to 1:1 to 2:1) gave **287x** as a light yellow solid (4.65 g, 11.3 mmol, 43%). mp 202-203 °C; R_f = 0.21 (1:1 CH_2Cl_2 /hexanes). Spectral data for **287x**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.50 (s, 18H), 3.75 (s, 3H), 5.69 (s, 1H), 7.18 (d, 1H, J = 2.0 Hz), 7.55-7.59 (m, 3H), 7.62-7.67 (m, 2H), 7.74 (d, 2H, J = 1.0 Hz), 7.87 (dd, 1H, J = 8.0, 1.5 Hz), 9.61 (d, 1H, J = 8.5 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.18, 35.99, 64.34, 112.41, 118.21, 119.69, 125.60, 125.86, 126.61, 127.27, 128.24, 128.32, 128.39, 130.26, 132.55, 134.37, 135.30, 139.99, 144.15, 154.52, 159.57;

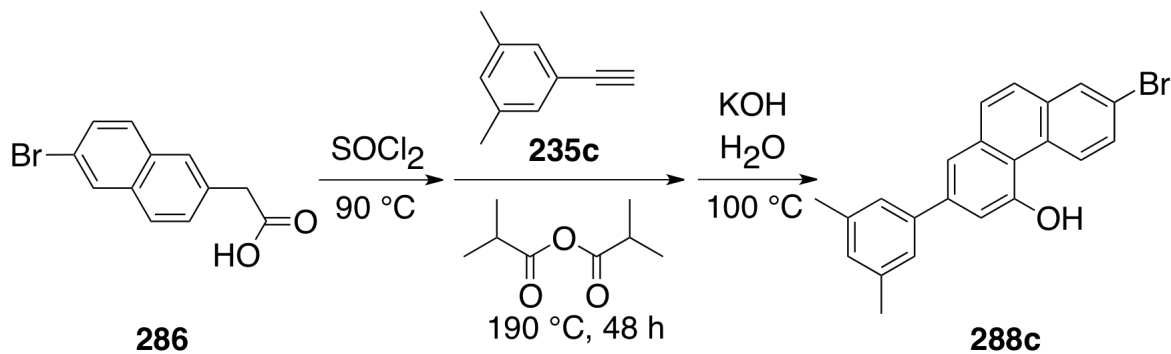
IR (thin film) 3521br m, 2961s, 1420s, 1227s cm^{-1} ; HRMS (ESI-) m/z calculated for $\text{C}_{29}\text{H}_{31}\text{O}_2$ ($\text{M}-\text{H}^+$) 411.2324, found 411.2312.



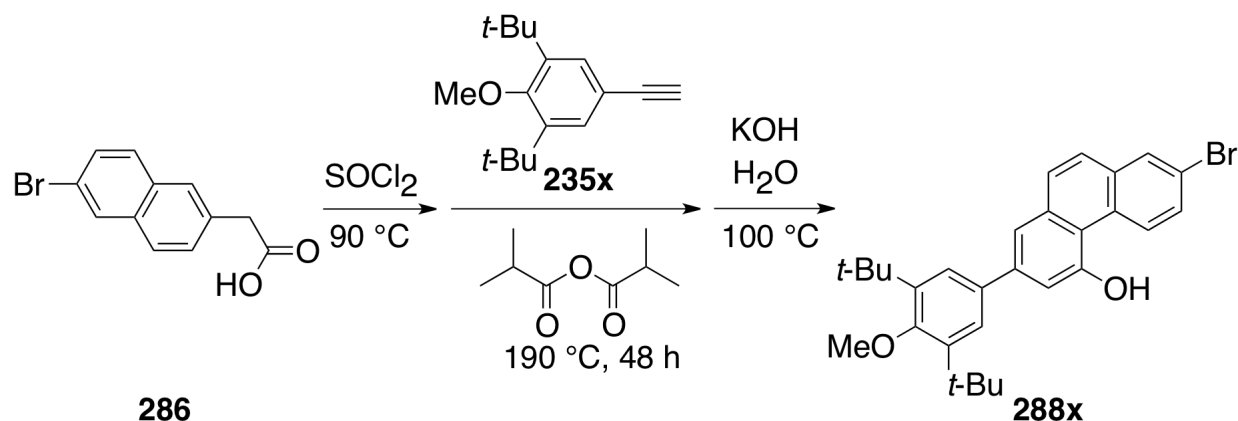
7-bromo-2-phenylphenanthren-4-ol 288a: The reaction of 2-(6-bromonaphthalen-2-yl)acetic acid **286** (4.23 g, 16.0 mmol), SOCl_2 (4.3 mL, 58.9 mmol), phenylacetylene **235a** (2.4 mL, 21.9 mmol) and $(i\text{-PrCO})_2\text{O}$ (5.4 mL, 32.5 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:2 to 1:1 to 2:1) gave **288a** as a yellow solid (2.54 g, 7.27 mmol, 45%). mp 168-169 $^\circ\text{C}$; R_f = 0.23 (2:1 CH_2Cl_2 /hexanes). Spectral data for **288a**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.74 (s, 1H), 7.20 (d, 1H, J = 2.0 Hz), 7.37-7.41 (m, 1H), 7.46-7.50 (m, 2H), 7.62 (d, 1H, J = 9.5 Hz), 7.68-7.72 (m, 4H), 7.74 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 2.0 Hz), 9.48 (d, 1H, J = 9.0 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 112.56, 118.22, 119.96, 120.02, 127.23, 127.78, 128.48, 128.78, 128.95, 129.60, 130.24, 130.31, 134.17, 135.11, 139.62, 139.92, 154.42 (1 sp^2 C not located); HRMS (ESI-) m/z calculated for $\text{C}_{20}\text{H}_{12}\text{O}^{79}\text{Br}$ ($\text{M}-\text{H}^+$) 347.0072, found 347.0069.



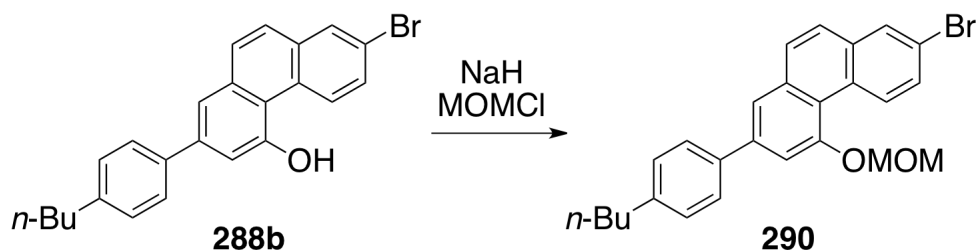
7-bromo-2-(4-butylphenyl)phenanthren-4-ol **288b**: The reaction of 2-(6-bromonaphthalen-2-yl)acetic acid **286** (6.63 g, 25.0 mmol), SOCl_2 (6.7 mL, 92 mmol), 1-butyl-4-ethynylbenzene **235b** (5.0 g, 31.6 mmol) and $(i\text{-PrCO})_2\text{O}$ (8.4 mL, 50.7 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:3 to 1:1 to 2:1) gave **288b** as a yellow solid (5.36 g, 13.2 mmol, 53%). mp 140-142 $^\circ\text{C}$; $R_f = 0.31$ (2:1 CH_2Cl_2 /hexanes). Spectral data for **288b**: ^1H NMR (CDCl_3 , 500 MHz) δ 0.95 (t, 3H, $J = 7.5$ Hz), 1.35-1.44 (m, 2H), 1.61-1.68 (m, 2H), 2.67 (t, 2H, $J = 7.5$ Hz), 5.68 (s, 1H), 7.20 (d, 1H, $J = 1.5$ Hz), 7.29 (d, 2H, $J = 8.0$ Hz), 7.60-7.62 (m, 3H), 7.70 (dd, 2H, $J = 9.0, 2.0$ Hz), 7.73 (d, 1H, $J = 9.0$ Hz), 7.99 (d, 1H, $J = 2.0$ Hz), 9.48 (d, 1H, $J = 9.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 13.95, 22.40, 33.60, 35.33, 112.50, 118.04, 119.80, 119.87, 127.04, 127.16, 128.52, 128.84, 129.04, 129.57, 130.23, 130.29, 134.15, 135.14, 137.19, 139.65, 142.75, 154.39; IR (thin film) 3517s, 2926s, 1559s, 1458s, 1390s, 1231s cm^{-1} ; HRMS (ESI $^-$) m/z calculated for $\text{C}_{20}\text{H}_{12}\text{O}^{79}\text{Br}$ (M-H^+) 403.0698, found 403.0684.



7-bromo-2-(3,5-dimethylphenyl)phenanthren-4-ol **288c**: The reaction of 2-(6-bromonaphthalen-2-yl)acetic acid **286** (1.33 g, 5.0 mmol), SOCl_2 (1.4 mL, 19 mmol), 1-ethynyl-3,5-dimethylbenzene **235c** (0.78 g, 6.0 mmol) and $(i\text{-PrCO})_2\text{O}$ (1.7 mL, 10 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH_2Cl_2 :hexanes 1:2 to 1:1 to 2:1) gave **288c** as a yellow solid (864 mg, 2.29 mmol, 46%). mp 203-204 $^\circ\text{C}$; $R_f = 0.30$ (2:1 CH_2Cl_2 /hexanes). Spectral data for **288c**: ^1H NMR (CDCl_3 , 500 MHz) δ 2.41 (s, 6H), 5.73 (s, 1H), 7.03 (s, 1H), 7.21 (d, 1H, $J = 1.5$ Hz), 7.32 (s, 2H), 7.61 (d, 1H, $J = 8.5$ Hz), 7.68-7.71 (m, 2H), 7.74 (d, 1H, $J = 9.0$ Hz), 7.99 (d, 1H, $J = 2.0$ Hz), 9.48 (d, 1H, $J = 9.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.43, 112.68, 118.10, 119.87, 119.99, 125.14, 127.13, 128.52, 128.82, 129.43, 129.54, 130.21, 130.29, 134.14, 135.06, 138.48, 139.89, 139.88, 154.32; HRMS (ESI $^-$) m/z calculated for $\text{C}_{22}\text{H}_{16}\text{O}^{79}\text{Br}$ (M-H^+) 375.0385, found 375.0384.

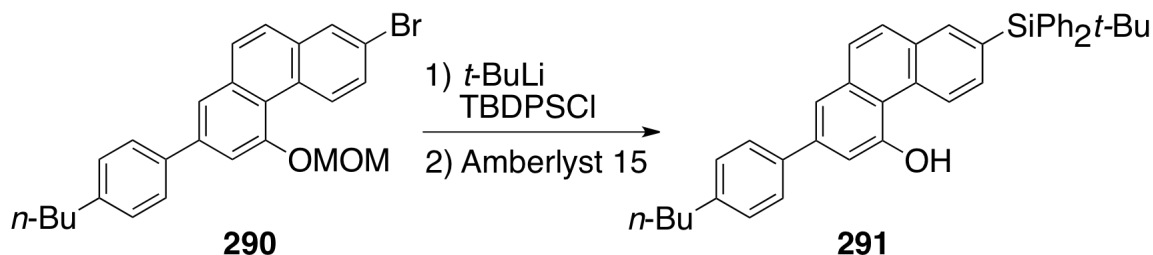


7-bromo-2-(3,5-di-tert-butyl-4-methoxyphenyl)phenanthren-4-ol **288x**: The reaction of 2-(6-bromonaphthalen-2-yl)acetic acid **286** (1.33 g, 5.0 mmol), SOCl_2 (1.4 mL, 19 mmol), 1,3-di-tert-butyl-5-ethynyl-2-methoxybenzene **235x** (1.46 g, 6.0 mmol) and $(i\text{-PrCO})_2\text{O}$ (1.7 mL, 10 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH_2Cl_2 :hexanes 1:2 to 1:1 to 2:1) gave **288x** as a yellow solid (614 mg, 1.25 mmol, 25%). mp 192-193 $^\circ\text{C}$; $R_f = 0.26$ (1:1 CH_2Cl_2 /hexanes). Spectral data for **288x**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.50 (s, 18H), 3.75 (s, 3H), 5.69 (s, 1H), 7.19 (d, 1H, $J = 2.0$ Hz), 7.56 (s, 2H), 7.61-7.64 (m, 2H), 7.70 (dd, 1H, $J = 9.0, 2.0$ Hz), 7.76 (d, 1H, $J = 9.0$ Hz), 7.99 (d, 1H, $J = 2.0$ Hz), 9.49 (d, 1H, $J = 9.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 32.17, 35.99, 64.35, 112.73, 117.83, 119.80, 119.81, 125.60, 127.13, 128.52, 128.86, 129.54, 130.21, 130.27, 134.10, 134.18, 135.09, 140.42, 144.23, 154.32, 159.67; IR (thin film) 3512br m, 2961s, 1560s, 1446s, 1227s, 1169s, 1115s cm^{-1} ; HRMS (ESI-) m/z calculated for $\text{C}_{29}\text{H}_{30}\text{O}_2$ ^{79}Br (M-H^+) 489.1429, found 489.1447.



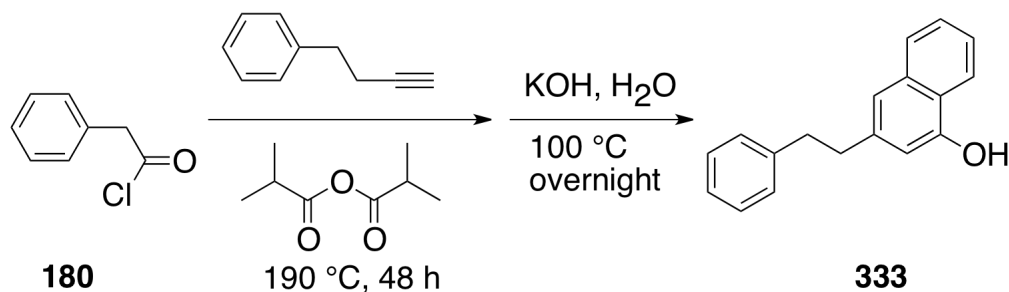
7-bromo-2-(4-butylphenyl)-4-(methoxymethoxy)phenanthrene 290: To a flame-dried 250 mL round bottom flask was added 7-bromo-2-(4-butylphenyl)phenanthren-4-ol **288b** (10.1 g, 24.9 mmol) and dry THF (80 mL) under N₂. The resulting solution was cooled to 0 °C and NaH (1.10 g, 60% in mineral oil, 27.5 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h. MOMCl (2.1 mL, 27.8 mmol) was then added to the mixture at 0 °C. The mixture was warmed up to room temperature and stirred for additional 24 h. NH₄Cl (sat. aq. 20 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The two phase residue was extracted with CH₂Cl₂ (30 mL × 3). The combined organic layer was washed with brine (20 mL), dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:3) gave **290** as a light yellow solid (10.7 g, 23.8 mmol, 96%). mp 84-85 °C; R_f = 0.31 (1:2 CH₂Cl₂/hexanes). Spectral data for **290**: ¹H NMR (CDCl₃, 500 MHz) δ 0.95 (t, 3H, *J* = 7.5 Hz), 1.35-1.44 (m, 2H), 1.61-1.68 (m, 2H), 2.67 (t, 2H, *J* = 8.0 Hz), 3.61 (s, 3H), 5.56 (s, 2H), 7.30 (d, 2H, *J* = 8.5 Hz), 7.61-7.67 (m, 4H), 7.70 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.74-7.76 (m, 2H), 8.00 (d, 1H, *J* = 2.5 Hz), 9.51 (d, 1H, *J* = 9.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 13.96, 22.39, 33.64, 35.34, 56.56, 95.27, 111.57, 119.74, 119.86, 120.57, 127.02, 127.21, 128.69, 128.75, 129.01, 129.51, 130.10, 130.36, 134.41, 134.75, 137.65, 139.81, 142.67, 156.42; IR (thin film) 2955s,

2928s, 2857m, 1455s, 1154s, 1046s cm^{-1} ; mass spectrum, m/z (% rel intensity) 450 M^+ (8, ^{81}Br), 448 M^+ (7, ^{79}Br), 418 (9, ^{81}Br), 416 (7, ^{79}Br), 337 (7), 281 (37), 252 (25), 131 (25). Anal calcd for $\text{C}_{26}\text{H}_{25}\text{BrO}_2$: C, 69.49; H, 5.61. Found: C, 69.45; H, 5.45.



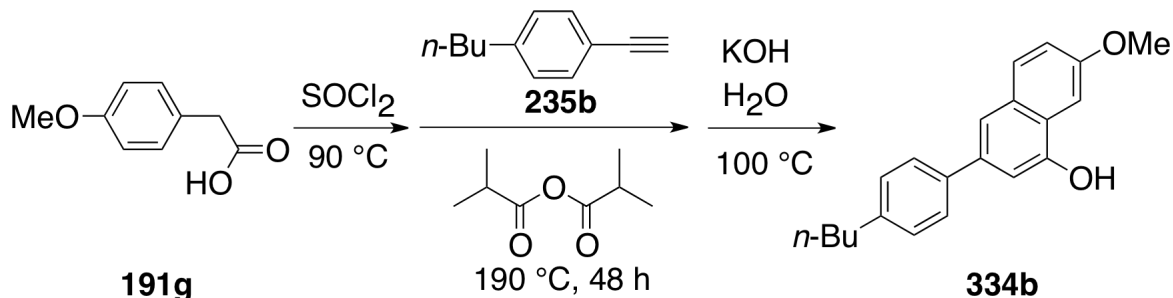
7-(tert-butyldiphenylsilyl)-2-(4-butylphenyl)phenanthren-4-ol 291: The following procedure was adapted from one for a related compound:¹⁵ To a 250 mL flame-dried round bottom flask was added 7-bromo-2-(4-butylphenyl)-4-(methoxymethoxy)phenanthrene **290** (2.87 g, 6.39 mmol) and dry THF (65 mL) under N_2 . The resulting solution was cooled to -78°C and $t\text{-BuLi}$ (1.7 M in pentane, 7.7 mL, 13.1 mmol) was added dropwise. The resulting mixture was stirred at -78°C for 1 h. TBDPSCI (1.8 mL, 7.06 mmol) was then added to the mixture at -78°C . The mixture was warmed up to room temperature and stirred for an additional 24 h. NaHCO_3 (sat. aq. 5 mL) was added to the mixture. The reaction mixture was partitioned between Et_2O (60 mL) and NaHCO_3 (sat. aq. 60 mL). The organic layer was washed with brine (30 mL), dried over MgSO_4 , filtered through Celite and concentrated to dryness. The product was partially purified by column chromatography on silica gel (30 mm x 250 mm, CH_2Cl_2 :hexanes 1:3). The partially purified product was dissolved in a mixture of THF and MeOH (130 mL, 1:1) and Amberlyst 15 (1.6 g) was added. The mixture was stirred at 65°C for 15 h under N_2 in a balloon. After cooling down to room temperature, the mixture was filtered through filter paper and concentrated to dryness.

Purification of the crude product by column chromatography on silica gel (30 mm x 300 mm, CH₂Cl₂:hexanes 1:2) gave **291** as a white solid in over two steps (1.73 g, 3.07 mmol, 48%). mp 176-178 °C; R_f = 0.26 (1:1 CH₂Cl₂/hexanes). Spectral data for **291**: ¹H NMR (CDCl₃, 500 MHz) δ 0.95 (t, 3H, *J* = 7.5 Hz), 1.24 (s, 9H), 1.37-1.42 (m, 2H), 1.61-1.68 (m, 2H), 2.67 (t, 2H, *J* = 7.5 Hz), 5.74 (s, 1H), 7.20 (d, 1H, *J* = 2.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.34-7.38 (m, 4H), 7.39-7.44 (m, 2H), 7.62-7.66 (m, 8H), 7.69-7.71 (m, 2H), 7.87 (dd, 1H, *J* = 8.5, 2.0 Hz), 8.06 (d, 1H, *J* = 1.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 13.95, 18.92, 22.39, 28.92, 33.61, 35.33, 112.07, 118.21, 119.60, 127.04, 127.16, 127.70, 128.70, 129.00, 129.20, 130.68, 131.70, 132.34, 134.05, 134.91, 135.62, 136.64, 137.37, 137.47, 139.46, 142.61, 154.83 (1 sp² C not located); IR (thin film) 3526br m, 2930s, 2857s, 1653s, 1558s, 1458s cm⁻¹; HRMS (ESI⁻) *m/z* calculated for C₄₀H₃₉OSi (M-H⁺) 563.2770, found 563.2784.

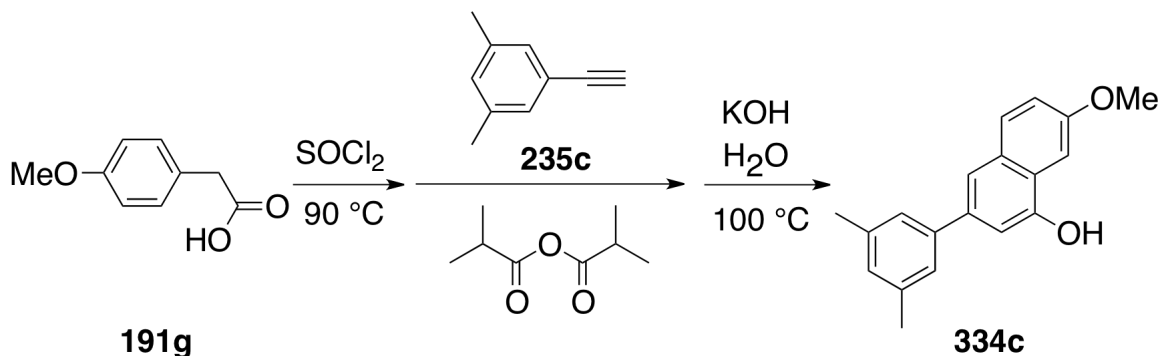


3-phenethyl-1-naphthol 333: The reaction of phenylacetyl chloride **180** (2.64 mL, 20.0 mmol), but-3-yn-1-ylbenzene (2.60 g, 20.0 mmol) and (*i*-PrCO)₂O (6.7 mL, 40 mmol) was performed according to the general procedure (Procedure Q). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:1 to 2:1 to 1:0) gave **333** as a brown oil (1.80 g, 7.26 mmol, 36%). R_f = 0.36 (CH₂Cl₂). Spectral data for **333**: ¹H NMR

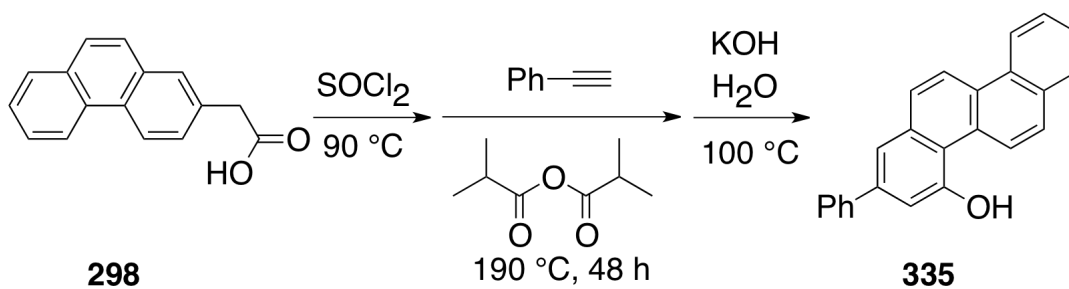
(CDCl₃, 500 MHz) δ 2.95-3.03 (m, 4H), 5.15 (s, 1H), 6.65 (d, 1H, J = 1.5 Hz), 7.17-7.21 (m, 3H), 7.23 (s, 1H), 7.26-7.30 (m, 2H), 7.39-7.47 (m, 2H), 7.71-7.73 (m, 1H), 8.09-8.11 (m, 1H).



3-(4-butylphenyl)-7-methoxynaphthalen-1-ol 334b: The reaction of 4-methoxyphenylacetic acid **191g** (4.15 g, 25.0 mmol), SOCl₂ (6.7 mL, 92 mmol), 1-butyl-4-ethynylbenzene **235b** (5.0 g, 31.6 mmol) and (*i*-PrCO)₂O (8.4 mL, 50.7 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:1 to 2:1 to 3:1) gave **334b** as a brownish yellow solid (3.32 g, 10.8 mmol, 43%). mp 96-99 °C; R_f = 0.24 (CH₂Cl₂). Spectral data for **334b**: ¹H NMR (CDCl₃, 500 MHz) δ 0.94 (t, 3H, J = 7.5 Hz), 1.36-1.41 (m, 2H), 1.60-1.67 (m, 2H), 2.65 (t, 2H, J = 7.5 Hz), 3.94 (s, 3H), 5.19 (s, 1H), 7.05 (d, 1H, J = 1.5 Hz), 7.16 (dd, 1H, J = 9.0, 2.5 Hz), 7.25 (d, 2H, J = 8.5 Hz), 7.44 (d, 1H, J = 7.5 Hz), 7.54-7.57 (m, 3H), 7.73 (d, 1H, J = 9.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 13.96, 22.40, 33.64, 35.29, 55.41, 99.85, 108.83, 118.35, 119.66, 124.30, 126.93, 128.87, 129.55, 130.51, 136.46, 138.24, 142.01, 150.68, 157.40; HRMS (ESI⁻) m/z calculated for C₂₁H₂₁O₂ (M-H⁺) 305.1542, found 305.1556.

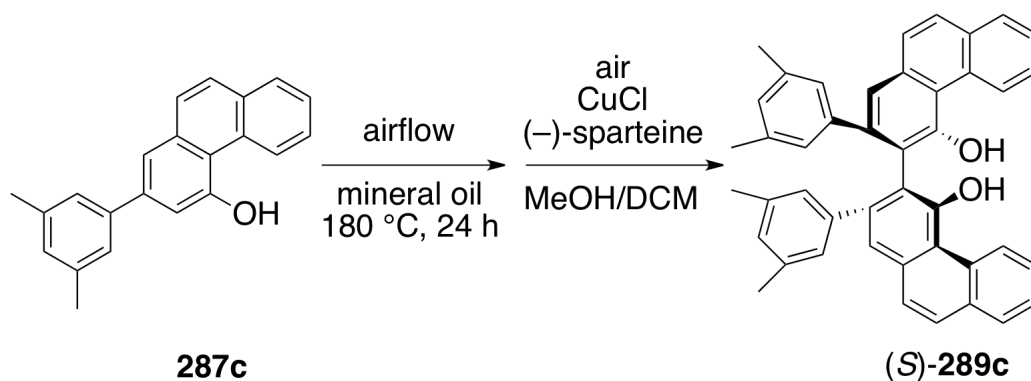


3-(3,5-dimethylphenyl)-7-methoxynaphthalen-1-ol 334c: The reaction of 4-methoxyphenylacetic acid **191g** (8.30 g, 50.0 mmol), SOCl₂ (13.3 mL, 182 mmol), 1-ethynyl-3,5-dimethylbenzene **235c** (7.15 g, 55.0 mmol) and (*i*-PrCO)₂O (16.8 mL, 101 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:1 to 2:1 to 1:0) gave **334c** as a brown solid (7.24 g, 26.2 mmol, 52%). mp 103-108 °C; R_f = 0.26 (CH₂Cl₂). Spectral data for **334c**: ¹H NMR (CDCl₃, 500 MHz) δ 2.38 (s, 6H), 3.95 (s, 3H), 5.17 (s, 1H), 6.98 (s, 1H), 7.06 (d, 1H, *J* = 1.5 Hz), 7.16 (dd, 1H, *J* = 8.5, 2.5 Hz), 7.26 (s, 2H), 7.44 (d, 1H, *J* = 2.5 Hz), 7.57 (s, 1H), 7.74 (d, 1H, *J* = 9.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 21.42, 55.41, 99.87, 109.00, 118.58, 119.64, 124.39, 125.05, 128.83, 129.58, 130.47, 136.72, 138.28, 140.95, 150.64, 157.43; IR (thin film) 3405br m, 2919m, 1599s, 1487s, 1267s, 1213s, 1175s cm⁻¹; HRMS (ESI-) *m/z* calculated for C₁₉H₁₇O₂ (M-H⁺) 277.1229, found 227.1227.



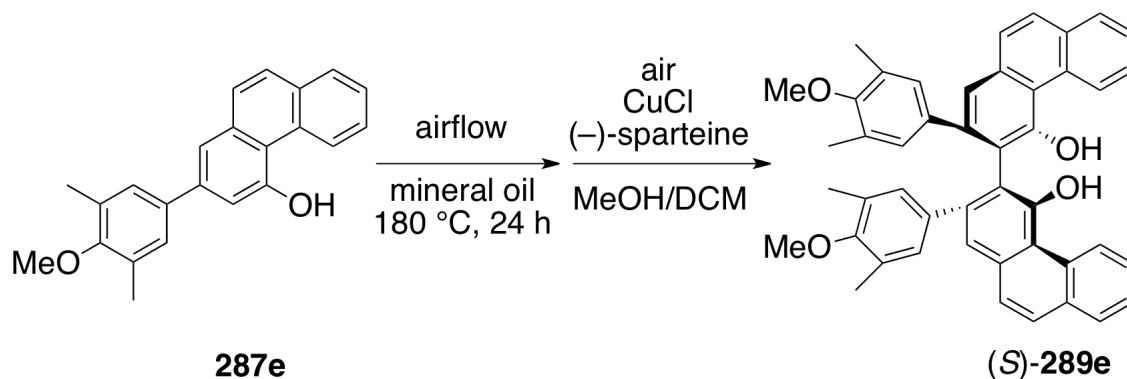
2-phenylchrysen-4-ol **335**: The reaction of 2-phenanthreneacetic acid **298** (10.4 g, 44.0 mmol), SOCl₂ (12 mL, 164 mmol), phenylacetylene (6.6 g, 60.0 mmol) and (*i*-PrCO)₂O (15 mL, 90 mmol) was performed according to the general procedure (Procedure I). Purification of the crude product by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 2:3 to 2:1) gave **335** as a orange solid (3.92 g, 12.3 mmol, 28%). mp 234-239 °C; R_f = 0.19 (2:1 CH₂Cl₂/hexanes). Spectral data for **335**: ¹H NMR (DMSO-d₆, 500 MHz) δ 7.42 (t, 1H, *J* = 7.5 Hz), 7.51 (d, 1H, *J* = 1.5 Hz), 7.54 (t, 2H, *J* = 8.0 Hz), 7.65-7.69 (m, 1H), 7.70-7.74 (m, 1H), 7.81 (dd, 2H, *J* = 8.0, 1.0 Hz), 7.89 (d, 1H, *J* = 2.0 Hz), 8.03-8.06 (m, 2H), 8.11 (d, 1H, *J* = 9.5 Hz), 8.88 (d, 1H, *J* = 9.0 Hz), 8.93 (d, 1H, *J* = 8.5 Hz), 9.90 (d, 1H, *J* = 9.5 Hz), 10.87 (s, 1H); ¹³C NMR (DMSO-d₆, 125 MHz) δ 111.12, 117.40, 118.81, 121.98, 123.34, 126.25, 126.28, 126.42, 126.70, 127.66, 127.89, 127.91, 128.23, 128.51, 129.03, 129.67, 131.02, 134.86, 138.31, 139.54, 156.70 (1 sp² C not located); HRMS (ESI-) *m/z* calculated for C₂₄H₁₅O (M-H⁺) 319.1123, found 319.1110.

6.4.4 Preparation of VAPOL derivatives



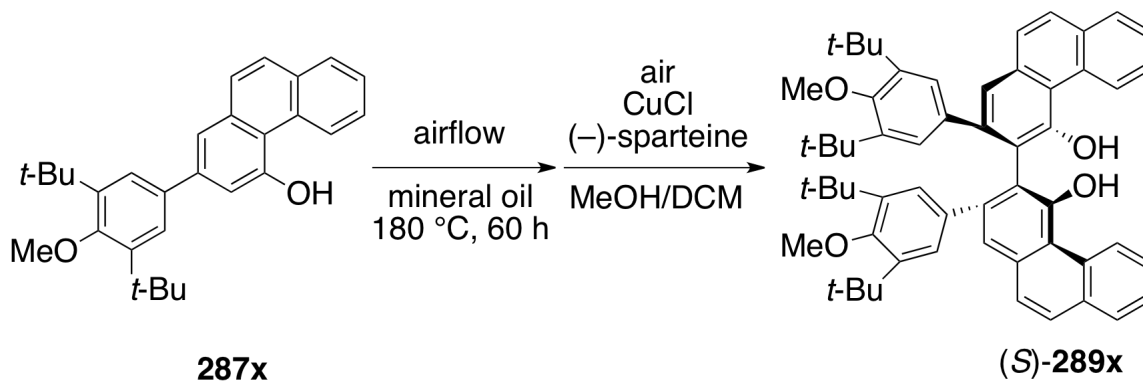
The synthesis of racemic **289c** was performed according to the general procedure (Procedure J) with 2-(3,5-dimethylphenyl)phenanthren-4-ol **287c** (9.37 g, 31.4 mmol). The mixture was stirred at 180 °C for 24 h. After cooling down to room temperature, CH₂Cl₂ (50 mL) and hexanes (50 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (−20 °C) and then filtered through filter paper. The yellow powder was washed with chilled CH₂Cl₂/hexanes and dried under vacuum to afford a yellow solid (5.00 g). Purification of the product remaining in the mother liquor by column chromatography on silica gel (50 mm x 250 mm, CH₂Cl₂:hexanes 1:2) gave racemic **289c** as an off-white solid (2.46 g). The total yield is 80% (7.46 g, 12.6 mmol). After de-racemization of racemic **289c** (4.75 g, 8.00 mmol) with CuCl (1.35 mg, 13.6 mmol) and (−)-sparteine (6.56 g, 28 mmol), the crude product was purified by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂/hexanes 2:5) to afford (*S*)-**289c** as a yellow solid (4.27 g, 7.19 mmol, 90%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 75:25 hexane/*i*PrOH at 254 nm, flow-rate: 2.0 mL/min). Retention times: *R*_t = 9.68 min for (*R*)-**289c** (minor) and *R*_t = 13.08 min for (*S*)-**289c** (major). mp 135-137 °C; *R*_f = 0.19 (1:2

CH₂Cl₂/hexanes). Spectral data for **289c**: ¹H NMR (CDCl₃, 500 MHz) δ 1.99 (s, 12H), 6.42 (s, 4H), 6.51 (s, 2H), 6.71 (s, 2H), 7.46 (s, 2H), 7.60-7.64 (m, 2H), 7.65-7.69 (m, 4H), 7.80 (d, 2H, *J* = 8.5 Hz), 7.92 (dd, 2H, *J* = 8.5, 1.5 Hz), 9.73 (d, 2H, *J* = 8.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 21.10, 116.15, 117.96, 122.94, 126.22, 126.76, 126.92, 126.93, 128.36, 128.40, 128.80, 129.11, 130.36, 132.79, 135.17, 136.76, 139.77, 141.88, 153.43; IR (thin film) 3482br s, 2917m, 1559s, 1456s, 1223s cm⁻¹; HRMS (ESI-) *m/z* calculated for C₄₄H₃₃O₂ (M-H⁺) 593.2481, found 593.2498. [α]_D²⁰ = +3.9 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**289c** (HPLC).



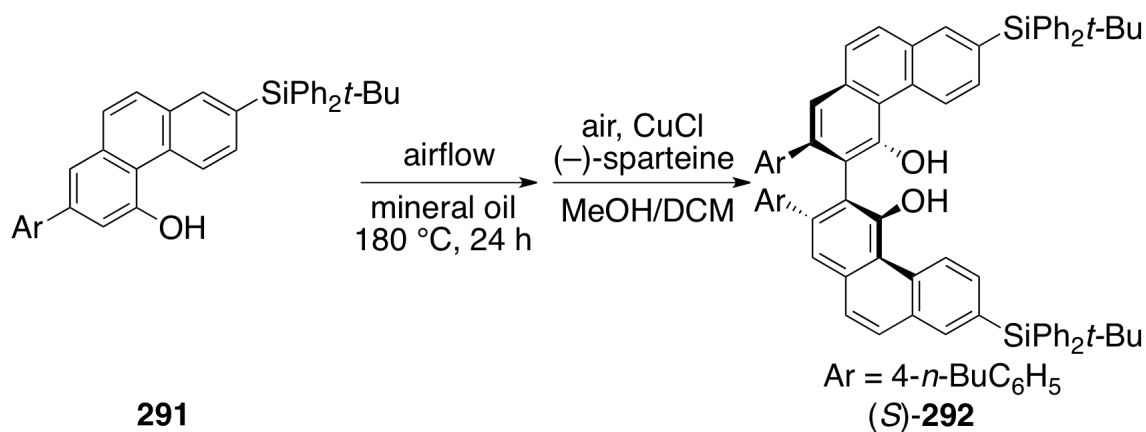
The synthesis of racemic **289e** was performed according to the general procedure (Procedure J) with 2-(4-methoxy-3,5-dimethylphenyl)phenanthren-4-ol **287e** (3.05 g, 9.30 mmol). The mixture was stirred at 180 °C for 24 h. Purification by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 2:1) and then washing with CH₂Cl₂/hexanes gave racemic **289e** as a yellow solid (1.84 g, 2.81 mmol, 60% yield). After de-racemization of racemic **289e** (3.25 g, 4.97 mmol) with CuCl (837 mg, 8.45 mmol) and (-)-sparteine (4.08 g, 17.4 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 2:1) to afford (*S*)-**289e** as an off-white solid (3.10 g, 4.74 mmol, 95%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column,

75:25 hexane/*i*PrOH at 254 nm, flow-rate: 2.0 mL/min). Retention times: R_t = 15.13 min for (*R*)-**289e** (minor) and R_t = 21.73 min for (*S*)-**289e** (major). mp 158-160 °C; R_f = 0.20 (2:1 CH₂Cl₂/hexanes). Spectral data for **289e**: ¹H NMR (CDCl₃, 500 MHz) δ 1.93 (s, 12H), 3.60 (s, 6H), 6.40 (s, 4H), 6.51 (s, 2H), 7.34 (s, 2H), 7.62 (t, 2H, J = 7.5 Hz), 7.65-7.68 (m, 4H), 7.81 (d, 2H, J = 9.0 Hz), 7.93 (d, 2H, J = 7.5 Hz), 9.72 (d, 2H, J = 8.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 15.89, 59.67, 116.14, 117.88, 122.84, 126.23, 126.91, 126.93, 128.38, 128.77, 129.16, 129.38, 129.66, 130.33, 132.79, 135.19, 135.36, 141.33, 153.43, 156.10; IR (thin film) 3482br s, 2932s, 1487s, 1372s, 1244s, 1225s, 1130s cm⁻¹; HRMS (ESI-) m/z calculated for C₄₆H₃₇O₄ (M-H⁺) 653.2692, found 653.2712. $[\alpha]_D^{20}$ = -16.5 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**289e** (HPLC).



The synthesis of racemic **289x** was performed according to the general procedure (Procedure J) with 2-(3,5-di-tert-butyl-4-methoxyphenyl)phenanthren-4-ol **287x** (4.20 g, 10.2 mmol). The mixture was stirred at 180 °C for 60 h. After cooling down to room temperature, hexanes (25 mL) were added to the flask and the mixture was stirred until all large chunks had been broken up. The suspension was cooled in a freezer (-20 °C) and then filtered through filter paper. The yellow powder was washed with chilled hexanes and dried under vacuum to afford racemic **289x** as an orange solid (3.44 g, 4.18 mmol, 82% yield). After de-racemization of racemic **289x** (3.39

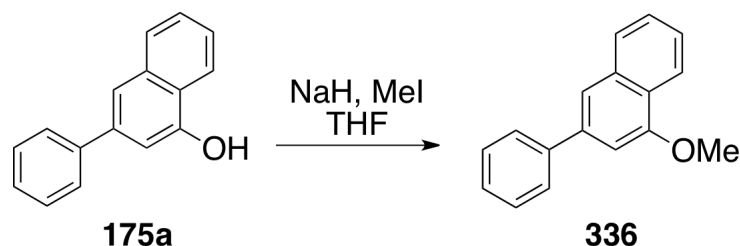
g, 4.12 mmol) with CuCl (693 mg, 7.00 mmol) and (–)-sparteine (3.38 g, 14.4 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:2) to afford (*S*)-**289x** as a yellow solid (3.19 g, 3.88 mmol, 94%). The optical purity was determined to be 97% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 75:25 hexane/*i*PrOH at 254 nm, flow-rate: 2.0 mL/min). Retention times: *R*_t = 10.30 min for (*R*)-**289x** (minor) and *R*_t = 18.67 min for (*S*)-**289x** (major). mp 150-153 °C; *R*_f = 0.26 (1:2 CH₂Cl₂/hexanes). Spectral data for **289x**: ¹H NMR (CDCl₃, 500 MHz) δ 1.08 (s, 36H), 3.21 (s, 6H), 6.16 (s, 2H), 7.14 (s, 4H), 7.49-7.54 (m, 4H), 7.71-7.77 (m, 6H), 7.82-7.85 (m, 2H), 9.34-9.37 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 31.74, 35.46, 63.78, 116.54, 118.38, 122.27, 125.99, 126.57, 126.80, 127.04, 128.14, 128.59, 129.00, 130.17, 132.54, 133.59, 135.34, 140.81, 142.83, 153.19, 158.84; IR (thin film) 3486br s, 2961s, 1412s, 1225s, 1115m cm⁻¹; HRMS (ESI–) *m/z* calculated for C₅₈H₆₂O₄ 822.4648, found 822.4680. [α]_D²⁰ = –200.4 (c 1.0, CH₂Cl₂) on >97% *ee* (*S*)-**289x** (HPLC).



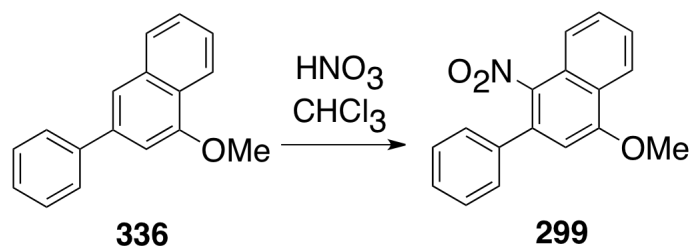
The synthesis of racemic **292** was performed according to the general procedure (Procedure J) with 7-(tert-butyldiphenylsilyl)-2-(4-butylphenyl)phenanthren-4-ol **291** (1.46 g, 2.58 mmol). The

mixture was stirred at 180 °C for 24 h. Purification by column chromatography on silica gel (30 mm × 250 mm, CH₂Cl₂/hexanes 1:4) gave racemic **292** as an off-white solid (812 mg, 0.72 mmol, 56% yield). After de-racemization of racemic **292** (563 mg, 0.50 mmol) with CuCl (84 mg, 0.85 mmol) and (–)-sparteine (0.41 g, 1.75 mmol), the crude product was purified by column chromatography on silica gel (30 mm × 200 mm, CH₂Cl₂/hexanes 1:3) to afford (*S*)-**292** as an off-white solid (486 mg, 0.43 mmol, 86%). The optical purity was determined to be >99% *ee* by HPLC analysis (Pirkle D-Phenylglycine column, 75:25 hexane/*i*PrOH at 254 nm, flow-rate: 2.0 mL/min). Retention times: *R*_t = 1.91 min for (*R*)-**292** (minor) and *R*_t = 2.21 min for (*S*)-**292** (major). mp 165-167 °C; *R*_f = 0.19 (1:3 CH₂Cl₂/hexanes). Spectral data for **292**: ¹H NMR (CDCl₃, 500 MHz) δ 0.88 (t, 3H, *J* = 7.5 Hz), 1.21-1.30 (m, 22H), 1.45-1.52 (m, 4H), 2.46 (t, 4H, *J* = 7.5 Hz), 6.52 (s, 2H), 6.59 (d, 4H, *J* = 8.0 Hz), 6.76 (d, 4H, *J* = 8.0 Hz), 7.35-7.45 (m, 14H), 7.64-7.67 (m, 10H), 7.73 (d, 2H, *J* = 8.5 Hz), 7.91 (dd, 2H, *J* = 8.5, 1.5 Hz), 8.11 (s, 2H), 9.67 (d, 2H, *J* = 8.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 13.89, 18.93, 22.20, 28.92, 33.47, 35.12, 115.92, 117.84, 123.15, 126.94, 127.59, 127.64, 127.73, 128.67, 129.25, 129.55, 130.84, 131.92, 132.93, 134.40, 134.82, 135.60, 136.63, 137.02, 137.65, 141.52, 141.88, 153.56; IR (thin film) 3490s, 2930s, 2857s, 1558s, 1456s, 1105s cm⁻¹; HRMS (ESI+) *m/z* calculated for C₈₀H₇₈O₂Si₂Na (M+Na⁺) 1149.5438, found 1149.5453. [α]_D²⁰ = +85.3 (c 1.0, CH₂Cl₂) on >99% *ee* (*S*)-**292** (HPLC).

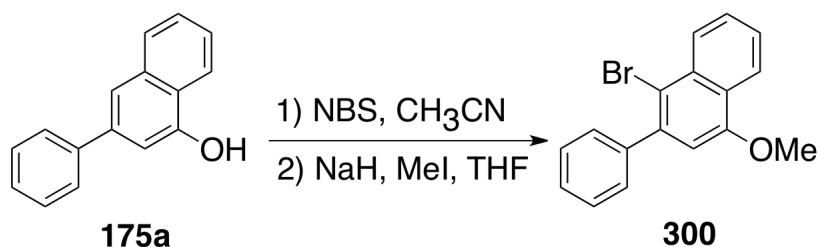
6.4.5 Functionalization of VANOL monomer



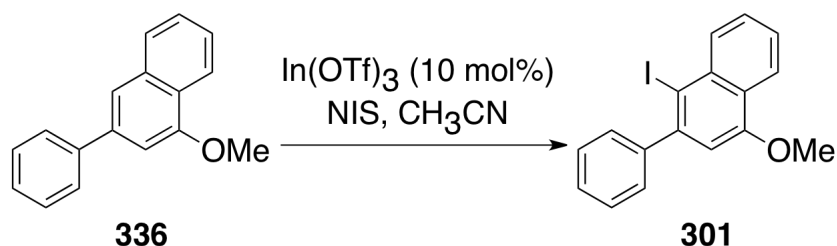
1-methoxy-3-phenylnaphthalene 336: To a flame-dried 250 mL round bottom flask was added 3-phenylnaphthalen-1-ol **175a** (3.30 g, 15.0 mmol) and dry THF (75 mL) under N₂. The resulting solution was cooled to 0 °C and NaH (0.8 g, 60% in mineral oil, 20 mmol) was added. The resulting mixture was stirred at 0 °C for 15 minutes. MeI (3.8 mL, 61 mmol) was then added to the mixture at 0 °C. The mixture was warmed up to room temperature and stirred for an additional 24 h. NH₄Cl (sat. aq. 30 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The residue was extracted with CH₂Cl₂ (30 mL × 3). The combined organic layer was washed with Na₂S₂O₃ (sat. aq. 20 mL × 2) and brine (20 mL) and then dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:10) gave **336** as a white solid upon storage (3.44 g, 14.7 mmol, 98%). mp 75-76 °C; R_f = 0.24 (1:4 CH₂Cl₂/hexanes). Spectral data for **336**: ¹H NMR (CDCl₃, 500 MHz) δ 4.07 (s, 3H), 7.06 (d, 1H, *J* = 1.5 Hz), 7.36-7.40 (m, 1H), 7.44-7.53 (m, 4H), 7.62 (s, 1H), 7.70-7.73 (m, 2H), 7.84 (dd, 1H, *J* = 8.0, 0.5 Hz), 8.26 (dd, 1H, *J* = 8.0, 0.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 55.61, 103.85, 118.42, 121.93, 124.86, 125.24, 126.83, 127.36, 127.44, 127.78, 128.79, 134.64, 138.96, 141.69, 155.84; IR (thin film) 3055m, 1581s, 1497s, 1401s, 1233s cm⁻¹; HRMS (ESI+) *m/z* calculated for C₁₇H₁₅O (M+H⁺) 235.1123, found 235.1131.



To a 250 round bottom flask was added 1-methoxy-3-phenylnaphthalene **336** (3.35 g, 14.3 mmol) and CHCl_3 (70 mL). To the stirred solution was added HNO_3 (5.5 mL) dropwise. The mixture was stirred at room temperature for 1 h. The resulting mixture was poured into H_2O (140 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (70 mL). The combined organic layer was dried over MgSO_4 , filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (35 mm x 250 mm, CH_2Cl_2 :hexanes 2:3) and then recrystallization from CH_2Cl_2 /hexanes gave **299** as a yellow solid (3.15 g, 11.3 mmol, 79%). mp 115-116 °C; R_f = 0.37 (1:1 CH_2Cl_2 /hexanes). Spectral data for **299**: ^1H NMR (CDCl_3 , 500 MHz) δ 4.05 (s, 3H), 6.75 (s, 1H), 7.41-7.48 (m, 5H), 7.55-7.59 (m, 1H), 7.63-7.67 (m, 1H), 7.78-7.81 (m, 1H), 8.31-8.34 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 56.08, 105.10, 121.66, 122.39, 124.62, 125.92, 126.63, 128.09, 128.61, 128.85, 129.31, 133.31, 137.48, 156.59 (1 sp^2 C not located); IR (thin film) 3061m, 1595s, 1520s, 1447s, 1354s, 1231s cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{17}\text{H}_{14}\text{NO}_3$ ($\text{M}+\text{H}^+$) 280.0974, found 280.0977.



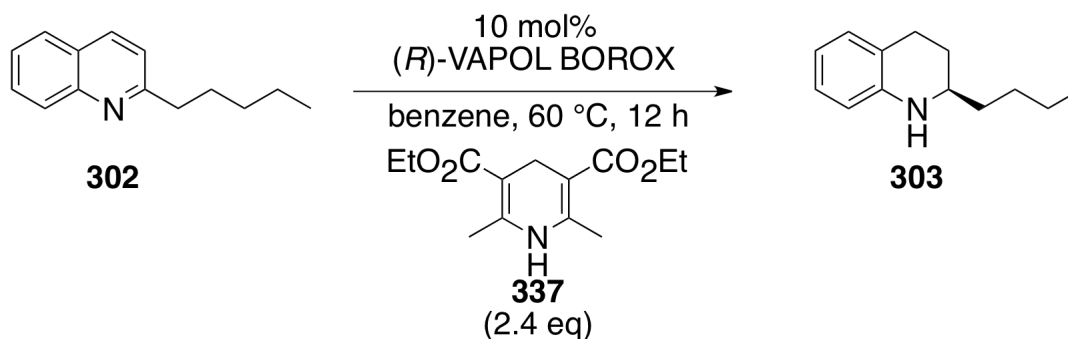
To a 100 mL flame-dried round bottom flask was added 3-phenylnaphthalen-1-ol **175a** (220 mg, 1.00 mmol), *N*-bromosuccinimide (178 g, 1.00 mmol) and dry CH₃CN (10 mL). The mixture was stirred at room temperature for 2 h. The mixture was treated with HCl (4N aq. 10 mL) and the organic solvent was removed by rotary evaporation. The residue was extracted with CH₂Cl₂ (10 mL x 3). The combined organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. The crude product was dissolved in dry THF (5 mL). The resulting solution was cooled to 0 °C and NaH (80 mg, 60% in mineral oil, 2.0 mmol) was added. The resulting mixture was stirred at 0 °C for 15 minutes. MeI (0.5 mL, 8.0 mmol) was then added to the mixture at 0 °C. The mixture was warmed up to room temperature and stirred for an additional 24 h. NH₄Cl (sat. aq. 3 mL) was added to the mixture and the organic solvent was removed by rotary evaporation. The residue was extracted with CH₂Cl₂ (3 mL x 3). The combined organic layer was washed with Na₂S₂O₃ (sat. aq. 3 mL x 2) and brine (3 mL) and then dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (2.5 mm x 300 mm, CH₂Cl₂:hexanes 1:30) gave **300** as a white solid upon storage (270 mg, 0.86 mmol, 86%). mp 80-82 °C; R_f = 0.34 (1:3 CH₂Cl₂/hexanes). Spectral data for **300**: ¹H NMR (CDCl₃, 500 MHz) δ 3.98 (s, 3H), 6.78 (s, 1H), 7.40-7.48 (m, 5H), 7.51-7.55 (m, 1H), 7.61-7.65 (m, 1H), 8.29 (dd, 1H, *J* = 8.5, 1.0 Hz), 8.35 (d, 1H, *J* = 8.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 55.76, 107.13, 113.16, 122.23, 125.87, 125.91, 127.54, 127.63, 128.00, 128.17, 129.56, 132.95, 140.55, 142.83, 154.63; IR (thin film) 3059m, 1593s, 1499s, 1387s, 1227s cm⁻¹; HRMS (EI+) *m/z* calculated for C₁₇H₁₃O⁷⁹Br (M⁺) 312.0150, found 312.0152.



1-iodo-4-methoxy-2-phenylnaphthalene 301: To a 100 mL flame-dried round bottom flask was added 1-methoxy-3-phenylnaphthalene **336** (1.40 g, 6.00 mmol), *N*-iodosuccinimide (1.48 g, 6.6 mmol), In(OTf)₃ (337 mg, 0.60 mmol) and dry CH₃CN (36 mL). The flask was then wrapped with aluminum foil. The mixture was stirred at room temperature for 12 h and H₂O (120 mL) was then added. The organic solvent was removed by rotary evaporation. The residue was extracted with CH₂Cl₂ (120 mL x 3). The combined organic layer was washed with Na₂S₂O₃ (sat. aq. 120 mL) and brine (120 mL) and then dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (30 mm x 250 mm, CH₂Cl₂:hexanes 1:8) gave **301** as a light yellow solid (2.09 g, 5.81 mmol, 97%). mp 94-95 °C; R_f = 0.29 (1:4 CH₂Cl₂/hexanes). Spectral data for **301**: ¹H NMR (CDCl₃, 500 MHz) δ 3.97 (s, 3H), 6.81 (s, 1H), 7.37-7.39 (m, 2H), 7.41-7.48 (m, 3H), 7.51 (t, 1H, *J* = 7.5 Hz), 7.59-7.63 (m, 1H), 8.24-8.29 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 55.73, 92.85, 106.59, 122.26, 125.37, 125.93, 127.59, 127.97, 128.60, 129.41, 132.95, 135.22, 145.91, 146.50, 155.54; IR (thin film) 1591s, 1499s, 1381s, 1227s cm⁻¹; HRMS (EI+) *m/z* calculated for C₁₇H₁₃OI (M⁺) 360.0011, found 360.0013.

6.4.6 Asymmetric transfer hydrogenation of 2-pentylquinoline

2-pentylquinoline **302** was kindly provided by Prof. Aaron Odom.¹¹⁰ The requisite Hantzsch ester **337** were prepared according to, or in a similar manner as, previously published procedures.¹¹¹

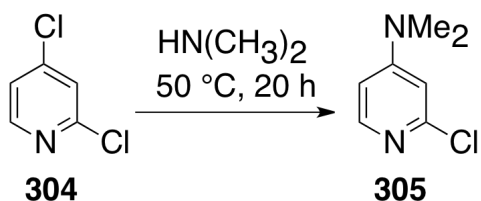


The (R)-VAPOL BOROX catalyst was prepared according to Procedure G with (R)-VAPOL 2,6-dimethylphenol, $\text{BH}_3 \cdot \text{SMe}_2$ and H_2O .

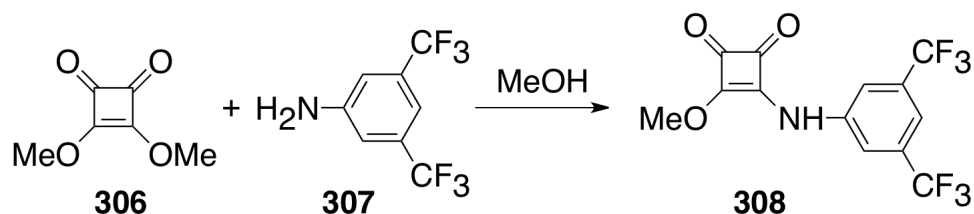
(R)-2-pentyl-1,2,3,4-tetrahydroquinoline **303**: A small vial (3.7 mL), fitted with a Teflon liner, was flame dried and cooled under argon. 2-pentylquinoline **302** (10 mg, 0.05 mmol, 1 equiv) was added from a stock solution in CH_2Cl_2 . The vial was directly subjected to gradual high vacuum to remove the CH_2Cl_2 . Hantzsch ester **337** was then added (31 mg, 0.12 mmol, 2.4 equiv) to the vial. The vial was evacuated and back-filled with argon. 10 mol% of the (R)-VAPOL BOROX catalyst was added from a stock solution in benzene (1 mL). The reaction mixture was flushed with argon above the solvent surface; the vial was capped and stirred at 60 °C for 12 h. The reaction was judged complete by TLC. The crude reaction mixture was subjected to rotary evaporation till dryness and finally to high vacuum to afford crude **303**. Purification of the crude product by column chromatography on silica gel (25 mm x 300 mm, EtOAc:hexanes 1:20) gave **303** as a colorless oil in >99% isolated yield (10 mg, 0.05 mmol). The optical purity was

determined to be >78% *ee* by HPLC analysis (Chiralpak AS column, 99:1 hexane/*i*PrOH at 222 nm, flow-rate: 0.7 mL/min). Retention times: R_t = 6.14 min for (*S*)-**303** (minor) and R_t = 6.89 min for (*R*)-**303** (major). R_f = 0.43 (1:5 EtOAc/hexanes). Spectral data for **303**: ^1H NMR (CDCl_3 , 600 MHz) δ 0.89 (t, 3H, J = 7.2 Hz), 1.27-1.42 (m, 6H), 1.45-1.49 (m, 2H), 1.54-1.62 (m, 1H), 1.92-1.97 (m, 1H), 2.68-2.74 (m, 1H), 2.76-2.83 (m, 1H), 3.20-3.24 (m, 1H), 3.74 (bs, 1H), 6.46 (d, 1H, J = 7.2 Hz), 6.58 (t, 1H, J = 7.2 Hz), 6.92-6.95 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 14.04, 22.63, 25.39, 26.43, 28.12, 31.95, 36.68, 51.59, 114.00, 116.85, 121.38, 126.68, 129.23, 144.73.

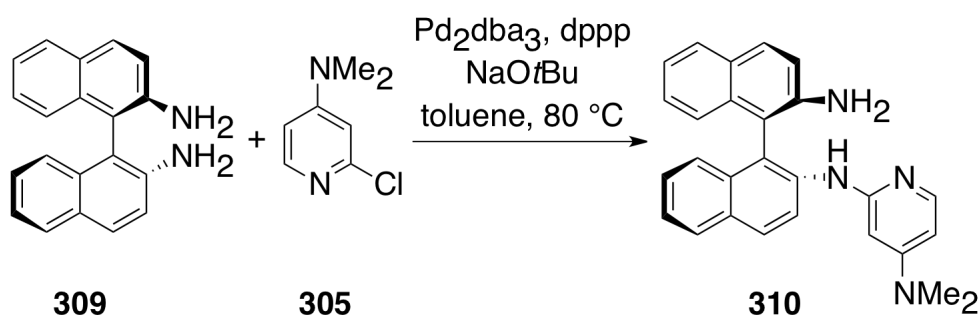
6.4.7 Preparation of squaramide-DMAP-BINAM



2-chloro-*N,N*-dimethylpyridin-4-amine **305**:¹⁰⁷ To a 50 mL round bottom flask was added 2,4-dichloropyridine **304** (2.61 g, 17.6 mmol) and dimethylamine (40% aq. 17.6 mL) under N_2 . The mixture was stirred at 50 °C for 20 h under N_2 . The crude product was extracted with Et_2O (20 mL x 3). The combined organic layer was dried over MgSO_4 , filtered through Celite and concentrated to dryness. Recrystallization from CHCl_3 (two crops) gave **305** as a white solid (1.89 g, 12.1 mmol, 69%). Spectral data for **305**: ^1H NMR (CDCl_3 , 600 MHz) δ 2.98 (s, 6H), 6.39 (dd, 1H, J = 9.5, 2.0 Hz), 6.46 (d, 1H, J = 2.0 Hz), 7.95 (d, 1H, J = 5.0 Hz); ^{13}C NMR (CDCl_3 , 150 MHz) δ 39.25, 105.43, 105.84, 149.06, 152.31, 156.09.

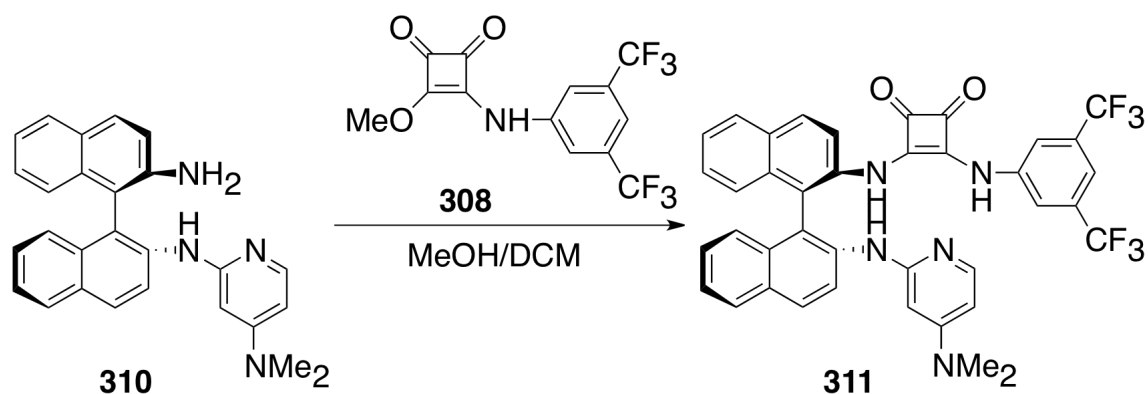


3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione **308**:¹¹³ To a 25 mL flame-dried round bottom flask was added 3,4-dimethoxy-3-cyclobutene-1,2-dione **306** (544 mg, 3.83 mmol) and MeOH (5.4 mL). To the solution was added 3,5-bis(trifluoromethyl)aniline **307** (623 μL , 4.02 mmol). The mixture was stirred at room temperature for 48 h under argon protection. Filtration by filter paper gave the first crop. The filtrate was concentrated to dryness. The crude product was washed with CH_2Cl_2 /hexanes and filtered by filter paper to afford the second crop. **308** was obtained as a light yellow solid (1.18 g, 3.48 mmol, 91%). mp 186-188 $^\circ\text{C}$ (lit.¹¹³ 179-181 $^\circ\text{C}$). Spectral data for **308**: ^1H NMR ($\text{DMSO}-d_6$, 600 MHz) δ 4.40 (s, 3H), 7.77 (s, 1H), 8.03 (s, 2H), 11.17 (s, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 39.25, 105.43, 105.84, 149.06, 152.31, 156.09.



*N*²-(2'-amino-[1,1'-binaphthalen]-2-yl)-*N*⁴,*N*⁴-dimethylpyridine-2,4-diamine **310**:¹⁰⁷ To a 25 mL flame-dried Schlenk flask was added (*R*)-BINAM **309** (457 mg, 1.61 mmol), Pd_2dba_3 (110 mg, 0.12 mmol), dppp (99 mg, 0.24 mmol) and NaOtBu (232 mg, 2.42 mmol). Dry toluene (13 mL) and 2-chloro-*N,N*-dimethylpyridin-4-amine **305** (251 mg, 1.61 mmol) were added to the mixture.

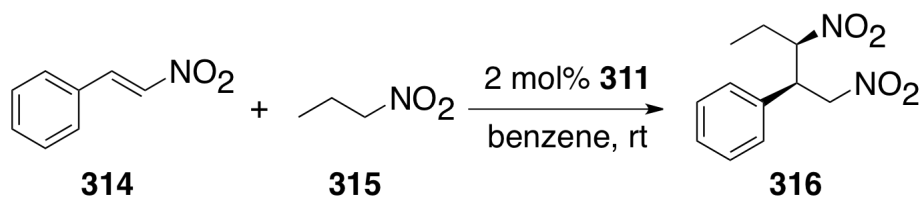
The mixture was freeze-thawed twice. The mixture was stirred at 80 °C for 36 h. The mixture was cooled to room temperature and filtered through a pad of Celite (rinsed with EtOAc). After removal of the solvent, the residue was partitioned between CH₂Cl₂ (30 mL) and H₂O (30 mL). The organic layer was dried over MgSO₄, filtered through Celite and concentrated to dryness. Purification of the crude product by column chromatography on silica gel (1st column, 25 mm x 200 mm, MeOH: CH₂Cl₂ 1:14; 2nd column, 25 mm x 200 mm, EtOAc:hexanes 1:2 to 1:1 to 1:0) gave **310** as a light yellow solid (331 mg, 0.82 mmol, 51%). R_f = 0.19 (1:14 MeOH/ CH₂Cl₂). Spectral data for **310**: ¹H NMR (CDCl₃, 600 MHz) δ 2.88 (s, 6H), 3.70 (bs, 1H), 5.87 (d, 1H, *J* = 2.0 Hz), 6.08 (dd, 1H, *J* = 5.0, 2.0 Hz), 6.25 (bs, 1H), 7.03 (d, 1H, *J* = 7.0 Hz), 7.10 (d, 1H, *J* = 7.5 Hz), 7.15 (td, 1H, *J* = 7.0, 1.0 Hz), 7.19-7.21 (m, 2H), 7.31 (td, 1H, *J* = 6.5, 0.5 Hz), 7.76-7.81 (m, 3H), 7.84 (d, 1H, *J* = 6.5 Hz), 7.92 (d, 1H, *J* = 6.5 Hz), 8.24 (d, 1H, *J* = 7.5 Hz); ¹³C NMR (CDCl₃, 150 MHz) δ 39.25, 91.16, 101.28, 111.99, 118.31, 120.50, 122.39, 123.89, 123.95, 125.00, 126.66, 126.89, 128.03, 128.11, 128.36, 128.84, 129.77, 130.12, 133.50, 134.00, 138.12, 142.79, 147.66, 156.02, 156.13 (2 sp² C not located).



To a 25 mL round bottom flask was added amine **310** (162 mg, 0.400 mmol), CH₂Cl₂ (0.4 mL) and MeOH (4 mL). Amine **308** (271 mg, 0.80 mmol) was then added to the mixture. The

resulting mixture was stirred at room temperature for 48 h. Purification of the crude product by column chromatography on silica gel (25 mm x 300 mm, EtOAc/hexanes 1:2 to 2:1) gave **311** as a yellow solid (261 mg, 0.367 mmol, 92%). mp 181-187 °C; R_f = 0.38 (EtOAc). Spectral data for **311**: ^1H NMR (DMSO- d_6 , 500 MHz) δ 2.66 (s, 6H), 5.76 (d, 1H, J = 7.0 Hz), 5.92 (d, 1H, J = 4.5 Hz), 6.92 (d, 1H, J = 8.5 Hz), 7.00 (d, 1H, J = 9.0 Hz), 7.24 (t, 1H, J = 7.5 Hz), 7.30 (t, 1H, J = 7.5 Hz), 7.37-7.41 (m, 2H), 7.47 (t, 1H, J = 7.5 Hz), 7.63-7.66 (m, 2H), 7.89 (s, 2H), 7.97-8.05 (m, 4H), 8.10 (d, 1H, J = 9.0 Hz). ^{13}C NMR (DMSO- d_6 , 500 MHz) δ 38.48, 89.71, 100.59, 114.91, 118.38, 119.87, 122.05, 123.50, 124.22, 124.30, 125.03, 125.33, 125.70, 126.42, 126.78, 128.25, 128.59, 128.79, 130.26, 130.70, 130.96, 131.22, 131.47, 132.78, 133.29, 134.33, 138.12, 140.65, 155.41, 163.62, 167.13, 181.80, 182.65 (1 sp^2 C not located). HRMS (ESI $^-$) m/z calculated for $\text{C}_{39}\text{H}_{26}\text{N}_5\text{O}_3\text{F}_6$ ($\text{M}-\text{H}^+$) 710.1991, found 710.1979.

6.4.8 Asymmetric addition of 1-nitropropane to nitrostyrene



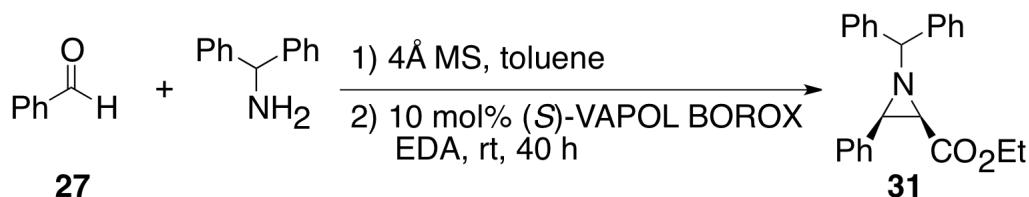
To a 25 mL flame-dried round bottom flask was added nitrostyrene (74.5 mg, 0.50 mmol), **311** (7.1 mg, 0.010 mmol) and dry toluene (1.25 mL). 1-nitropropane (1.25 mL, 14 mmol) was added and the resulting mixture was stirred at for 80 h. *Syn:anti* = 88:12 was determined from the ^1H NMR spectrum of the crude reaction mixture. Purification of the crude product by column chromatography on silica gel (25 mm x 250 mm, EtOAc/hexanes 1:6) gave *syn*-**311** as a clear oil

(83 mg). The total yield of *syn*- and *anti*-**311** was 79% (94 mg, 0.395 mmol). Spectral data for **311**: ^1H NMR (CDCl_3 , 500 MHz) δ 1.00 (t, 3H, $J = 7.5$ Hz), 1.82-1.88 (m, 1H), 1.96-2.03 (m, 1H), 4.00-4.05 (m, 1H), 4.73-4.79 (m, 2H), 4.84-4.89 (m, 1H), 7.12-7.15 (m, 2H), 7.31-7.34 (m, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 10.32, 24.28, 46.47, 76.23, 90.97, 127.87, 129.08, 129.27, 133.69.

6.4.9 One-pot imine formation-AZ reaction

Procedure I:

Illustrated for *(2R,3R)*-ethyl-1-benzhydryl-3-phenylaziridine-2-carboxylate **31**^{26g}

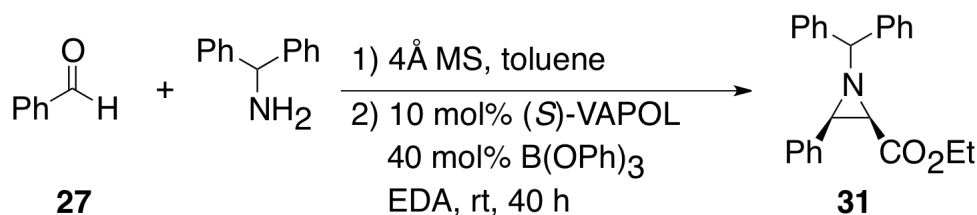


To a 25 mL flame-dried round bottom flask filled with argon was added benzhydrylamine (183 mg, 1 mmol), 4 Å MS (1 g) and dry toluene (2 mL). After stirring for 2 minutes, benzaldehyde **27** (116 mg, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 2 h under the protection of argon. At the same time the catalyst was prepared *in situ*: to a flame-dried 25 mL Schlenk flask filled with argon was added (*S*)-VAPOL (54 mg, 0.1 mmol) and triphenyl borate (116 mg, 0.4 mmol). The mixture was dissolved in dry toluene (2 mL). After the addition of H_2O (0.9 mg, 0.1 mmol), the Schlenk flask was sealed and heated at 80 °C for 1 hour. Then a vacuum (0.5 mm Hg) was applied for half an hour with continual heating at 80 °C. The Schlenk flask containing the catalyst was cooled to room temperature and then dry toluene (2 mL) was

added. The catalyst solution was transferred via syringe to the round bottom flask containing imine generated *in situ*. After 5 minutes, EDA (114 μ L, 1.1 mmol) was added. The mixture was stirred at room temperature for 40 hours. Purification of the crude product by column chromatography on silica gel (35 mm x 400 mm column, EtOAc/hexanes 1:19) gave **31** as a white solid in 66% isolated yield (235 mg, 0.66 mmol) with 93% *ee* by HPLC analysis.

Procedure II:

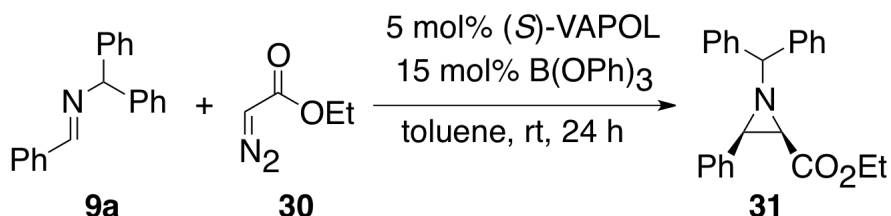
Illustrated for *(2R,3R)*-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate **31**^{26g}



To a 25 mL round bottom flask filled with argon was added benzhydrylamine (183 mg, 1 mmol), 4 Å MS (1 g) and dry toluene (2 mL). After stirring for 2 minutes, benzaldehyde **27** (116 mg, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 2 h under the protection of argon. To a 25 mL round bottom flask was added (*S*)-VAPOL (54 mg, 0.1 mmol) and triphenyl borate (116 mg, 0.4 mmol). The mixture was dissolved in dry toluene (2 mL). This solution was then transferred via syringe to the round bottom flask containing imine generated *in situ*. After 5 minutes, EDA (114 μ L, 1.1 mmol) was added. The mixture was stirred at room temperature for 40 h. Purification of the crude product by column chromatography on silica gel (35 mm x 400 mm column, EtOAc/hexanes 1:19) gave **31** as a white solid in 70% isolated yield (251 mg, 0.70 mmol) with 94% *ee* by HPLC analysis.

Procedure III:

Illustrated for *(2R,3R)*-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate **31**^{26g}



To a 10 mL round bottom flask was added imine **9a** (271 mg, 1.0 mmol), (*S*)-VAPOL (27 mg, 0.05 mmol), triphenyl borate (43.5 mg, 0.15 mmol). The mixture was dissolved in dry toluene (2 mL). After 5 minutes of stirring ethyl diazoacetate (119 μ L, 1.15 mmol) was added. The resulting mixture was stirred at room temperature for 24 h. Purification of the crude product by column chromatography on silica gel (35 mm x 400 mm column, EtOAc/hexanes 1:19) gave **31** as a white solid in 80% isolated yield (286 mg, 0.80 mmol) with 92% *ee* by HPLC analysis.

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