CATALYTIC ASYMMETRIC SYNTHESIS ENABLED BY VANOL/VAPOL BOROX CATALYSTS

By

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ABSTRACT

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The development of a catalytic asymmetric method for the direct aminoallylation of aldehydes is described that is based on a chiral polyborate catalyst generated from the vaulted biaryl ligand VANOL. This method is scalable since it is chromatography free and it gives rise to unprotected homo-allylic amines with excellent asymmetric inductions over a broad range of substrates including both aryl and aliphatic aldehydes. The unique catalyst system developed for this protocol involves the synergistic interplay between a chiral Brønsted acid and a non-chiral Brønsted acid.

The mode of synergetic catalysis and the origin of enantioselection observed in this reaction are investigated using a combination of experimental kinetic isotope effects (KIEs), NMR spectroscopy (^{11}B and ^{13}C) and theoretical calculations. The results from these mechanistic studies provide fine details of the enantioselectivity determining transition state geometry.

This direct aminoallylation of aldehydes protocol was then extended to the preparation of 1,3-homo-allylic amino alcohols utilizing an unprecedented catalyst-controlled aza-Cope rearrangement and subsequently applied to the total syntheses of the Sedum alkaloids.

A highly enantioselective route for the introduction of aziridines into functionalized organic molecules was developed via a tandem acylation and aziridination of $TMSCHN_2$. The products are synthetically useful intermediates that can be readily elaborated.

To,
my husband Quanxuan and our daughter Aimee

ACKNOWLEDGEMENTS

One of the joys of completion is to look over the journey past and remember all the people who have helped and supported me along this long but fulfilling road. It would not have been possible to write this doctoral thesis without the help and support of the kind people around me, to only some of whom it is possible to give particular mention here.

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CHAPTER ONE
CHIRAL HOMO-ALLYLIC AMINES IN ORGANIC CHEMISTRY

1.1 Introduction

Chiral homo-allylic amines have been recognized in biologically active natural products, including angustifoline[1] and cryptophycin 337.[2] They have also been identified in synthetic medicinal compounds, such as eponemycin.[3]

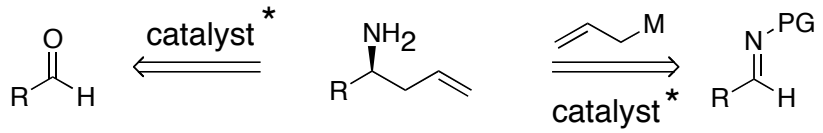
In addition, chiral homo-allylic amines have served as key intermediates in total syntheses of complex natural product, such as indolizomycin,[4] the aminosugar of vancosamine,[5] and desoxoprosopinine,[6] as well as halichlorinespirocycle.[7]

Perhaps the most significant aspect of chiral homo-allylic amines relies on their synthetic versatility as chiral building blocks for the construction of a broad range of multi-functional organic compounds. The rich chemistry with the alkene moiety provides great access to amino alcohols, aminoalkyl epoxides,[8] amino acids and aminoalkyl cyclopropane.[9] Furthermore, with the development of ring-closing metathesis and the hydroformylation reaction, various nitrogen-containing heterocycles, such as azetidines, piperidines, azepines, and pyrrolidine derivatives can be assembled quickly.

1.2 Main approaches towards the catalytic asymmetric synthesis of chiral homo-allylic amines

A measure of the value of chiral homo-allylic amines in organic synthesis is the large volume of work that has been devoted to their construction. Two main methods have been reported for the catalytic asymmetric synthesis of homo-allylic amines as outlined in Scheme 1. 1.

Scheme 1. 1 Two approaches for catalytic asymmetric synthesis of homo-allylic amines



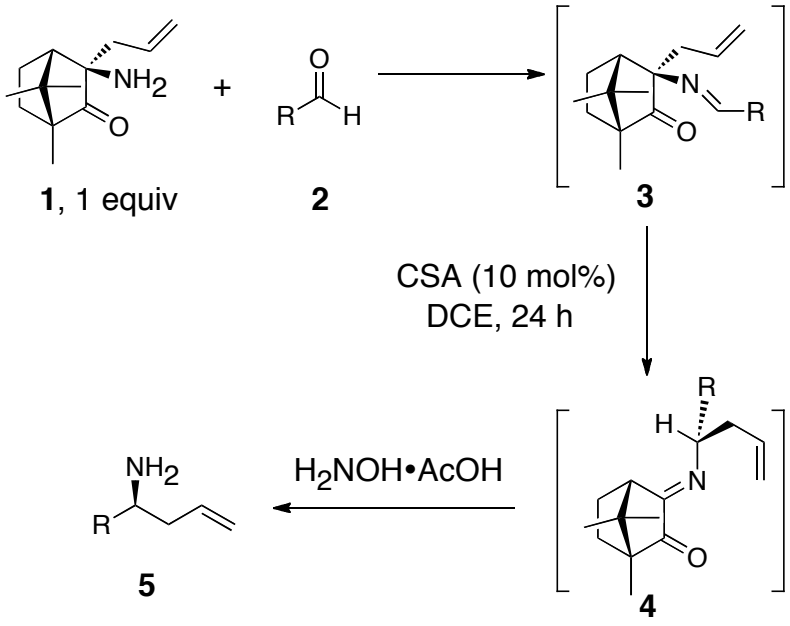
Aminoallylation of aldehydes Allylation of imines

The development of catalytic asymmetric allylation of imines has received much attention.[10] Although significant progress has been made in this area, the catalytic asymmetric allylation of aliphatic imines remains a considerable challenge and the use of basic allylmetallic reagents limits the application of the methodology for base-sensitive substrates.

In contrast to allylation of imines, less progress has been made for the catalytic asymmetric amino-allylation of aldehydes; only one report has appeared thus far. [11] Although amino-allylation of aldehydes is more direct given the fact that a huge variety of aldehydes are commercially available, the purification of imines, especially aliphatic imines, can be a hassle.

In 2006, Kobayashi reported a stoichiometric asymmetric amino-allylation of aldehydes involving an aza-Cope rearrangement of imines **3** derived from 3-bytenyl-1-amines of the type **1** as shown in Scheme 1. 2. They were able to sterically drive the reversible Cope-rearrangement to the isomer **4** which formally represents the "transfer amino-allylation" of the aldehyde **2**. Kobayashi's method involves a stoichiometric auxiliary in the form of a chiral amine **1** and has been adopted for use in natural product syntheses.[12]

Scheme 1. 2 Kobayashi's asymmetric amino-allylation of aldehydes

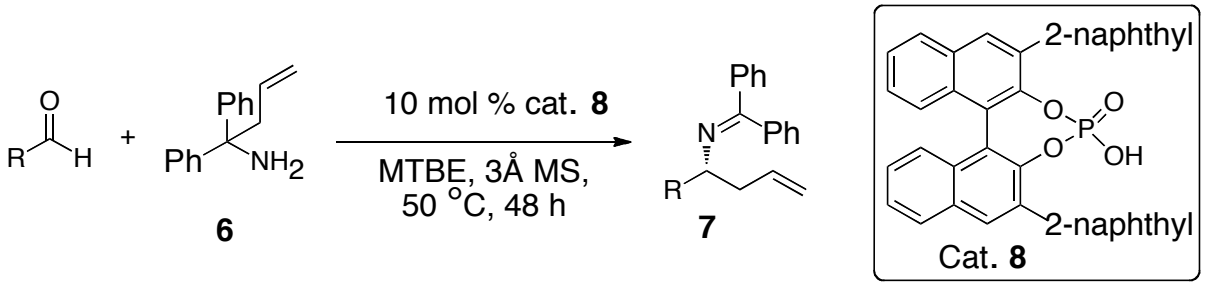


In 2008, Ruiping and co-workers developed a catalytic asymmetric amino-allylation of aldehydes on the basis of a condensation – aza-Cope rearrangement sequence[11] (Scheme 1. 3).

It was found that two phenyl groups were sufficient to electronically drive the equilibrium to the isomer **7**. The aza-Cope rearrangement was catalyzed by 10 mol% chiral phosphoric acid **8**, affording moderate to good enantioselectivity with aromatic aldehydes. However, a lacuna in the only existing method for the asymmetric catalytic amino-allylation of aldehydes is the sub-class of aliphatic aldehydes.

Scheme 1. 3 Ruiping's catalytic asymmetric amino-allylation of aldehydes

Scheme 1.3 (cont'd)



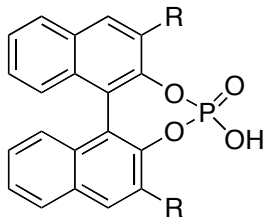
The development of a more efficient *catalytic asymmetric amino-allylation of aldehydes* protocol that gives excellent enantioselectivity for both aromatic and aliphatic substrates has remained an elusive, albeit an actively pursued goal in the field.

CHAPTER TWO
DIRECT CATALYTIC ASYMMETRIC AMINO-ALLYLATION OF ALDEHYDES – SYNERGISM OF A CHIRAL BOROX BRØNSTED ACID AND BENZOIC ACID

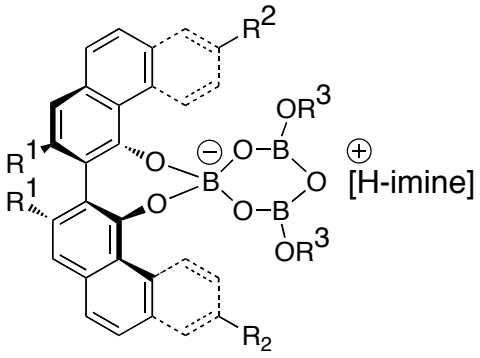
2.1 Introduction

The field of chiral Brønsted acid catalysis has grown to great prominence in a very short period of time.[13] Phosphoric acid derivatives of BINOL and BINOL derivatives are by far the most important members of the family of strong chiral Brønsted acids, due to the great diversity of catalysts by introduction of substituents primarily into the 3,3'-positions of BINOL and to a lesser extent at the 6,6'-positions.

Scheme 2. 1 A new class of chiral Brønsted acid BOROX **9**



phosphoric acids derived from BINOL and BINOL derivatives

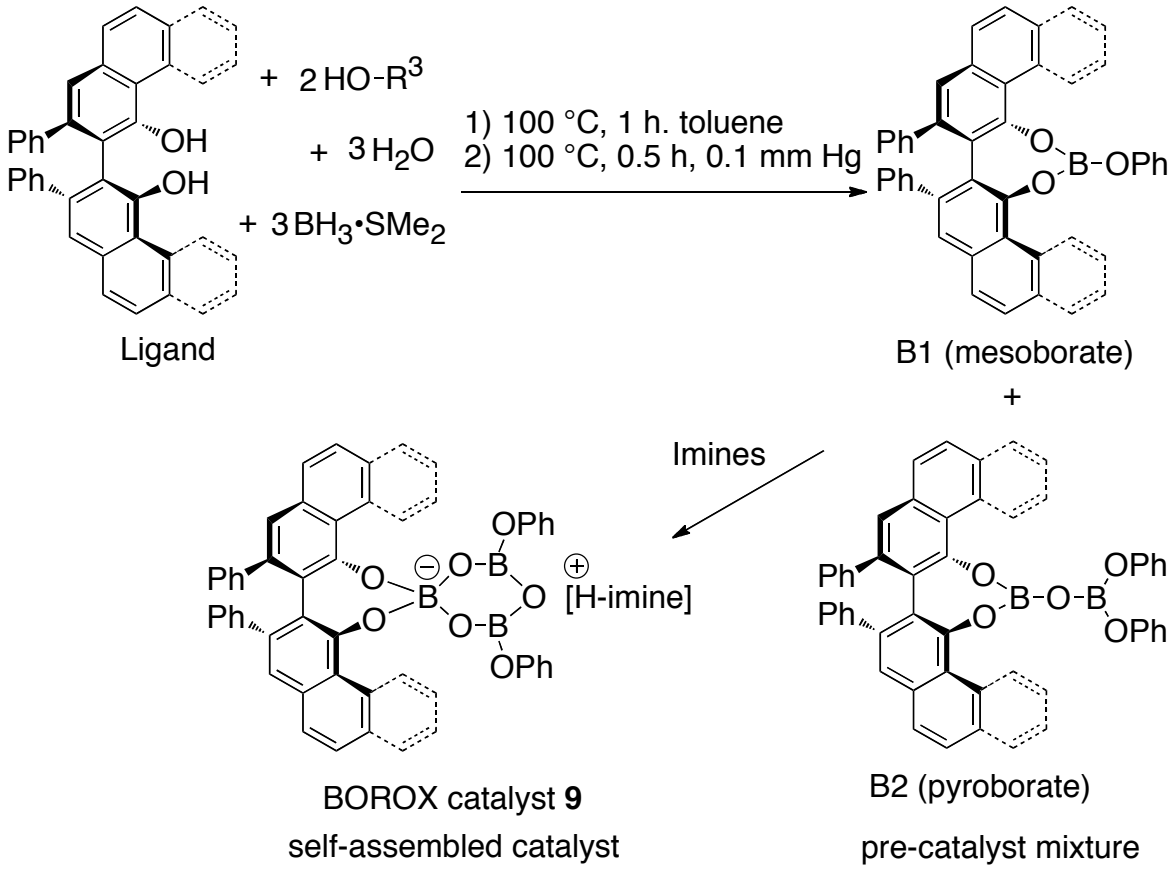


BOROX catalyst **9**

In the course of development of a catalytic asymmetric method for the synthesis of *cis*-aziridines, our former group members have discovered a new class of strong chiral Brønsted acids in the form of the boroxinate species **9** (Scheme 2. 1) that exists as an ion pair consisting of a chiral boroxinate anion derived from either the VANOL **12** or VAPOL **13** ligand (Figure 2. 1) and a protonated iminium.[14] A pre-catalyst mixture mesoborate B1 and pyroborate B2 were formed initially when ligand VANOL or VAPOL was heated with 4 equivalent of $B(OPh)_3$ and 1equivalent of H_2O. NMR and crystal

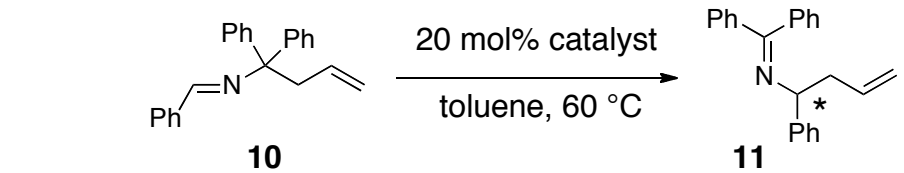
structure evidence revealed that addition of an imine to this pre-catalyst mixture resulted in the self-assembly of BOROX catalyst **9** (Scheme 2. 2). Boroxinate assembly can be induced by the imine either from the ligand and 4 equivalent of commercial $B(OPh)_3$ or from the ligand and 3 equivalnet of BH_3•SMe_2, 2 equivalent of phenol and 3 equivalent of H_2O.

Scheme 2. 2 Self-assembled BOROX catalyst **9** with imines

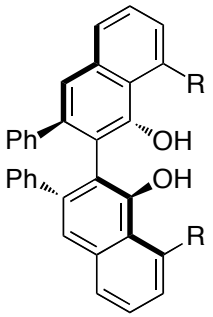


2.2 Initial results of the catalytic asymmetric aza-Cope rearrangement with chiral Brønsted acid BOROX 9

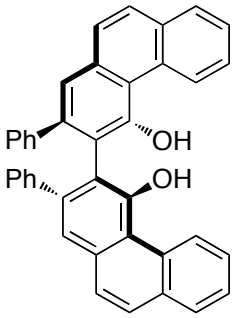
Figure 2. 1 Initial results with chiral Brønsted acid BOROX **9**



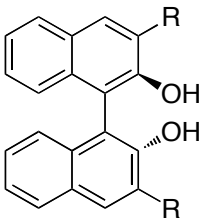
10 **11**



(*S*)-VANOL (R=H)



(*S*)-VAPOL, **13**



(*R*)-BINOL

	% ee	% yield
12, R=H,	19	82
14, R=Ph,	3	70

% ee	% yield
4	67

	% ee	% yield
15, R=H,	4	49
16, R=Ph,	5	ND

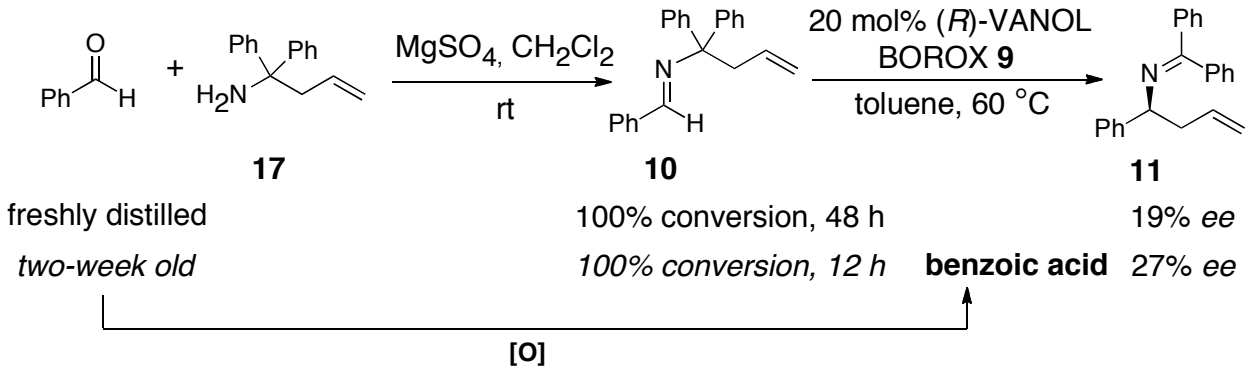
Catalyst made from 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$, 2 equiv of phenol and 3 equiv of H_2O at 100 °C for 1 h, followed by full vacuum, 100 °C, 30 min.

For ease of optimization, imine **10** was chosen to initially examine the aza-Cope rearrangement with BOROX catalysts derived from various ligands as shown in Figure 2. 1. The standard conditions for imine **10** will then be translated to other aldehydes later on. We hoped that imine **10** could induce the self-assembly of the active BOROX catalyst **9** and in the same time frame, that BOROX **9** would catalyze the aza-Cope rearrangement to afford the masked homo-allylic amines **11**. With 20 mol% BOROX catalyst derived from (*S*)-VANOL **9**, 19 % *ee* and 82% yield were obtained. When a sterically hindered VANOL derivative **14** was utilized, the *ee* dropped to 3%. A decrease in ee was also observed with BOROX catalysts prepared from VAPOL **13**, BINOL **15** and BINOL derivative **16**.

The background reaction test with imine **10** at 60 °C in toluene revealed that the aza-Cope rearrangement did not occur under thermochemical conditions in the absence of catalyst.

2.3 Serendipitous discovery of the synergistic effect of benzoic acid on BOROX catalyst 9

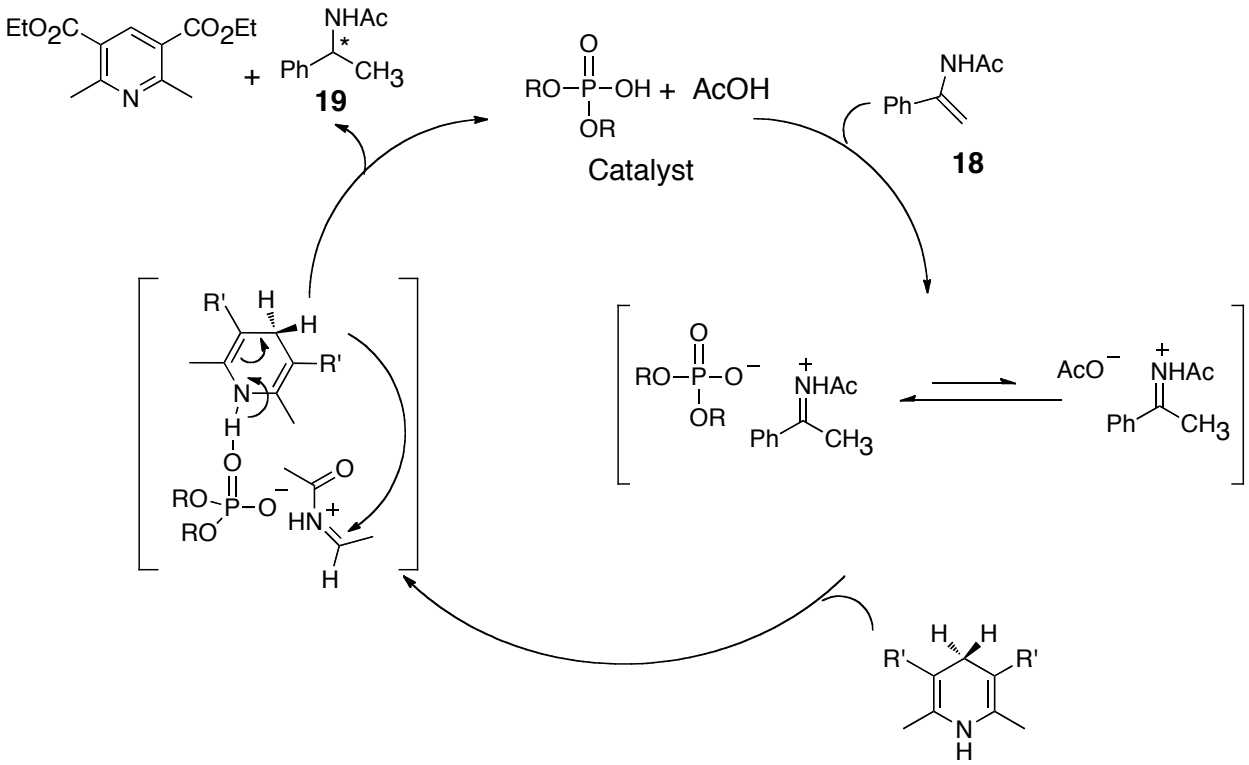
Scheme 2. 3 Synergistic interplay of BOROX **9** and benzoic acid



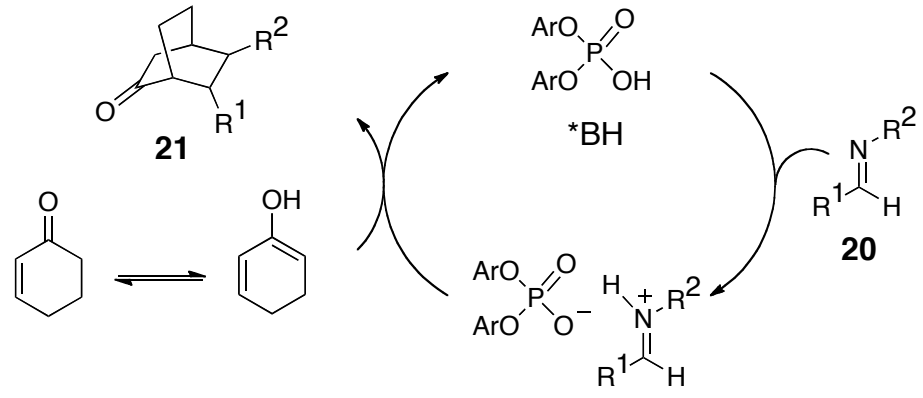
During the course of optimization, it was found that the rearrangement of imine **10** prepared from a sample of benzaldehyde that had not been distilled for two-weeks led to a higher induction with the VANOL BOROX catalyst **9** (27% ee, 69% yield, Scheme 2. 3). It was speculated that a small amount of benzaldehyde was oxidized to benzoic acid, and that its presence in a catalytic amount was responsible for the enhanced asymmetric induction (Scheme 2. 3).

To test this assumption, 10 mol% benzoic acid was thus added to the reaction mixture. A significant increase in ee (from 27 % ee without benzoic acid vs. 45% ee with benzoic acid) was observed for the VANOL-derived BOROX catalyst **9**.

Scheme 2. 4 Orthogonal interplay of chiral and non-chiral Brønsted acids



Antilla's asymmetric hydrogenation of enamides catalyzed by a dual acid system

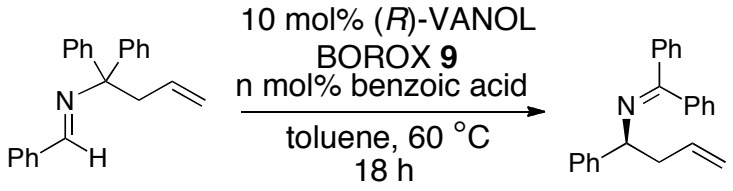


Ruiping's coorperative Brønsted acid catalyzed synthesis of isoquinuclidines

The orthogonal interplay of a chiral Brønsted acid and a non-chiral Brønsted acid has been reported by Rueping's group in 2006 and Antilla's group in 2009.[15,16] In the former reaction, the two Brønsted acids were involved in two parallel steps, while for the

latter, an achiral Brønsted acid was utilized to keep a sufficient concentration of an aryl iminium and the addition of the achiral acid did not affect the asymmetric induction. However, for our approach, the addition of benzoic acid quickly led to a color change of the reaction mixture and significant enhancement in the enantioselection was achieved, which clearly indicated a synergistic interaction of these two Brønsted acids on the asymmetric induction. To the best of our knowledge, this is the first example of the non-orthogonal coexistence of a chiral and an achiral Brønsted acid in asymmetric catalysis.

Table 2. 1 Study of effect of the amount of benzoic acid on the asymmetric induction



10 **11**

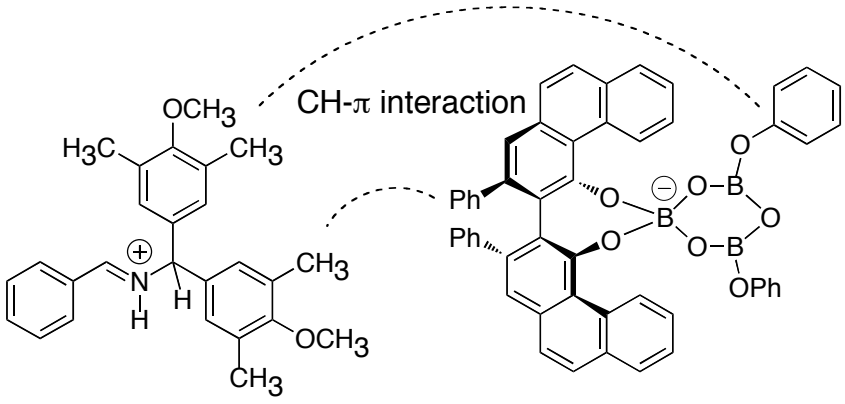
Entry[a]	n	%Yield[b]	%ee[c]
1	0	77	25
2	1	80	40
3	5	85	69
4	10	81	72
5	15	81	72
6	20	83	70
7	40	84	68
8	60	84	66

a. Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in toluene at 0.2 M in imine **10** for 18 h and went to 100% completion at the indicated temperature. Catalyst **9** was prepared by heating 1 equiv of ligand, 3 equiv of BH_3•SMe_2, 2 equiv of PhOH, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. b. Isolated yield after silica gel column chromatography. c. Chiral HPLC.

An equal amount of benzoic acid with the chiral VANOL-BOROX catalyst led to the maximum *ee* (Table 2. 1, entry 5), and any further increase in the amount of benzoic acid resulted in a marginal decrease in enantioselectivity (Table 2. 1, entry 3 and 4). Under the same reaction conditions, with just benzoic acid itself, at the absence of VANOL-BOROX **9** catalyst, the aza-Cope rearrangement did not occur.

2.4 Mapping the protecting group for aza-Cope rearrangement with BOROX 9

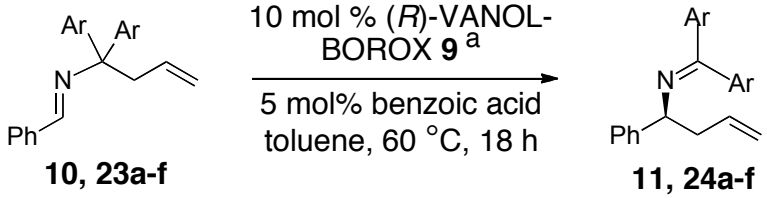
Figure 2. 2 CH- π interaction between BOROX catalyst and imine in Wulff *cis*-aziridination reaction



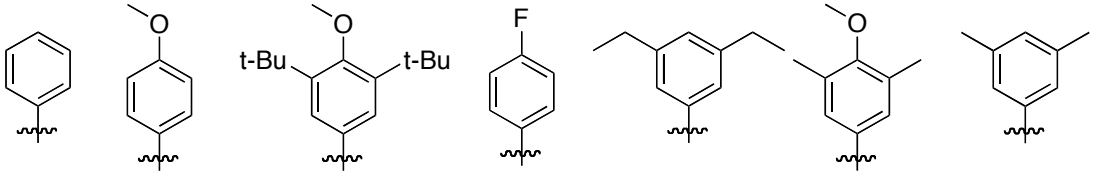
Inspired by the crucial non-covalent CH-π interaction (Figure 2. 2) between the boroxinate catalyst and the imine substrate in our previously reported aziridination protocol, [14,17] we turned our attention to the engineering of this potential modular interaction with different diarylmethyl groups in the aminoallylation of aldehydes. A correlation between the asymmetric induction and the electronic and steric effects of various diarylmethyl groups was established by comparing the diarylmethyl groups with the benchmark diphenylmethyl group **10**. As shown in Figure 2. 3, the introduction of an electron-donating group (Figure 2. 3, compound **23a**, 23% *ee*) into the aryl group greatly abated the induction, while for **23c** an electron-withdrawing substituent hardly caused a

change. However, installation of two methyl groups to the electron-rich aryl group (compound **23e**, 64% *ee*) could cancel the adverse effect of the methoxyl group, conveying a notable gain in *ee*. Conversely, for the aziridination reaction that we have previously examined, the presence of the methoxyl group and two methyl groups in the 3- and 5- positions was equally important to the enantioselection.[17h,k] We then decided to replace the two methyl groups in **23e** with even larger *t*-butyl groups (compound **23b**, 39% *ee*), however, the *ee* greatly dropped by 25%. Based on the results obtained for compounds **23a**, **23b** and **23e**, a new modular group (compound **23f**, 69% *ee*) was designed for this reaction, which, as we expected, gave the optimal asymmetric induction amongst all the diarylmethyl groups evaluated.

Figure 2. 3 Optimization of the aryl groups for maximum asymmetric induction



Ar =



	10	**23a**	**23b**	**23c**	**23d**	**23e**	**23f**
% yield [b]	76	47	51	76	71	70	85
% ee [c]	42	23	39	40	40	64	69

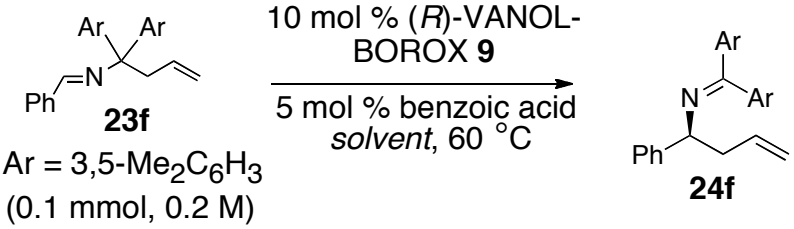
[a.] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in toluene at 0.2 M in imine for 18 h and went to 100% completion at the indicated temperature. Catalyst **9** was prepared by heating 1 equiv of ligand, 3 equiv of BH_3•SMe_2, 2 equiv of PhOH, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The catalyst

Figure 2.3 (cont'd)

solution was transferred to a Schlenk test tube containing imine, directly followed by addition of benzoic acid at room temperature. The reaction mixture was heated to 60 °C. [b.] Isolated yield after silica gel column chromatography. [c.] Chiral HPLC.

2.5 Optimization of the solvent for the aza-Cope rearrangement with BOROX catalyst 9

Table 2. 2 Solvent screening for the aza-Cope rearrangement of imine **23f**



23f

Ar = 3,5-$Me_2C_6H_3$

(0.1 mmol, 0.2 M)

24f

Entry[a]	Solvent	Time (h)	%Yield **24f**[b]	%ee **24f**[c]
1	trifluorotoluene	18	73	30
2	benzene	18	78	60
3	toluene	18	85	69
4	xylenes	18	86	75
5	*p*-xylene	32	82	72
6	*o*-xylene	24	83	70
7	*m*-xylene	18	92	78
8	mesitylene	18	86	78
9	*t*-butylbenzene	18	63	68
10	anisole	18	80	53
11	THF	18	77	-15
12	MTBE	18	79	33
13	CH_3CN	24	75	-6
14	ethylacetate	18	83	14
15	dichloroethane	18	79	3
16	CCl_4	24	82	67
17	cyclohexane	32	78	47

[a.] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in toluene at 0.2 M in imine **23f** for 18 h and went to 100% completion at the indicated temperature. Catalyst

Table 2.2 (cont'd)

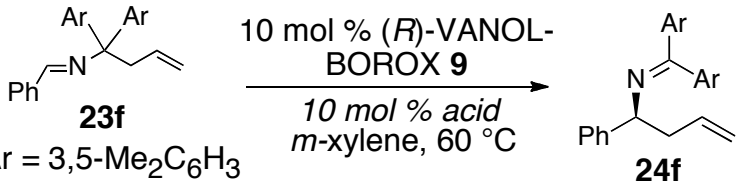
9 was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$, 2 equiv of PhOH, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The catalyst solution was transferred to a Schlenk test tube containing imine, directly followed by addition of benzoic acid at room temperature. [b.] Isolated yield after silica gel column chromatography. [c.] Chiral HPLC.

To further optimize the reaction conditions, we varied the solvent and found that the highest asymmetric induction was observed when the reaction was carried out in *m*-xylene and mesitylene at 60 °C (Table 2. 2, entry 7 and 8). However, considering the high boiling point of mesitylene (165 °C), we decide to use *m*-xylene as the solvent of choice. The solvent study was carried out before we found equal amount of benzoic acid with respect to catalyst **9** gave the maximum enantioselectivity.

2.6 Study of different achiral acids as additive

Although a broad range of achiral acids were examined, benzoic acid as additive gave superior yields and asymmetric induction than any of the other types of acids screened (Table 2.3). Introduction of electron-donating substituents into benzoic acid led to subtle changes in the enantioselectivity (entry 21 and 22). Electron-withdrawing substituents greatly abated the asymmetric induction (entry 23). Steric tuning of various benzoic acids seemed not to affect the asymmetric induction (entry 10-12) unless two substituents were introduced into the *ortho*-positions simultaneously (entry 27 and 35).

Table 2. 3 Effects of various acids on the BOROX catalyst **9** in the aza-Cope rearrangement



23f

Ar = 3,5-$Me_2C_6H_3$

(0.1 mmol, 0.2 M)

24f

Entry[a]	Acid (pKa)	Time (h)	%Yield **24f**[b]	%ee **24f**[c]
1	TFA (-0.26)	18	79	17
2	diphenyl hydrogen phosphate (1)	22	77	19
3	benzoic acid (4.2)	18	92	78
4	acetic acid (4.8)	22	78	63
5	trimethylacetic acid	18	82	67
6	Adamantane Carboxylic Acid	18	79	66
7	Chloroacetic Acid (2.86)	18	74	40
8	$CF_3SO_2NH_2$ (6.3)	18	86	23
9	diethyl phosphoramidate	18	76	20
10	phenylboronic acid (7)	18	78	31
11	phenol (10)	18	76	23
12	2-Naphthylacetic Acid (~4.31)	18	79	70
13	4-ethoxyphenylacetic acid	18	79	71
14	phenylacetic acid	18	76	70
15	Trifluoro-*p*-tolylacetic acid	18	77	65
16	Diphenylacetic acid	18	78	54
17	2-fluorobenzoic acid (3.3)	18	82	70
18	3-fluorobenzoic acid (3.9)	18	81	73
19	4-fluorobenzoic acid (4.1)	18	84	76
20	4-methoxybenzoic acid (4.6)	18	72	63
21	4-propoxybenzoic acid	18	78	77
22	4-dimethylaminobenzoic acid (5.1)	18	81	77
23	4-nitrobenzoic acid (3.3)	18	76	63
24	4-tert-butylbenzoic acid	18	72	77
25	4-trifluoromethylbenzoic acid	18	78	73
26	4-phenylbenzoic acid	18	76	76
27	2,4,6-trimethylbenzoic acid	18	71	29
28	1-naphthalenecarboxylic acid (3.7)	18	79	75
29	2-methylbenzoic acid (3.9)	18	78	74
30	3-methylbenzoic acid (4.2)	18	78	77
31	4-methylbenzoic acid (4.3)	18	75	77
32	3,5-dimethylbenzoic acid	18	79	75
33	3,5-di-*tert*-butylbenzoic acid	18	78	76

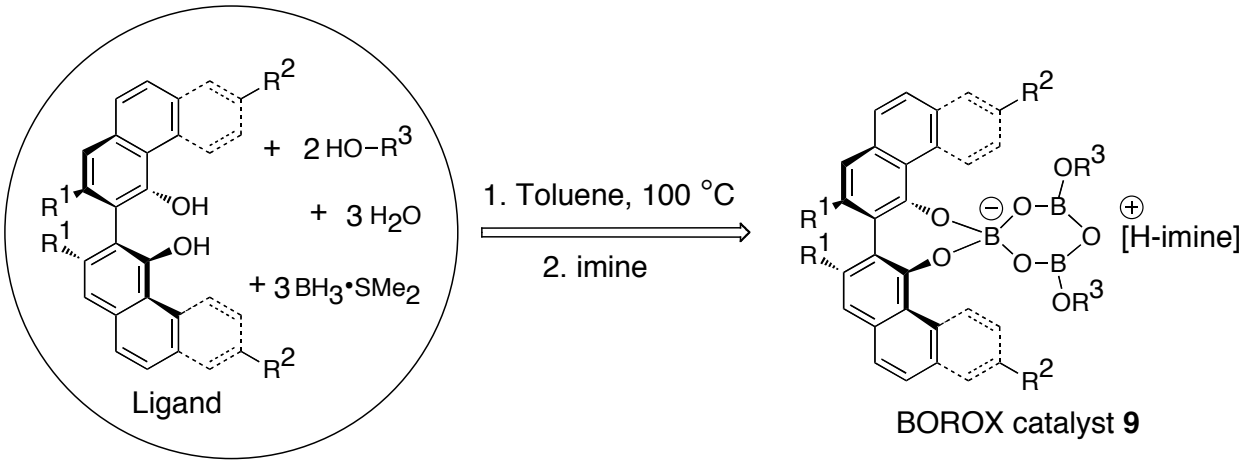
Table 2.3 (Cont'd)

34	Phthalic acid	18	57	12
35	9-Anthracenecarboxylic acid	18	77	25

[a.] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in toluene at 0.2 M in imine **23f** for 18 h and went to 100% completion at the indicated temperature. Catalyst **9** was prepared by heating 1 equiv of ligand, 3 equiv of BH_3•SMe_2, 2 equiv of PhOH, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The catalyst solution was transferred to a Schlenk test tube containing imine, directly followed by addition of benzoic acid at room temperature. [b.] Isolated yield after silica gel column chromatography. [c.] Chiral HPLC.

2.7 Diversity of BOROX catalyst 9

Figure 2. 4 Two dimensional diversity of the BOROX **9** catalyst



As in the case for BINOL phosphoric acid, diversity in the boroxinate **9** can also be achieved by preparing the catalyst from substituted biaryl ligands, most easily by varying the nature of the substituents R^1 and R^2 (Figure 2. 4). However, a second dimension to the diversity of the boroxinate catalyst is possible by variation of the substituent R^3 that is derived from an alcohol or phenol (Figure 2. 4). The practicality of

this diversity is greatly enhanced by the fact that the catalysts are assembled in-situ from the ligand, BH_3•SMe_2, phenol or alcohol and H_2O upon the addition of imine.

2.7.1 Tuning the BOROX catalyst 9 with phenol modules

The effect of the change in the BOROX catalyst **9** structure by varying the R^3 group of the phenol or alcohol used in catalyst generation was explored (Table 2. 4). A number of different phenols and alcohols were examined and the results are shown in Table 2. 4**.** The highest selectivity is observed with 2,4,6-trimethylphenol (Table 2. 4**,** entry 9). The asymmetric induction drops to 51% with electron poor *para*-nitrophenol (Table 2. 4, entry 18). The largest perturbation is noted with bulky anthracen-9-ylmethanol, where asymmetric induction drops dramatically to 35% (Table 2. 4, entry 26).

Table 2. 4 Screening various phenols and alcohols

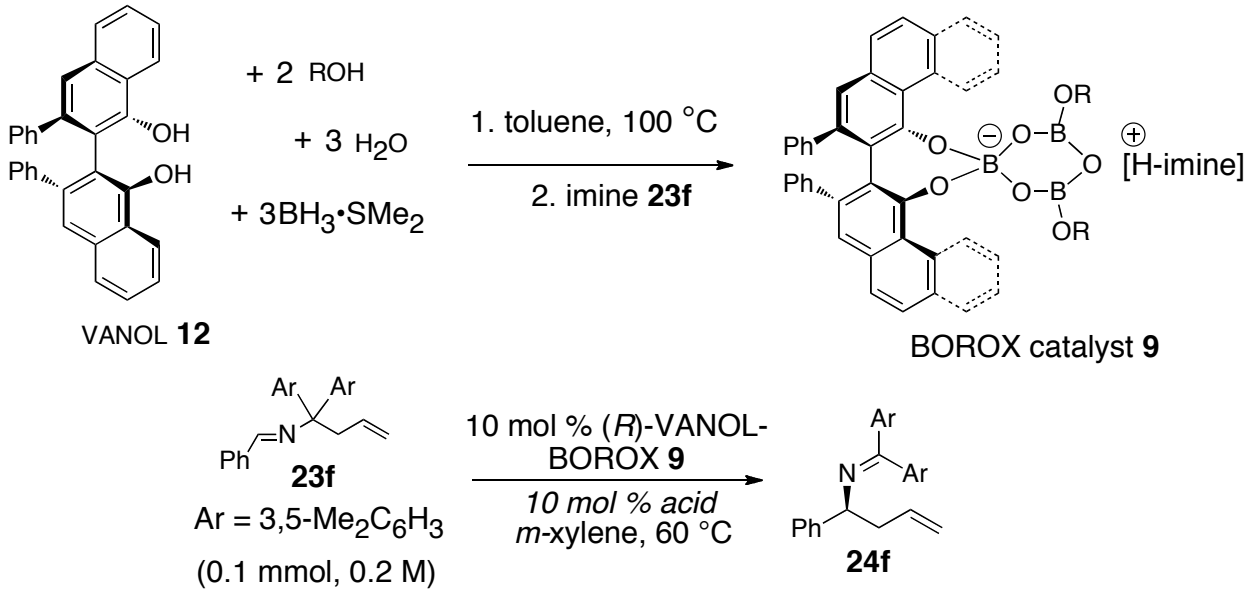


Table 2.4 (Cont'd)

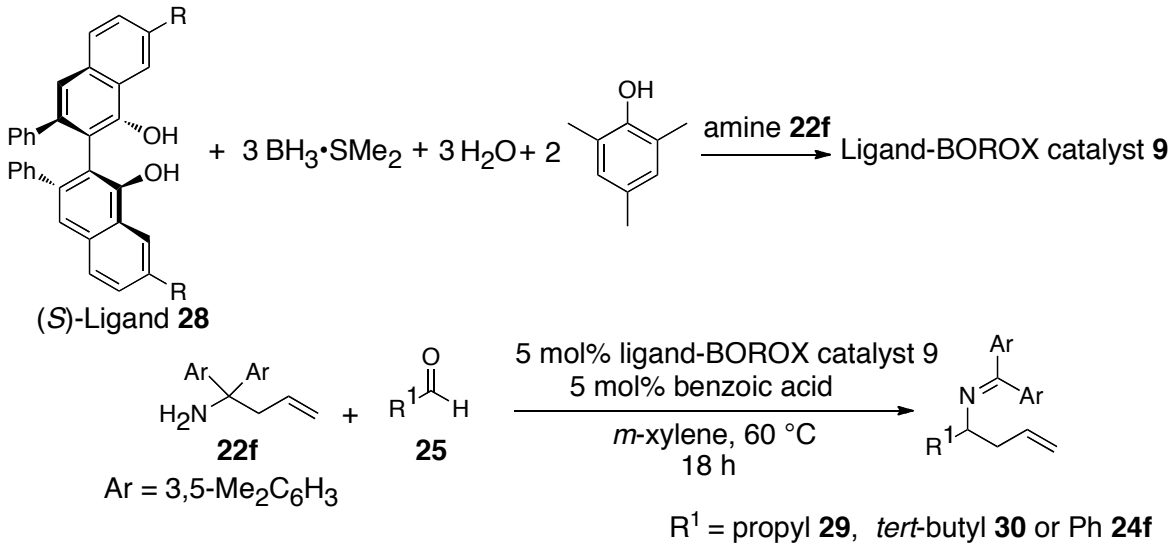
Entry[a]	Phenol	%Yield[b]	%ee[c]
1	phenol	89	78
2	2,6-dimethylphenol	79	81
3	2,6-diisopropylphenol	78	80
4	2,6-di-*tert*-butylphenol	76	76
5	2,6-diphenylphenol	74	76
6	2-isopropylphenol	72	80
7	2-*tert*-butylphenol	74	80
8	2-phenylphenol	72	78
9	2,4,6-trimethylphenol	79	83
10	2,4,6-tri-*tert*-butylphenol	72	72
11	4-methylphenol	72	77
12	4-isopropylphenol	73	77
13	4-phenylphenol	69	73
14	3,5-dimethylphenol	71	77
15	1-naphthol	74	77
16	2-naphthol	72	73
17	4-methoxyphenol	71	77
18	4-nitrophenol	74	51
19	9-phenanthrol	72	77
20	2,6-dimethoxyphenol	72	65
21	3,4,5-trimethoxyphenol	73	78
22	2,6-dipropyl-4-tert-butylphenol	74	79
23	1-adamantanol	75	77
24	*n*-butanol	73	74
25	cyclohexanol	73	74
26	anthracen-9-ylmethanol	52	35

a. Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in toluene at 0.2 M in imine **23f** for 18 h and went to 100% completion at the indicated temperature. Catalyst **9** was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$, 2 equiv of PhOH, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The catalyst solution was transferred to a Schlenk test tube containing imine, directly followed by addition of benzoic acid at room temperature. b. Isolated yield after silica gel column chromatography. c. Chiral HPLC.

2.7.2 Tuning the BOROX catalyst 9 with various ligands

The second parameter that can be varied to produce large numbers of boroxinate catalysts for screening is the ligand itself. The investigation was conducted after we have optimized the reaction conditions for a direct aminoallylation of aldehydes which is presented in section 2.8. Hence, the current study involves screening the aza-Cope rearrangement with amine **22f** and aldehydes with two different families of ligands; 7,7'-substituted derivatives and 4,4'-substitued ligands. Benzaldehyde **25a**, *n*-butyraldehyde **25o** and trimethylacetaldehyde **25t** were evaluated so that the optimization could include the three major classes of aldehydes. Several different substituents at 7,7' positions were investigated including *t*-butyl, *para*-*t*-butylphenyl, methoxyl, halide and TMS protected acetylene. For benzaldehyde, with 7,7'-fluoro-VANOL as an exception (Table 2.5, entry 12), all the ligands screened either give lower ee's than VANOL ligand (entry 18 and 21) or result in greatly reduced reaction conversions (entry 6, 9, 15, 24, 27). For *n*-butyraldehyde, all the ligands screened give lower *ee*'s in the range of 37-93%. While for trimethylacetaldehyde, 7,7'-methyl-VANOL gives the optimal asymmetric induction 79% *ee,* followed by 7,7'-fluoro-VANOL, which affords 74% *ee*. However, similar to the benzaldehyde case, with other ligands screened for trimethylacetaldehyde, compared with VANOL ligand, either lower enantioselectivity (entry 13, 19, 22) or reduced conversion is observed (entry 4, 7, 25).

Table 2. 5 Tuning the BOROX catalyst **9** with 7,7'-substituted ligands



Entry[a]	R	R^1	Conversion (%)[b]	Yield (%)[c]	ee (%)[d]
1	H	*tert*-butyl	100	94	72
2	H	propyl	100	81	95
3	H	phenyl	100	91	80
4	*tert*-butyl	*tert*-butyl	0	ND	ND
5	*tert*-butyl	propyl	100	81	37
6	*tert*-butyl	phenyl	32	ND	ND
7	*p*-tert-butylphenyl	*tert*-butyl	69	ND	ND
8	*p*-tert-butylphenyl	propyl	92	82	77
9	*p*-tert-butylphenyl	phenyl	22	ND	ND
10	fluoro	*tert*-butyl	100	83	74
11	fluoro	propyl	100	91	92
12	fluoro	phenyl	100	81	82
13	Methoxy	*tert*-butyl	100	64	63
14	Methoxy	propyl	100	55	92
15	Methoxy	phenyl	21	ND	ND
16	Me	*tert*-butyl	100	87	79
17	Me	propyl	100	82	93
18	Me	phenyl	100	78	75
19	Br	*tert*-butyl	100	51	45
20	Br	propyl	100	88	92
21	Br	phenyl	100	79	51
22	I	*tert*-butyl	100	78	30

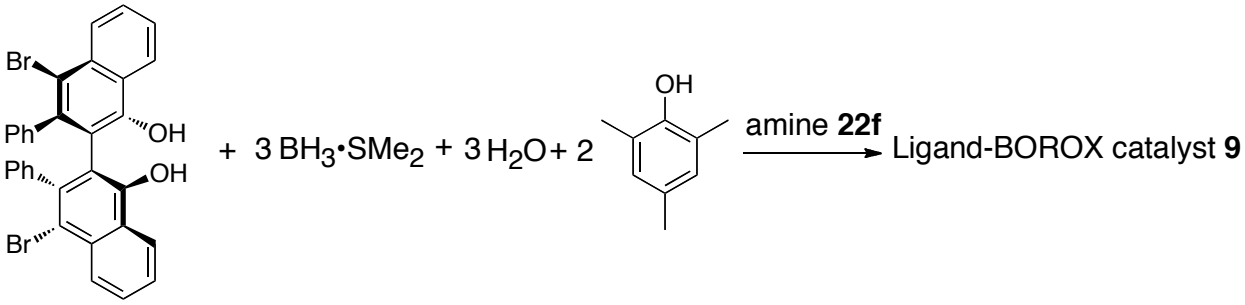
Table 2.5 (cont'd)

23	I	propyl	100	83	77
24	I	phenyl	37	ND	ND
25	—≡—TMS	*tert*-butyl	36	ND	ND
26	—≡—TMS	propyl	88	71	55
27	—≡—TMS	phenyl	0	ND	ND

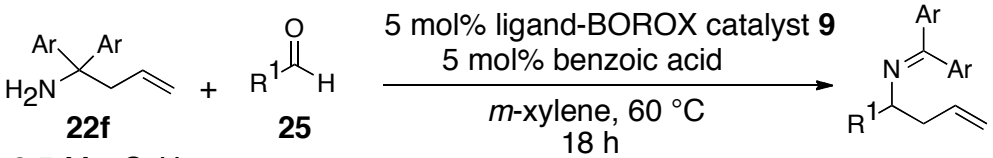
[a.] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in *m*-xylene at 0.2 M in amine **22f** with 1.1 equiv. of aldehydes **25** for 18 h and went to 100% completion at 60 °C. Catalyst was prepared by heating 1 equiv of VANOL ligand, 3 equiv of BH_3•SMe_2, 2 equiv of 2, 4, 6-trimethylphenol, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. Catalyst **9** was transferred to a Schlenk test tube containing flame-dried molecular sieves and amine **22f**. The mixture was stirred for 30 minutes at 60 °C, followed by the direct addition of aldehyde **25** and benzoic acid. [b.] Triphenylmethane as internal standard. [c.] Isolated yield after silica gel chromatography. [d.] Chiral HPLC analysis.

A bromo substituent in the 4 and 4'-position also have large influence (Table 2. 6), which was not expected given the fact that these positions are remote from the active site of BOROX **9** catalyst.

Table 2. 6 Tuning the BOROX catalyst **9** with 4,4'-substituted ligands



(*S*)-Ligand **31**



22f **25**

Ar = 3,5-$Me_2C_6H_3$

R^1 = propyl **29**, *tert*-butyl **30** or Ph **24f**

Table 2.6 (cont'd)

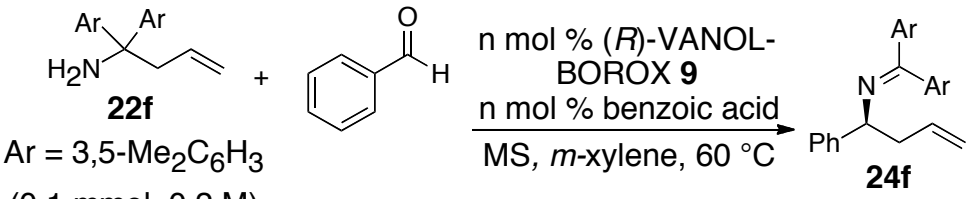
Entry[a]	R^1	Conversion (%)[b]	Yield (%)[c]	ee (%)[d]
1	*tert*-butyl	100	83	72
2	propyl	88	65	67
3	phenyl	100	74	43

[a.] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in *m*-xylene at 0.2 M in amine **22f** with 1.1 equiv. of aldehydes **25** for 18 h and went to 100% completion at 60 °C. Catalyst was prepared by heating 1 equiv of VANOL ligand, 3 equiv of BH_3•SMe_2, 2 equiv of 2, 4, 6-trimethylphenol, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. Catalyst **9** was transferred to a Schlenk test tube containing flame-dried molecular sieves and amine **22f**. The mixture was stirred for 30 minutes at 60 °C, followed by the direct addition of aldehyde **25** and benzoic acid. [c.] Isolated yield after silica gel chromatography. [d.] Chiral HPLC analysis.

2.8 Direct aminoallylation of benzaldehyde

At this point, it was decided to determine whether the conditions that have been optimized for the Cope rearrangement of a pre-formed imine could be translated to a direct aminoallylation of benzaldehyde. Interestingly, only 10% conversion was obtained after 18 h with 4 Å MS (Table 2. 7, entry 1). However, with 5 Å MS, the reaction was complete in 18 h, and to our delight, a comparable enantioselection was achieved (Table 2. 7, entry3). It was found that 5 Å molecular sieves could slowly catalyze the reaction (Table 2. 7, entry 7) and thus effort was extended to optimize the reaction for a minimum amount of molecular sieves to palliate the background reaction and to find the lowest effective catalyst loading. The optimal procedure gave 92% yield and 80% ee with 5 mol % catalyst and 50 mg of 5 Å molecular sieves per 0.1 mmol of amine (Table 2. 7, entry 6).

Table 2. 7 Optimization of molecular sieve loading



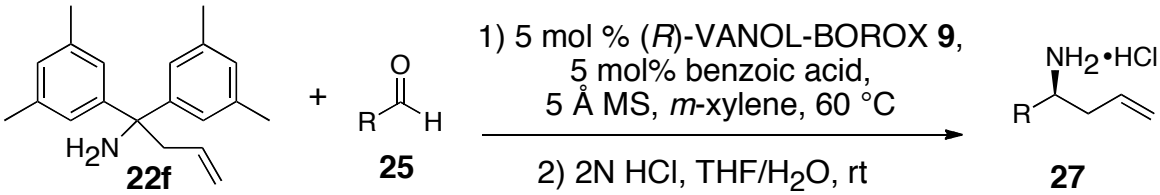
Entry[a]	n mol (%)	MS	MS loading (mg)	Yield (%)[b]	Conv. (%)[c]	ee (%)[d]
1[e]	10	4Å	300	–	10	–
2[e]	10	5Å	300	84	100	71
3	10	5Å	100	82	100	76
4	10	5Å	10	72	100	53
5	5	5Å	100	82	100	75
6	5	5Å	50	92	100	80
7	0	5Å	300	–	15	–

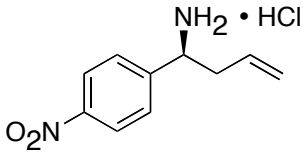
[a.] Unless otherwise specified, all reactions were performed on a 0.1 mmol scale in *m*-xylene at 0.2 M in amine **22f** with 1.1 equiv. of aldehydes for 18 h and went to 100% completion at 60 °C. Catalyst was prepared by heating 1 equiv of VANOL ligand, 3 equiv of BH_3•SMe_2, 2 equiv of 2, 4, 6-trimethylphenol, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. Catalyst **9** was transferred to a Schlenk test tube containing flame-dried molecular sieves and amine **22f**. The mixture was stirred for 30 minutes at 60 °C, followed by the direct addition of benzaldehyde and benzoic acid. [b.] Isolated yield after silica gel column chromatography. [c.] Percent completion of the reaction as determined by the ^{1}H NMR spectrum of the crude reaction mixture. [d.] Chiral HPLC. [e.] Molecular sieves added after stirring VANOL BOROX catalyst **9** and amine **22f** for 30 min at 60 °C.

2.9 Substrate scope for direct aminoallylation of aryl aldehydes

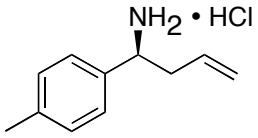
Next, the scope of the catalytic asymmetric allylation of aromatic aldehydes with VANOL BOROX catalyst **9** was tested (Scheme 2. 5). Notably, all the reactions were run on gram-scale; the amines **27** were purified by dissolution into aqueous acid and then extraction of the impurities with ethyl acetate, which afforded analytically pure

Scheme 2. 5 Substrate scope for direct catalytic asymmetric aminoallylation of aromatic aldehydes with VANOL BOROX catalyst [a,b]

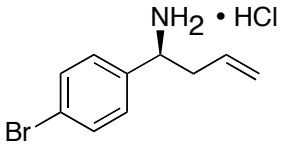




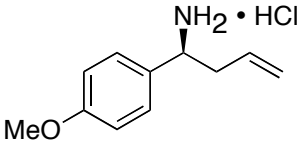
27a, 80% y, 97% ee



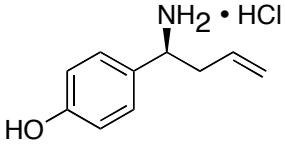
27b, 94% y, 87% ee



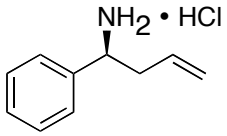
27c, 81% y, 95% ee



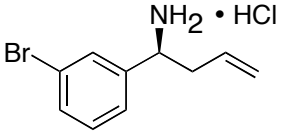
27d, 94% y, 85% ee



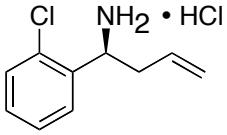
27e, 84% y, 93% ee



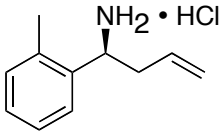
27f, 91% y, 80% ee



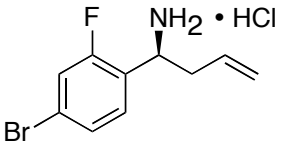
27g, 83% y, 90% ee



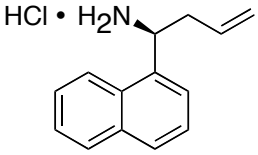
27h, 99% y, 93% ee



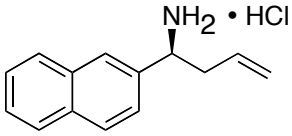
27i, 90% y, 80% ee



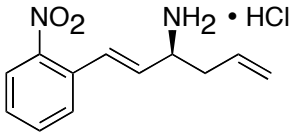
27j, 81% y, 95% ee



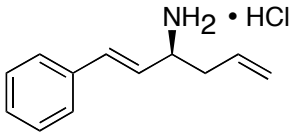
27k, 86% y, 90% ee



27l, 77% y, 80% ee



27m, 84% y, 94% ee



27n, 85% y, 90% ee

Scheme 2.5 (cont'd)

[a.] Unless otherwise specified, all reactions were performed on a 4 mmol scale in *m*-xylene at 0.2 M in amine **22f** with 1.1 equi of aldehyde for 18-30 h and went to 100% completion at the indicated temperature, except for **25d**, which was complete in 55 h. Catalyst was prepared by heating 1 equiv of VANOL ligand, 3 equiv of BH_3•SMe_2, 2 equiv of 2, 4, 6-trimethylphenol, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. Catalyst **9** was transferred to a Schlenk test tube containing flame-dried molecular sieves and amine **22f**. The mixture was stirred for 30 minutes at 60 °C, followed by the direct addition of aldehydes and benzoic acid. Subsequent hydrolysis usually takes 3-18 h. [b.] Asymmetric inductions were measured on corresponding imines **26a-n** isolated from a separate aza-Cope rearrangement.

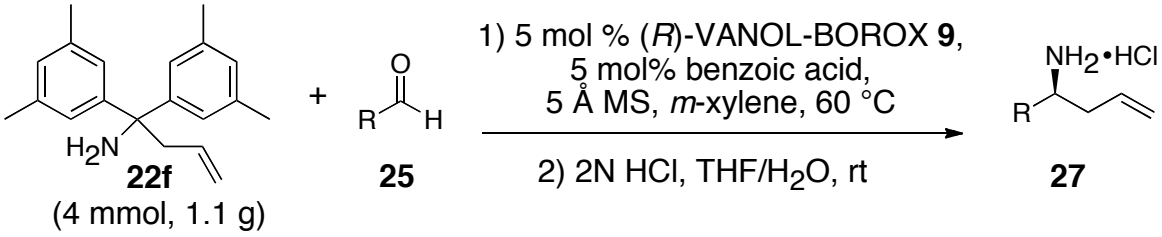
homoallylic amine hydrochlorides suitable for prolonged storage or immediate use. A wide range of aromatic aldehydes with varying electronic and steric demands were found to undergo the aminoallylation with both high *ee* and yield. The asymmetric inductions were measured in a separate reaction in which the corresponding imines were isolated and fully characterized. Substrates bearing *para*-electron-withdrawing substituents are particularly effective, with enantioselectivities between 93-97% *ee* (Scheme 2. 5, **25a, c**, **e**, **j**). The functionally rich substrates such as aldehydes **25m** and **25n** work exceedingly well, and upon hydrolysis, the former affords 84% yield with 94% *ee*, and the latter, 85% yield and 90% *ee*. Electron-rich and sterically demanding substrates such as aldehydes **25b** and **25d** also shows good *ee* and yields with this methodology.

2.10 Substrate scope for direct aminoallylation of aliphatic aldehyde

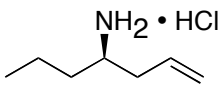
Aminoallylation of aliphatic substrates had been a lacuna in the only existing report of catalytic asymmetric aminoallylation of aldehydes;[11] thus in the development of a

general asymmetric aminoallylation protocol, inclusion of aliphatic aldehydes is a certain prerequisite. It was found that 1° and 2° aldehydes both performed well and provided good yields and excellent levels of asymmetric inductions with this new methodology (Scheme 2. 6, entry **27o**-**s**). Although an excellent yield was obtained for the sterically demanding 3° substrate **25 t**, only a moderate induction was observed.

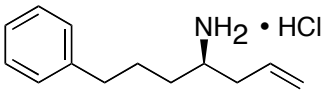
Scheme 2. 6 Substrate scope for direct catalytic asymmetric aminoallylation of aliphatic aldehydes with the VANOL BOROX catalyst [a,b]



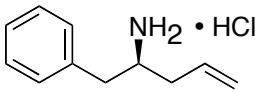
22f (4 mmol, 1.1 g) + **25** → **27**



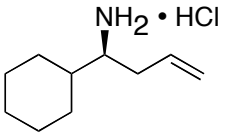
27o, 81% y, 95% ee



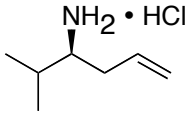
27p, 71% y, 94% ee



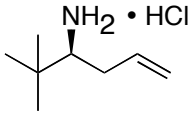
27q, 57% y, 90% ee



27r, 85% y, 92% ee



27s, 75% y, 93% ee



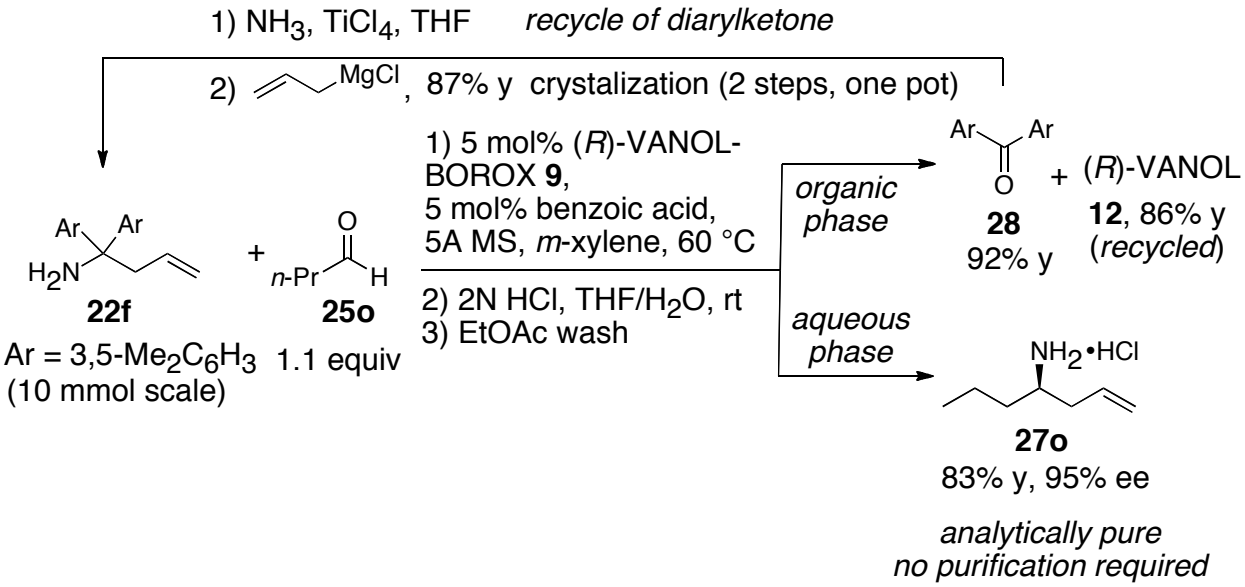
27t, 94% y, 72% ee

[a.] Unless otherwise specified, all reactions were performed on a 4 mmol scale in *m*-xylene at 0.2 M in amine **22f** with 1.1 equi of aldehyde for 18-30 h and went to 100% completion at the indicated temperature, except for **25t**, which was complete in 96 h. Catalyst was prepared by heating 1 equiv of VANOL ligand, 3 equiv of BH_3•SMe_2, 2 equiv of 2, 4, 6-trimethylphenol, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. Catalyst **9** was transferred to a Schlenk test tube containing flame-dried molecular sieves and amine **22f**. The mixture was stirred for 30 minutes at 60 °C, followed by the direct addition of aldehydes and benzoic acid. Subsequent hydrolysis usually takes 3-18 h. [b.] Asymmetric inductions were measured on corresponding imines **26o-t** isolated from a separate aza-Cope rearrangement.

2.11 Scale-up, recycle of starting amine and VANOL Ligand

Considering that a large fraction of the starting amine **22f** is incorporated into diaryl ketone **28** after hydrolysis, to make the current method more practical, we developed an efficient route to recycle diaryl ketone **28** (Scheme 2. 7). Compound **28** was initially converted to the corresponding diaryl ketimine via condensation with ammonia, and without isolation, the ketimine was allylated and purified by crystallization to afford the desired compound **22f** with 87% yield in a one-pot manner.

Scheme 2. 7 Recycle of diaryl ketone **28**

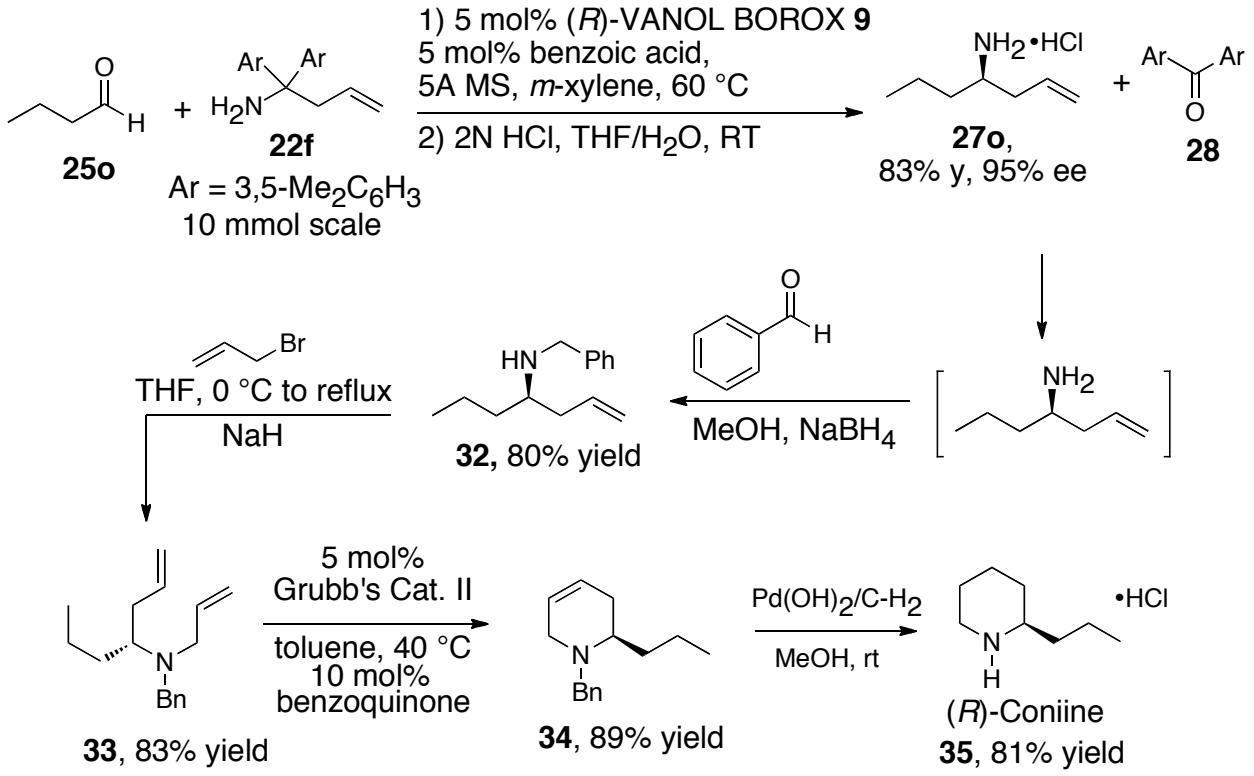


2.12 Total synthesis of (*R*)-Coniine

The piperidine subunit is one of the ubiquitous pharmaceutical cores and widely present in bioactive molecules and natural products.[18] Coniine, a popular target for the demonstration of chiral methodology in the piperidine field, has been synthesized with ring-closing metathesis approach.[19] However, all the synthesis with the RCM method involved chiral auxiliaries which is mainly due to the limited catalytic asymmetric

methods for access to aliphatic homoallylic amines. To demonstrate the utility of our methodology, especially for aliphatic substrates, the total synthesis of Coniine **35** was conducted (Scheme 2. 8)

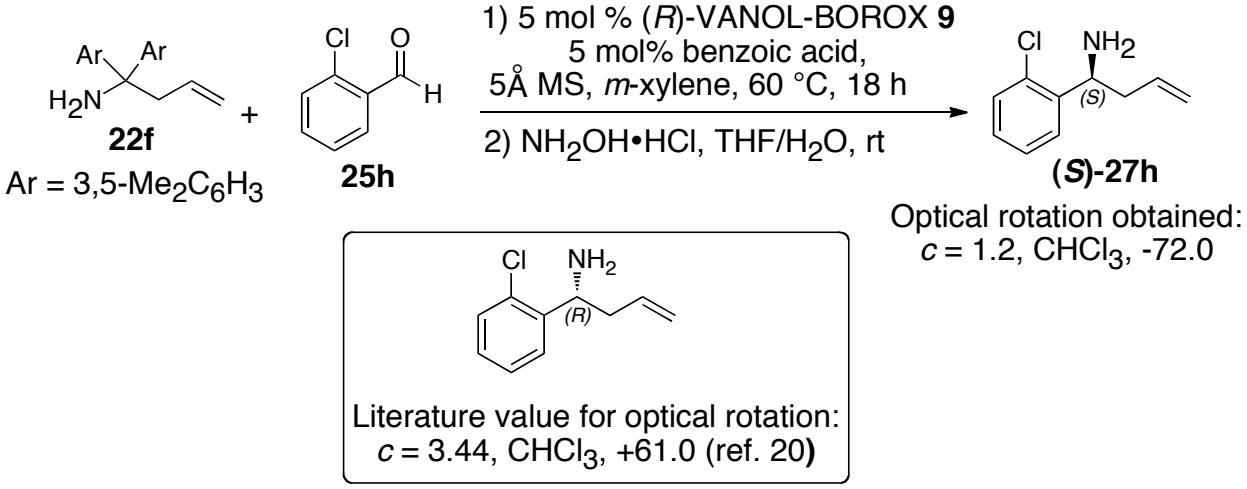
Scheme 2. 8 Total synthesis of (*R*)-Coniine

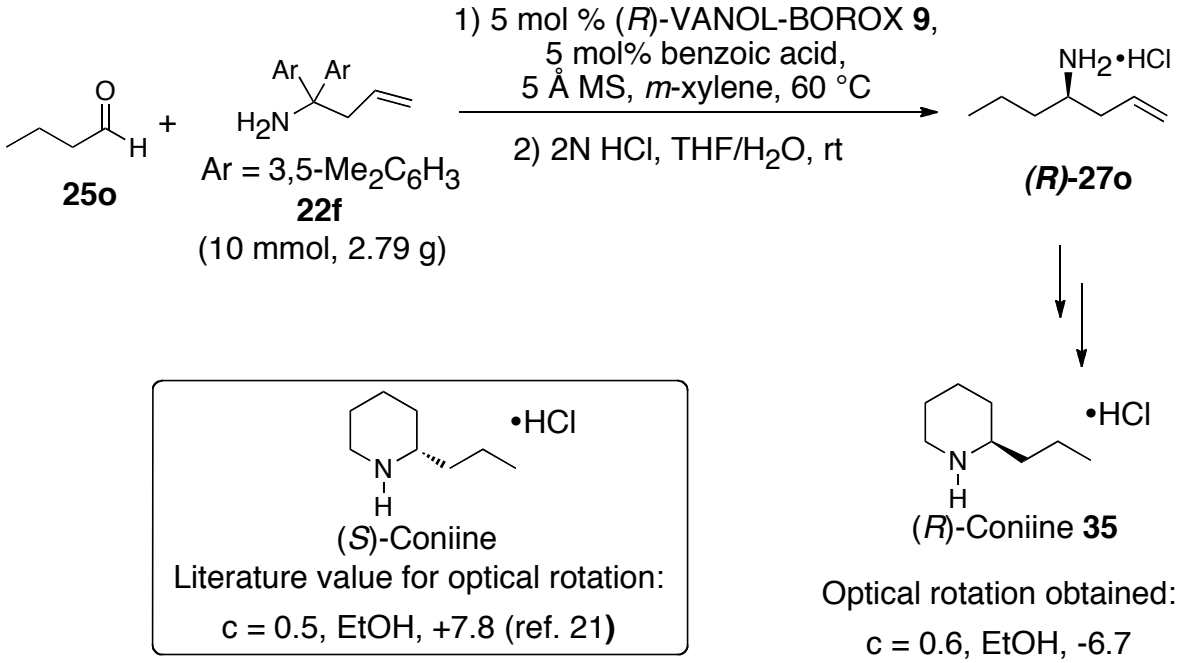


2.13 Determination of the absolute configuration of amine 27h and 27o from the direct catalytic asymmetric aminoallylation of aldehydes 25h and 25o

The absolute configuration of the major enantiomer of amines **27h** was determined by comparing their optical rotations with literature values[20](Scheme 2. 9). The homo-allylic amines **27h** prepared by this protocol result from a *Si* face attack of the allyl fragment on the imine complex by the catalyst prepared from (*R*)-VANOL. The absolute configuration of all other homo-allylic amines were assumed to be the same as **27h**.

Scheme 2. 9 Absolute configuration in the direct catalytic asymmetric aminoallylation of aldehydes





The product **27o** from the reaction of *n*-butanal with the (*R*)-VANOL catalyst gave the (*R*)-configuration also from Si-face addition. This was confirmed when (*R*)-**27o** was converted to (*R*)-Coniine **35** and the comparison of its rotation with that reported in the

literature.[21] On this basis, it was assumed that the other aliphatic aldehydes substrates also gave Si-face addition with (*R*)-VANOL. Note that common to both aryl and aliphatic aldehydes is that the reaction occurs by addition to the Si-face of the aldehyde (imine).

2.14 Conclusion

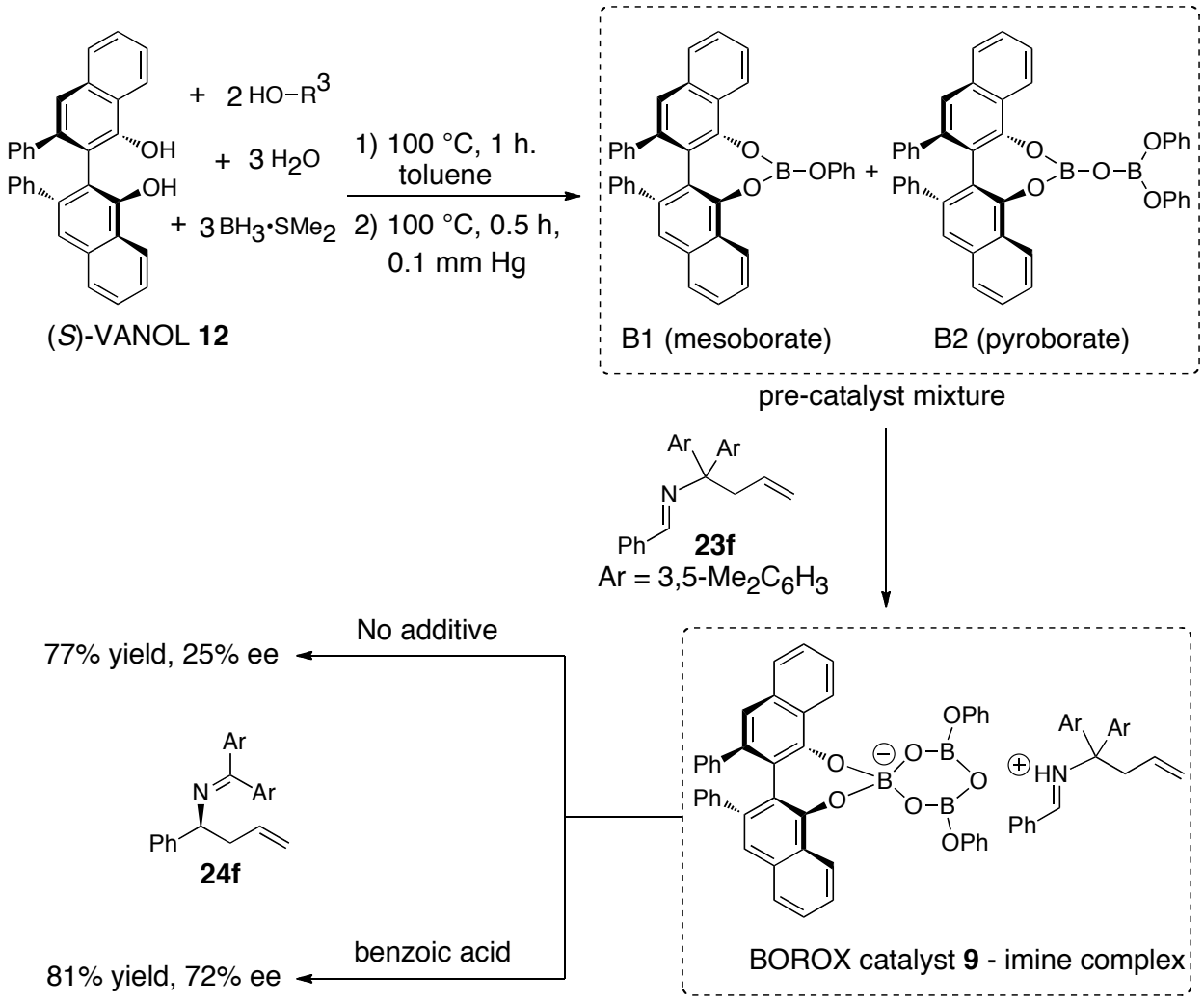
In summary, we have developed a highly enantioselective protocol for aminoallylation of aldehydes, involving an aza-Cope rearrangement of an in-situ generated imine which upon hydrolysis provides the homoallyic amine in high asymmetric inductions over a broad range of aromatic, alkenyl and aliphatic substrates. The successful catalyst system results from the incorporation of a molecule of benzoic acid into the VANOL boroxinate catalyst. This method was applied to the asymmetric total synthesis of Coniine.

CHAPTER THREE
MECHANISTIC STUDIES OF THE CHIRAL BRØNSTED ACID CATALYZED AZA-COPE REARRANGEMENT – UNDERSTANDING THE SYNERGISYM OF CHIRAL AND ACHIRAL BRØNSTED ACIDS

3.1 Introduction

Chapter 2 describes the development of a general protocol for the synthesis of chiral homo-allylic amines via a direct catalytic asymmetric aminoallylation of aldehydes with BOROX catalyst **9**.[22] During the course of the optimization, we noticed an interesting phenomenon that the addition of benzoic acid greatly enhanced the asymmetric enantioselectivity of the aminoallylation reaction (Scheme 3. 1). The chiral Brønsted acid BOROX **9** catalyzes the aza-Cope rearrangement of **23f** in toluene to furnish **24f** in 77% yield and 25% ee. The addition of 1.0 equivalent of benzoic acid (w.r.t. BOROX **9**) improves the enantioselectivity to 72%, while maintaining excellent yields. This chapter focuses on a combined experimental and computational study that reveals a synergistic interplay of the chiral BOROX catalyst **9** and benzoic acid. This work was carried out in collaboration with Dr. Mathew Vetticatt.

Scheme 3. 1 Synergistic interplay of chiral BOROX catalyst **9** and benzoic acid in aza-Cope rearrangement



3.2 Probing the role of benzoic acid additive in the aza-Cope rearrangement catalyzed by the chiral BOROX catalyst 9

Our initial studies focused on identifying the role played by benzoic acid in catalyzing the aza-Cope rearrangement. The results from a systematic study of the effect of the amount of benzoic acid on the enantioselectivity and rate of the aza-Cope rearrangement catalyzed by BOROX catalyst **9** is presented in Figure 3. 1. Maximum enantioselectivity was achieved with the addition of 1.0 equivalent of benzoic acid (w.r.t

BOROX **9**), which also resulted in a 30% increase in reaction rate compared to the reaction without any additives. A marginal decrease in enantioselectivity and an approximate 30% decrease in reaction rate were observed when the amount of benzoic acid was increased beyond 1.0 equivalent. It is hence reasonable to propose that the active catalyst species consists of a 1:1 combination of chiral BOROX **9** and benzoic acid.

Figure 3. 1 Study of the effect of the equivalents of benzoic acid on enantioselectivity and reaction rate of the aza-Cope rearrangement catalyzed by BOROX catalyst **9**

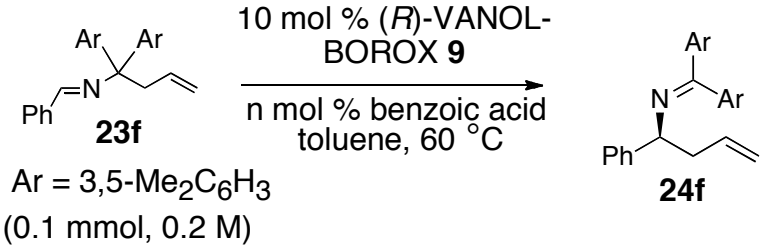
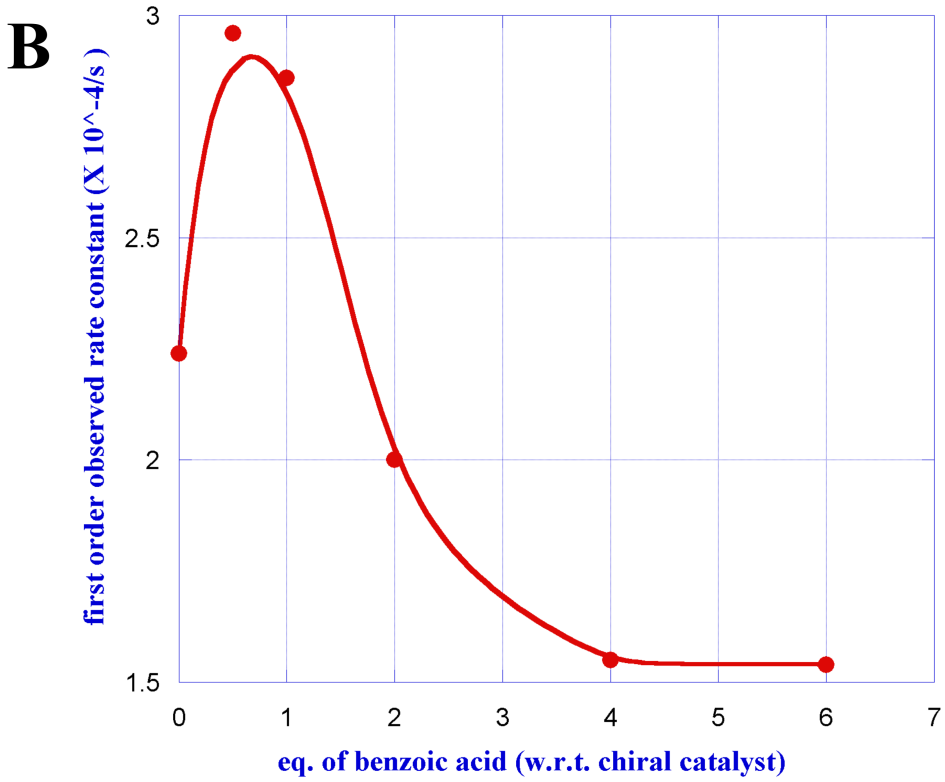


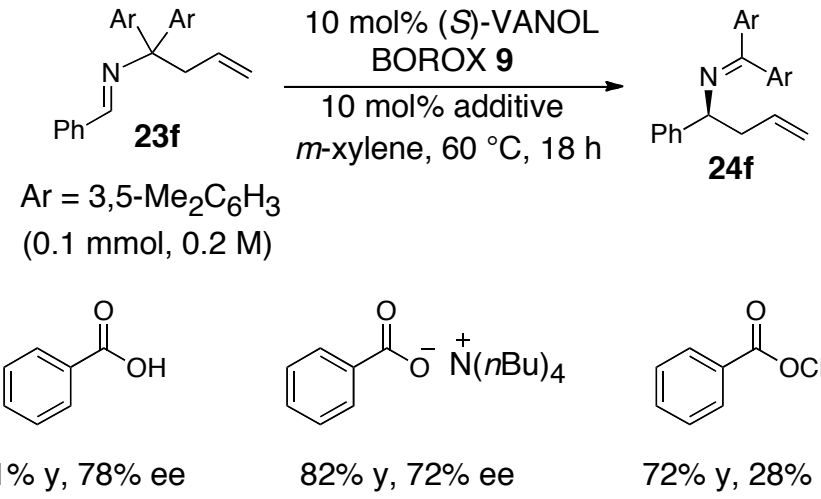
Figure 3.1 (cont'd)



"For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this thesis (or dissertation)."

Three possible roles for benzoic acid were envisioned for this reaction, a) as a Brønsted acid co-catalyst (proton donor); b) as a conjugate base (benzoate anion donor); or c) inducing a steric effect. To further narrow down the role of benzoic acid, the following experiments in Scheme 3.2 were designed and carried out.

Scheme 3. 2 Probing the role of benzoic acid

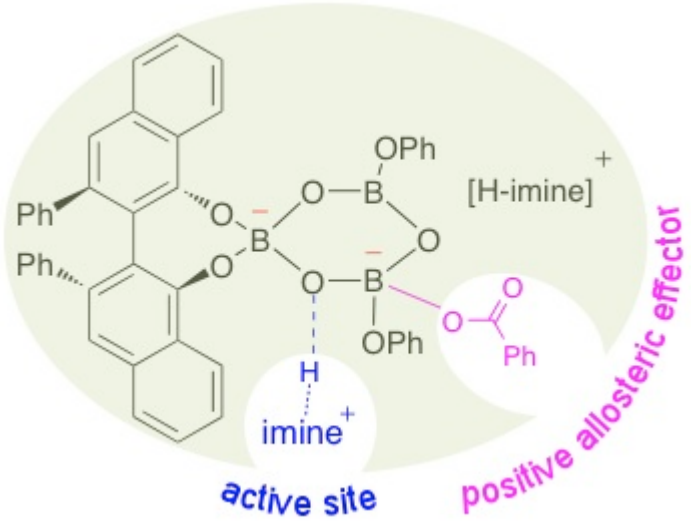


When a structural surrogate – methyl benzoate – was used as additive, product **24f** was obtained in 72% yield and only 28% ee. This result is almost identical to the reaction carried out with no achiral acid additive. However, when tetrabutylammonium benzoate was used as the additive instead of benzoic acid, **24f** was obtained in 82% yield with 72% ee. Finally, there was no observable product formation when **23f** was heated to 60 ºC with 20 mol% benzoic acid as the sole Brønsted acid catalyst. These results taken together suggest that the conjugate base of benzoic acid (and not the proton of benzoic acid or steric factors) is vital to the enhancement of enantioselectivity observed in this reaction. Any further reference to the role of benzoic acid in the remainder of this chapter could also be a reference to the benzoate anion.

Our next question is how does benzoate anion increase the enantioselectivity of the aza-Cope rearrangement? Is the benzoic acid intimately associated with the substrate at the transition state of the reaction? Or is the dramatic increase in enantioselectivity a

result of a covalent modification of the catalyst-imine complex **9** by benzoic acid, in which benzoate acid acts as an allosteric effector (Figure 3. 2)?

Figure 3. 2 Allosteric regulation of BOROX catalyst **9** with benzoic acid



3.3 Experimental ^{13}C kinetic isotope effects (KIEs)

^{13}C KIEs are powerful experimental probes of the TS geometry of a reaction and are sensitive to small variations in the TS geometry. By measuring ^{13}C KIEs for the aza-Cope rearrangement we can probe subtle differences, if any, in the transition state geometry of the reaction, with and without added benzoic acid.

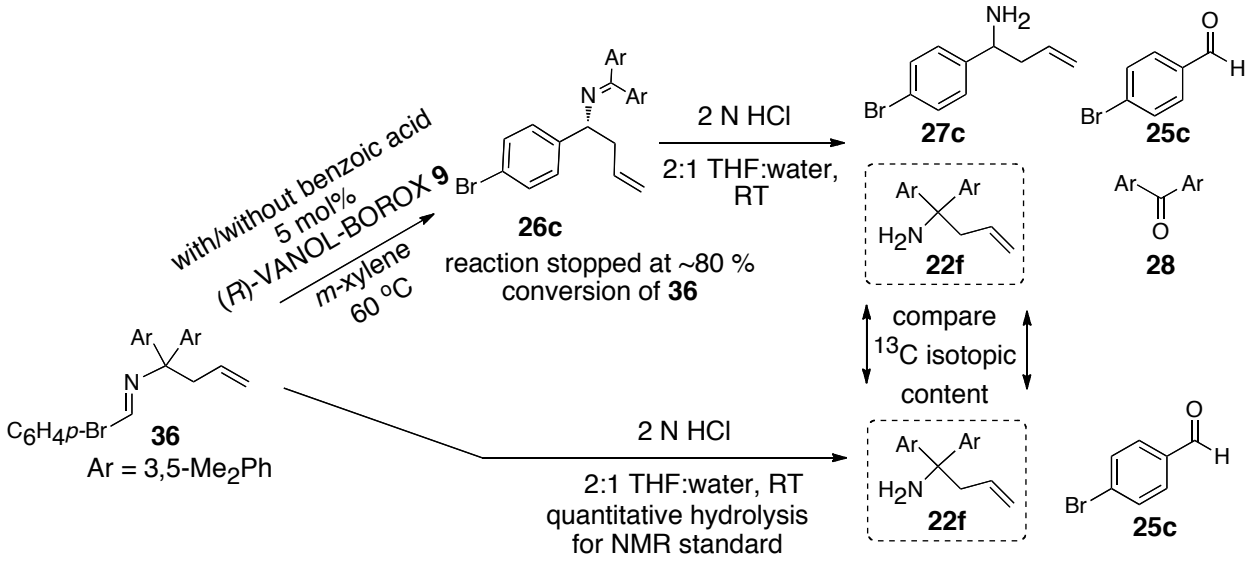
3.3.1 Design of experiment

The ^{13}C KIEs for the aza-Cope rearrangement of *p*-bromobenzaldehyde derived imine **36** catalyzed by (*S*)-VANOL-BOROX catalyst **9**, with and without benzoic acid additive, were determined using Singleton's NMR methodology[23] at natural abundance. *p*-Bromobenzaldehyde is one of the best substrates in the aza-Cope rearrangement (Scheme 2. 5, **27c,** 81% yield and 95% ee), with which we expect to see a larger

difference in energy in the major transition state and minor transition state. There are two main approaches to measure ^{13}C KIEs by this method; these are described below.

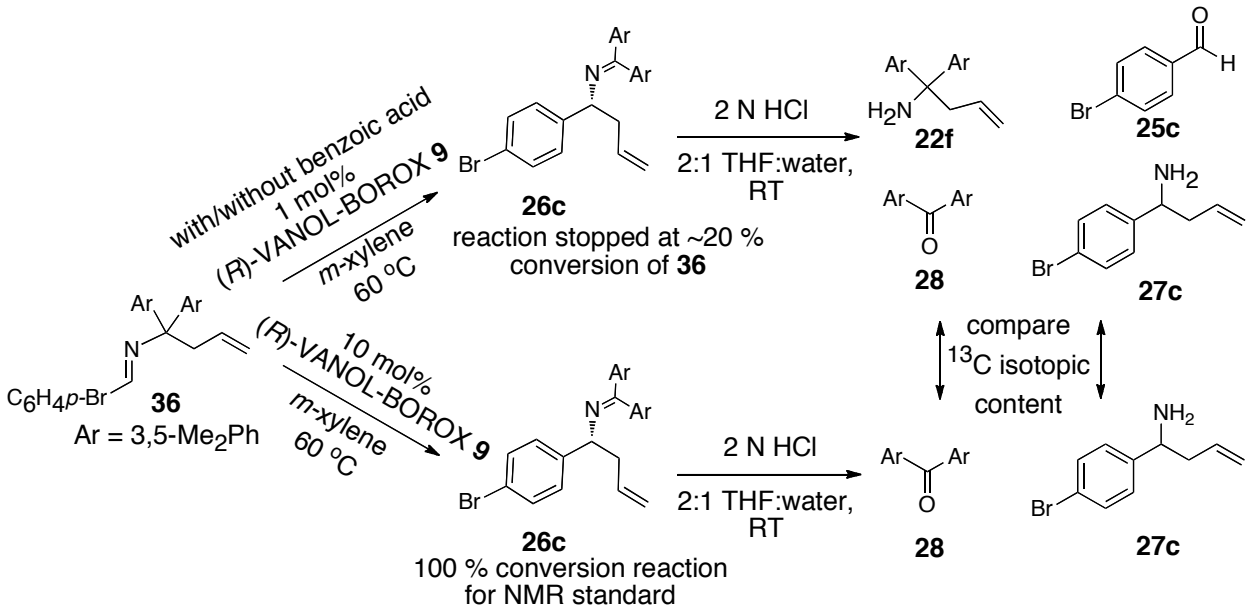
Starting material KIEs: Reactions proceed to high conversion (~ 80% conversion) and the starting material is recovered. The ^{13}C isotopic composition of the recovered starting material is measured using NMR method at natural abundance, which is compared to that of unreacted starting material drawn from the same bottle.

Scheme 3. 3 Design of starting material KIE measurement



Product KIEs: Reactions proceed to low conversion (~ 20% conversion) and the product is isolated. The isotopic composition of this product is measured using NMR method at natural abundance, which is compared to that of a product isolated from a 100% conversion reaction (the starting material is drawn from the same bottle originally used for the reaction).

Scheme 3. 4 Design of product KIE measurement



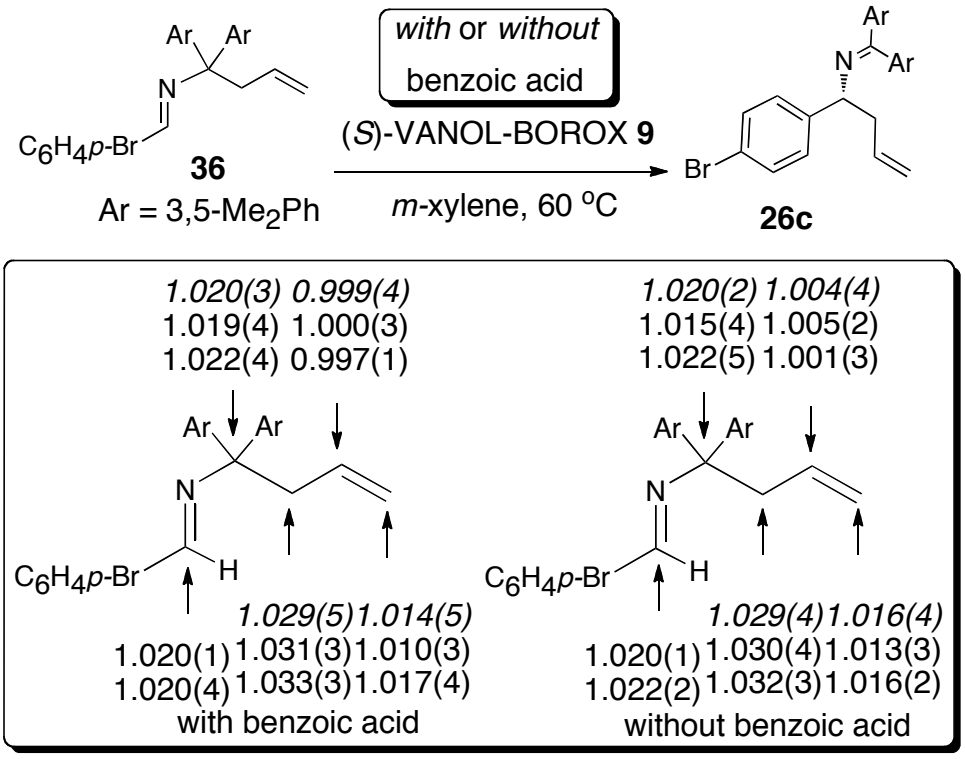
3.3.2 Experimental KIEs

For each case (with and without benzoic acid), three independent experiments – two from product KIEs measurement (non-italicized) and one from starting material KIEs measurement (italicized) – were conducted for the determination of KIEs. The resulting KIEs, for the carbon atoms undergoing bonding changes, are shown in Figure 3. 3. Each of the three KIE numbers comes from an independent experiment (with 6 measurements per experiment).

The observation of a non-trivial ^{13}C KIE on all carbon atoms of **36** involving bond-forming and bond-breaking events with hybridization changes is consistent with the concerted six-membered transition state that is expected for this reaction.[24] More importantly, comparative analysis of the ^{13}C KIEs in the two cases (with and without benzoic acid additive) reveals that the KIE at each of these carbon atoms are indistinguishable. The qualitative interpretation of this result is that *addition of benzoic*

*acid does not significantly alter the bond distances at the transition state of the aza-Cope rearrangement of **36**.*

Figure 3. 3 Experimental ^{13}C KIEs for the aza-Cope rearrangement of **36** catalyzed by (*S*)-VANOL-BOROX catalyst **9**



3.4 Spectral data in support of a covalent modification of the catalyst-imine complex by benzoic acid

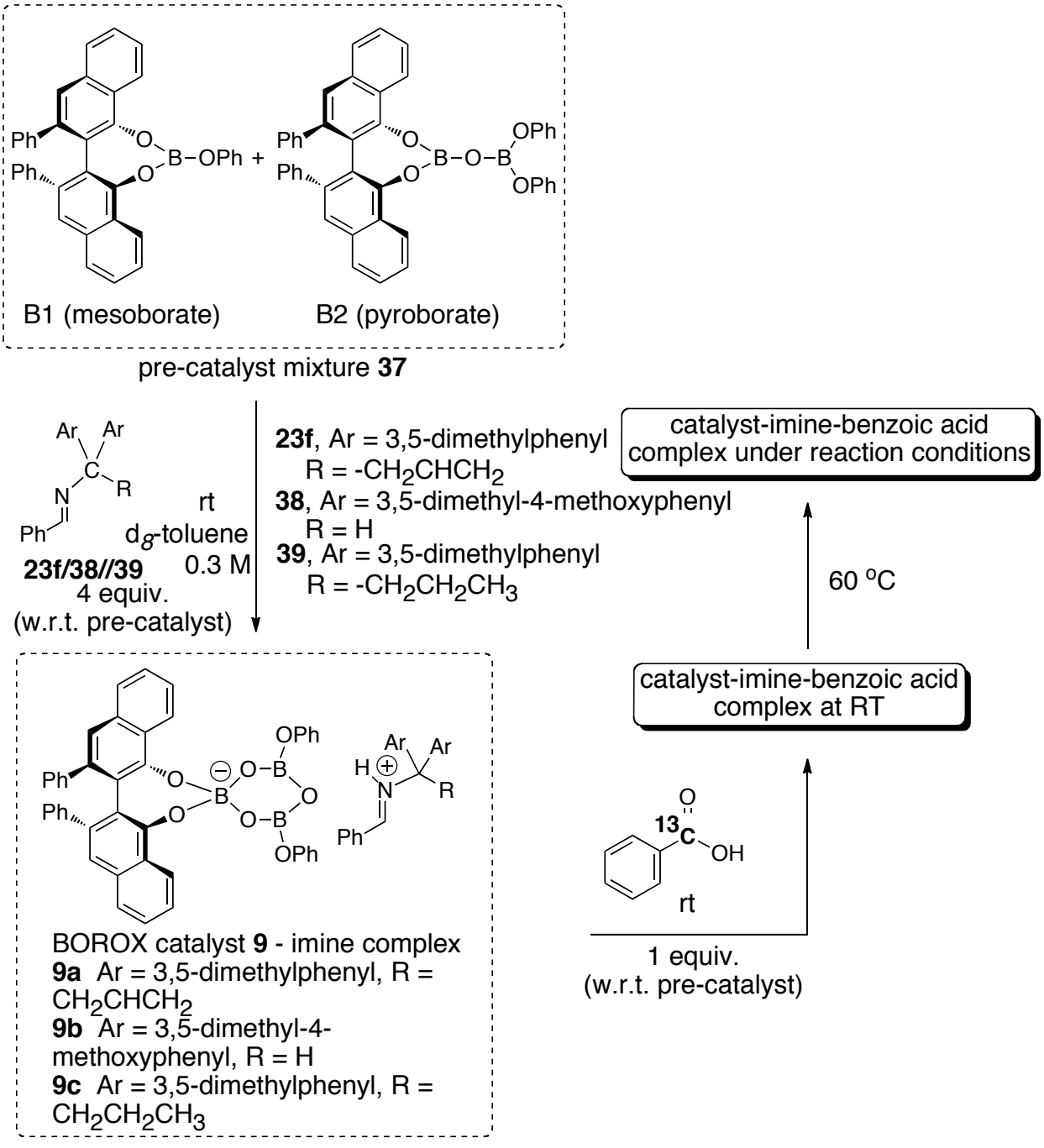
The results from the KIE study suggest that the benzoic acid might not be intimately associated with the substrate at the transition state of the reaction. Is the dramatic increase in enantioselectivity then a result of a covalent modification of the catalyst-imine complex **9** by benzoic acid? Our next step was to study the effect of addition of benzoic acid on catalyst structure using 1-^{13}C labeled benzoic acid as a convenient probe for NMR analysis under standard experimental conditions. From the change in

chemical shift of the ^{13}C label and the number of new species formed with incorporation of ^{13}C, we could determine the nature of catalyst modification by benzoic acid. The corresponding changes in the ^{11}B NMR could be used as an additional handle for understanding modification of catalyst structure.

3.4.1 Design of ^{13}C and ^{11}B NMR experiments

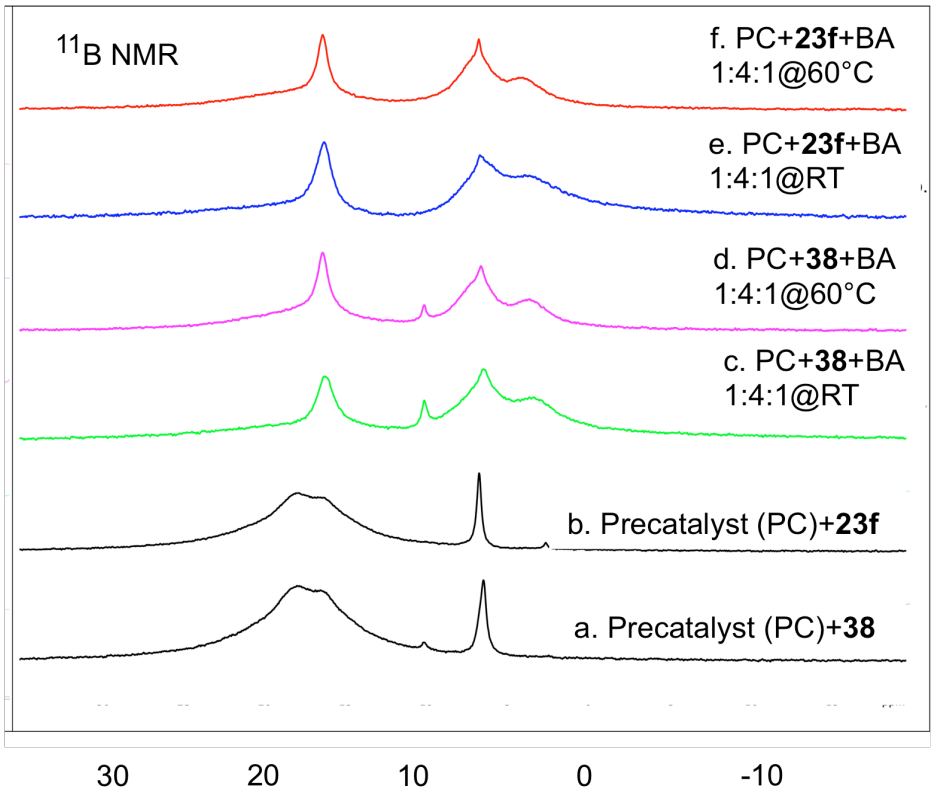
Scheme 3.5 outlines the design of the NMR experiments. A 0.07 M stock solution of precatalyst mixture was prepared in d_8-toluene. For a standard experiment, ~0.05 mmol of the precatalyst (0.7 mL of stock solution) was added to an NMR tube from the stock solution. This was followed by addition of 0.2 mmol of an imine (**23f/38/39** as a solid) at room temperature leading to the assembly of a catalyst-imine complex. Finally 0.05 mmol of 1-^{13}C benzoic acid was added to the NMR tube and the resulting mixture heated to 60 °C. A series of NMR spectra (^{13}C, ^{11}B and ^{1}H) were obtained at each stage. Since imine **23f** would react under these conditions, we used two additional unreactive imines – MEDAM imine **38** and an unreactive substrate analogue imine **39**, where the allyl group was reduced to a propyl group – to aid in the interpretation of the experiment using **23f** as the imine.

Scheme 3. 5 Design of ^{13}C and ^{11}B NMR experiments



3.4.2 Interpretation of ^{13}C NMR and ^{11}B NMR with 1-^{13}C-benzoic acid

Figure 3. 4 ^{11}B NMR spectra of catalyst modification studies



Pre-catalyst was prepared by heating 0.050 mmol VANOL ligand, 0.15 mmol BH_3•SMe_2, 0.10 mmol 2, 4, 6-trimethylphenol, and 0.15 mmol H_2O in 2 mL toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The resulting mixture was dissolved in 0.7 mL of d_8-toluene and transferred to a quartz NMR tube. 4 equiv. of imine **23f** or **38** was added to the NMR tube. Lastly, 1-^{13}C-labeled benzoic acid was added.

Figure 3. 4 and Table 3. 1 show the results from the ^{11}B NMR experiments involving the (*S*)-VANOL BOROX catalyst prepared from imines **23f** and **38** as described in Scheme 3. 5. Addition of imines **23f** or **38** to the pre-catalyst mixture results in the

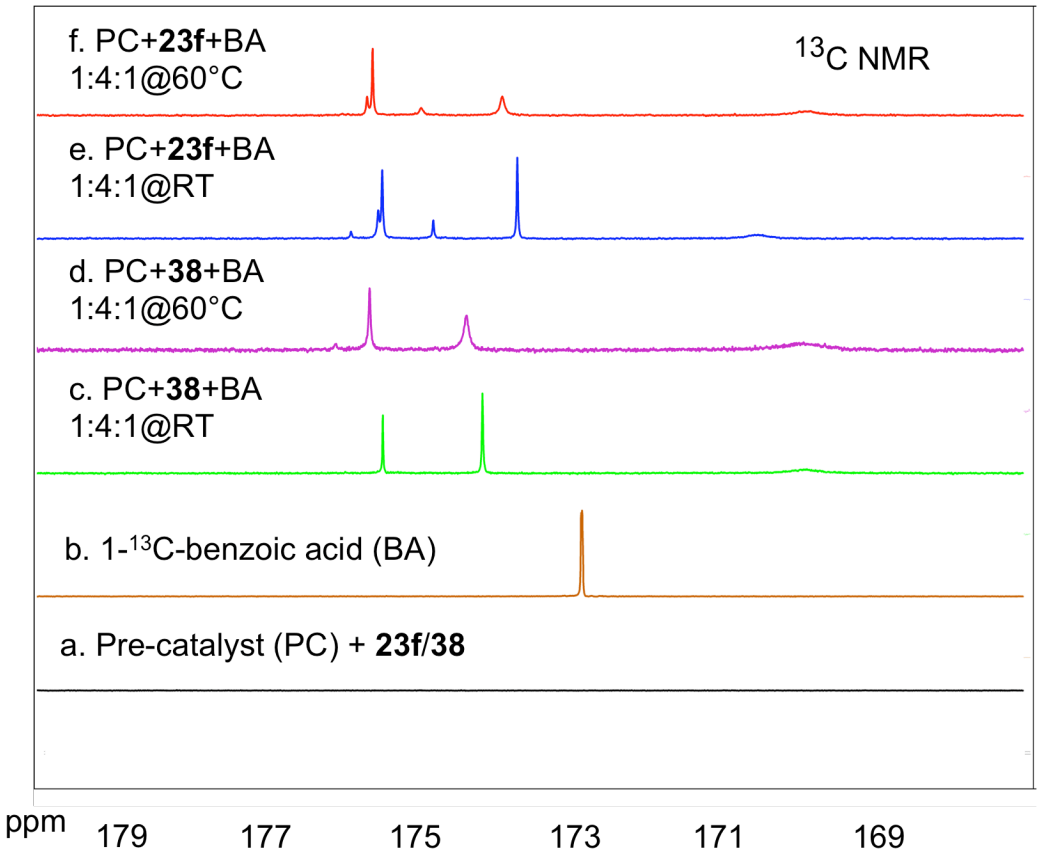
formation of boroxinate catalyst-imine complex **9a** and **9b** as evidenced by the appearance of sharp peak for the tetra-coordinated boron at ~ 6.0 ppm and the broad peak at ~ 16.0 ppm for the tri- coordinated boron atoms in the ^{11}B NMR spectra of these complexes (Figure 3. 4, a and b).

Table 3. 1 The integration of peaks observed in the ^{11}B NMR (**Figure 3. 4**)

Entry	Integration (from 0 to 9 ppm)	Integration (from 13 to 20 ppm)
a	1	5
b	1	7
c	2	1
d	2	1
e	2	1
f	2	1

The ^{13}C label in benzoic acid appears at 172.9 ppm (Figure 3.5, b). The most downfield carbon peak for 9a and 9b is the iminium carbon peak at 158.0 ppm and 157.0 ppm respectively and so there are no peaks in the expanded region of the ^{13}C spectra of these catalyst-imine complexes (Figure 3.5, a). The addition of benzoic acid to the catalyst-MEDAM imine complex 9b resulted in the appearance of two new peaks at 174.2 and 175.6 ppm (Figure 3.5, c). Intriguingly, the corresponding ^{11}B NMR spectrum revealed a new broad peak at ~ 4.0 ppm (in addition to the peak at 6.0 ppm) and a significant decrease in the intensity of the peak at 16.0 ppm (Figure 3.5, c; Table 3.1, c), suggesting the in-situ formation of a tetra-coordinated boron via addition of benzoate anion to one of the tri-coordinated boron centers in BOROX catalyst 9. These characteristics persist when the sample is heated to 60 °C (Figure 3.5, d).

Figure 3. 5 ^{13}C NMR spectra of catalyst modification studies using 1-^{13}C-benzoic acid

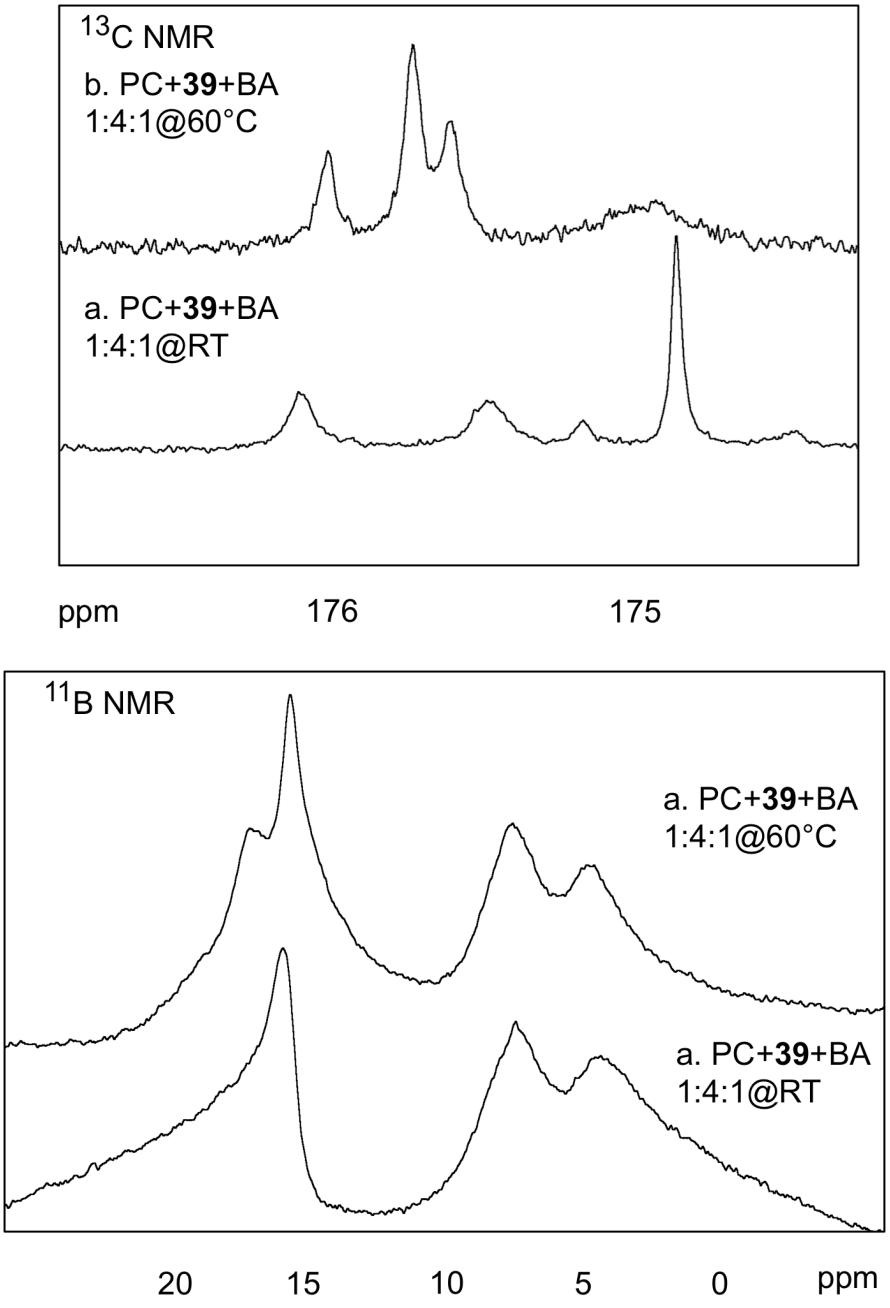


Pre-catalyst was prepared by heating 0.050 mmol VANOL ligand, 0.15 mmol BH_3•SMe_2, 0.10 mmol 2, 4, 6-trimethylphenol, and 0.15 mmol H_2O in 2 mL toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The resulting mixture was dissolved in 0.7 mL of d_8-toluene and transferred to a quartz NMR tube. 4 equiv. of imine **23f** or **38** was added to the NMR tube. Lastly, 1-^{13}C-labeled benzoic acid was added.

Slightly different results were obtained when benzoic acid was added to the reactive catalyst-imine complex **9a** prepared from imine **23f** (Scheme 3.5). Four new peaks were observed – two peaks similar to those observed with complex **9b** and two peaks of lower intensity (Figure 3.5, e). The ^{11}B NMR however, looks near identical to that of the complex **9b** (Figure 3.4, e). Once again, these features remain unchanged when the

sample is heated to 60 °C (Figure 3.4 and Figure 3.5, f). Our initial thought was that the two additional peaks in the ^{13}C NMR spectra e could be the product ketimine **24f** bound to the catalyst. A control experiment was conducted where **24f** was added to the pre-catalyst mixture, followed by the addition of ^{13}C labeled benzoic acid. This resulted in the appearance of the same 4 peaks, indicating that (a) each of these peaks correspond to a certain conformation of the catalyst-imine complex **9a** and (b) conversion of that conformation to the corresponding catalyst-product complex does not change the chemical environment around the ^{13}C label in the modified catalyst. The two additional peaks in the ^{13}C NMR spectra of the aza-Cope imine **23f** as compared to MEDAM imine **38** possibly results from that the imine substrate could be added either from the top or from the bottom of the BOROX catalyst **9** – benzoate adduct. We probed this hypothesis by using the structural analogue of **23f** – imine **39** with the reduced allyl group (Figure 3.6). When complexed with the catalyst **9c** or in the catalyst-imine-benzoic acid complex, **39** should behave in a fashion very similar to **23f**. As expected, when **39** was added to the catalyst-imine complex **9c**, we were able to observe the appearance of four peaks in ^{13}C NMR – similar to the spectra e and f in Figure 3.5. The corresponding ^{11}B NMR spectra were also very similar to **e** and **f** in Figure 3.4

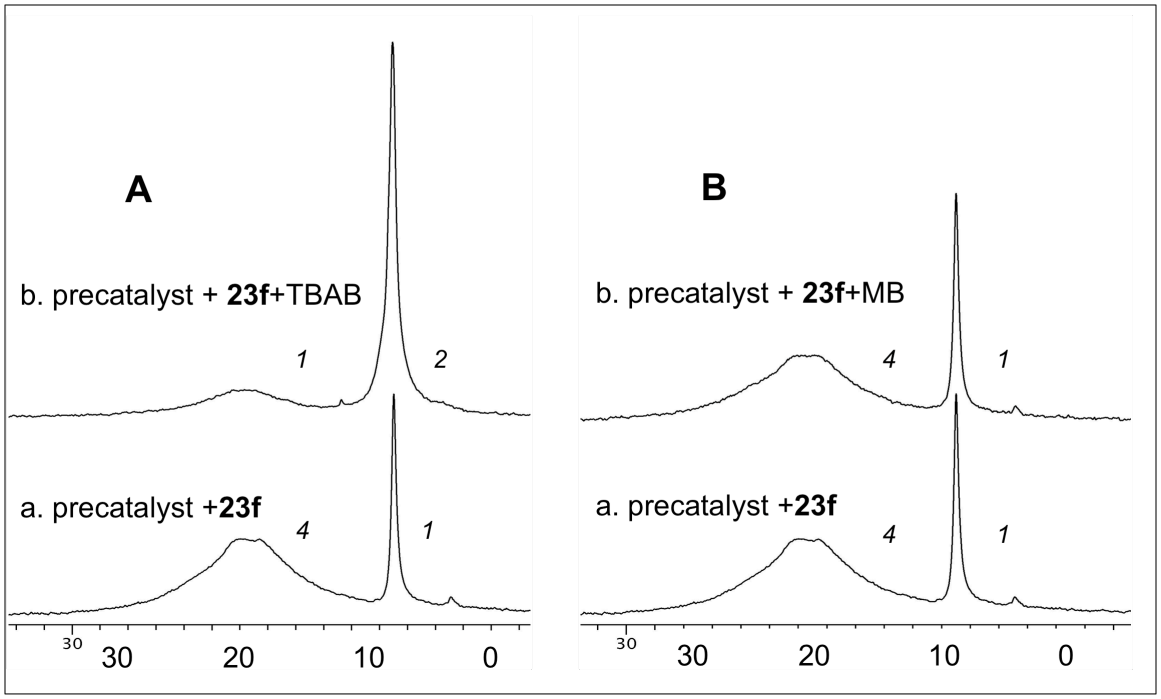
Figure 3. 6 NMR spectra of catalyst modification studies with imine **39** using 1-^{13}C-benzoic acid



Pre-catalyst was prepared by heating 1 equiv of VANOL ligand, 3 equiv of BH_3•SMe_2, 2 equiv of 2, 4, 6-trimethylphenol, and 3 equiv of H_2O in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg.

3.4.3 ^{13}C NMR and ^{11}B NMR with tetrabutylammonium benzoate and methyl benzoate

Figure 3. 7 ^{11}B NMR with tetrabutylammonium benzoate and methyl benzoate (Integrations shown in *italic*)



Pre-catalyst was prepared by heating 0.050 mmol VANOL ligand, 0.15 mmol BH_3•SMe_2, 0.10 mmol 2, 4, 6-trimethylphenol, and 0.15 mmol H_2O in 2 mL toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The resulting mixture was dissolved in 0.7 mL of d_8-toluene and transferred to a quartz NMR tube. 4 equiv. of imine **23f** was added to the NMR tube. Lastly, TBAB or MB was added.

When a structural surrogate – methyl benzoate – was used as additive, product **24f** was obtained in 72% yield and only 28% ee. This result is almost identical to the reaction carried out with no achiral acid additive. However, when tetrabutylammonium benzoate was used as the additive instead of benzoic acid, an 82% yield and 72% ee of **24f** was obtained. In the ^{11}B NMR study to probe the active catalyst for the aza-Cope

rearrangement, covalent modification of one of the tri-coordinated boron's was observed with the addition of benzoic acid (Figure 3. 4). Not surprisingly, while tetrabutylammonium benzoate was utilized as an additive, the ^{11}B NMR also presents evidence for the covalent modification of one of the tri-coordinated boron's (Figure 3. 7 A). However, when methyl benzoate was employed as an additive, we did not note a change in the ^{11}B NMR spectra upon the addition of methyl benzoate to the pre-catalyst mixture (Figure 3. 7 B).

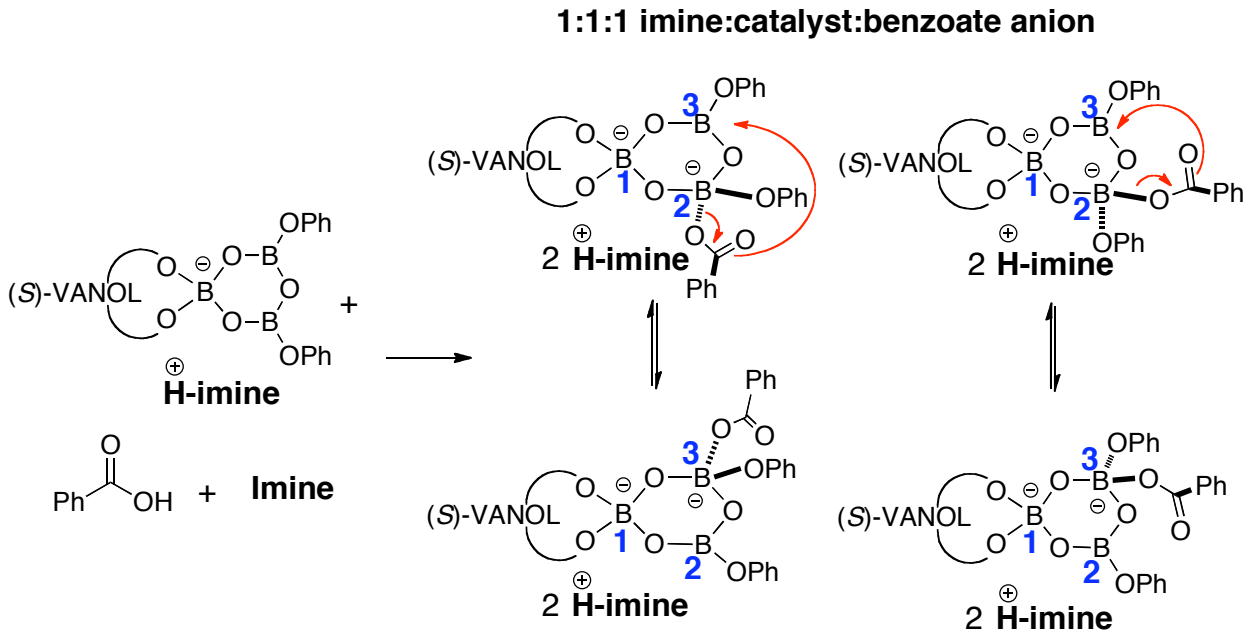
3.5 Possible active catalyst structures

We have four pieces of information that give us a clue about how the catalyst is modified upon addition of benzoic acid – (1) The likely role of benzoic acid is as a benzoate anion donor, (2) The tetracoordinate boron center in **9a/9b** is unchanged upon addition of benzoic acid, (3) The benzoate anion covalently modifies the catalyst-imine complex (**9a/9b**) by generating at least one additional tetra-coordinate boron center by addition to one of the two tri-coordinated boron centers in **9a/9b** and (4) In all cases, there are two major NMR distinguishable catalyst species formed upon addition of benzoic acid. We interpret these key observations as follows.

The tri-coordinate boron atoms in **9a/9b** are prochiral centers. The addition of benzoic acid to one of the tricoordinate boron atoms of **9a/9b** forms a boronate ester and new chiral boron center. This chiral center combined with the axial chirality of (*S*)-VANOL leads to in-situ formed diastereomeric pairs of the catalyst-imine complex (depending on the facial selectivity of boronate ester formation). At this point, we tentatively assign the two major peaks in the ^{13}C NMRs in Figure 3. 4, **c-f** to these

diastereomeric catalyst species. Based on relative integration of these two ^{13}C (labeled) peaks, it appears as though these diastereomeric complexes are formed in a 1.4:1 ratio.

Scheme 3. 6 Possible structures of modified catalyst



A key issue to be considered is that of double addition of benzoic acid (or benzoate anion) to the catalyst-imine complex i.e. all boron atoms being tetra-coordinated. In order to probe this possibility, we conducted an experiment where we used a 10:1 equivalent mixture of MEDAM imine **38**: pre-catalyst and allowed it to sit at room temperature for 6 hours to ensure complete formation of **9b**. This was followed by the addition of 10 equivalents of benzoic acid. The ^{11}B NMR of this mixture revealed a significant boron peak at ~16 ppm suggesting that at least one of the boron atoms is still tri-coordinated. This observation, along with the results presented in Figure 3. 1 A, lend support catalyst modification occurring by the addition of only one benzoate anion to the catalyst-imine complex. Scheme 3. 6 represents the simplest, most likely model that is

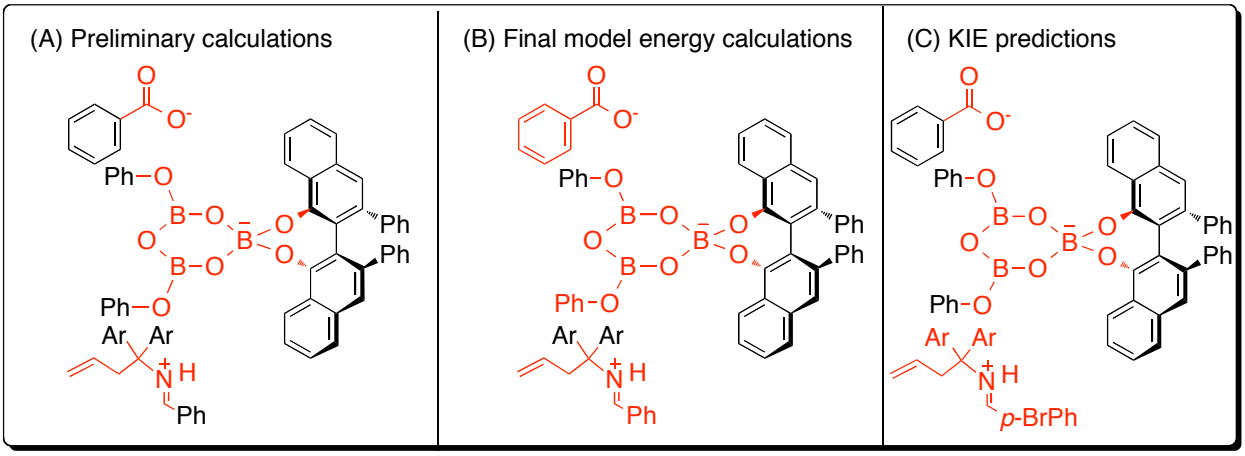
consistent with our NMR and other mechanistic studies. The addition of the benzoate anion to either face of one of the tri-coordinate boron atoms B2 or B3 results in a chiral di-anion with two protonated imines to balance the -2 negative charges. The two diastereomeric catalyst species can also be interconverted by migration of benzoate anion from B2 to B3 (and vice versa) across the same face of the boroxinate ring. In the following section, we present a thorough evaluation of this model using theoretical calculations. The goal is to compare the experimental enantioselectivity and ^{13}C KIEs, with and without benzoic acid additive, to the predicted energy difference and KIEs of the relevant transition state geometries leading to the two enantiomers of product.

3.6 Transition state models

The division of layers for the initial screening of transition state geometries is shown in Scheme 3.7A. All the oxygen and boron atoms, all heavy atoms (and attached hydrogen atoms) involved in the six-membered aza-Cope transition state were modeled using the DFT (B3LYP/6-31+G**) method. The aromatic groups in the substrate and catalyst were modeled using the semi-empirical method (AM1). In calculations with the benzoic acid additive, the carboxylate group was treated with the B3LYP/6-31+G** while the phenyl ring was calculated using AM1 method. After the initial screening, all the transition structures within 3 kcal/mol of the lowest energy structures for each enantiomer were re-calculated using an expanded high layer using B3LYP (with a 6-31+G** basis set) method as shown in Scheme 3.7B. In the expanded model, the following portions were calculated using the high level DFT method in order to get the best possible energy predictions – (a) the imine substrate excluding the aromatic portion of the protecting group, (b) the boroxinate core, (c) one of the phenoxy groups (proximal

to the substrate binding pocket) and (d) benzoic acid. For simplicity of presentation, the transition state geometries presented in the following sections are only the lowest energy transition structures for each enantiomer (with and without benzoic acid) obtained using the ONIOM Scheme outlined in Scheme 3.7B. The relative energies of the transition state geometries are derived from the Gibbs free energy estimates obtained from the ONIOM calculations carried out as illustrated in Scheme 3.7B. The arbitrary numbering scheme used in the discussion that follows is also included in Scheme 3.6

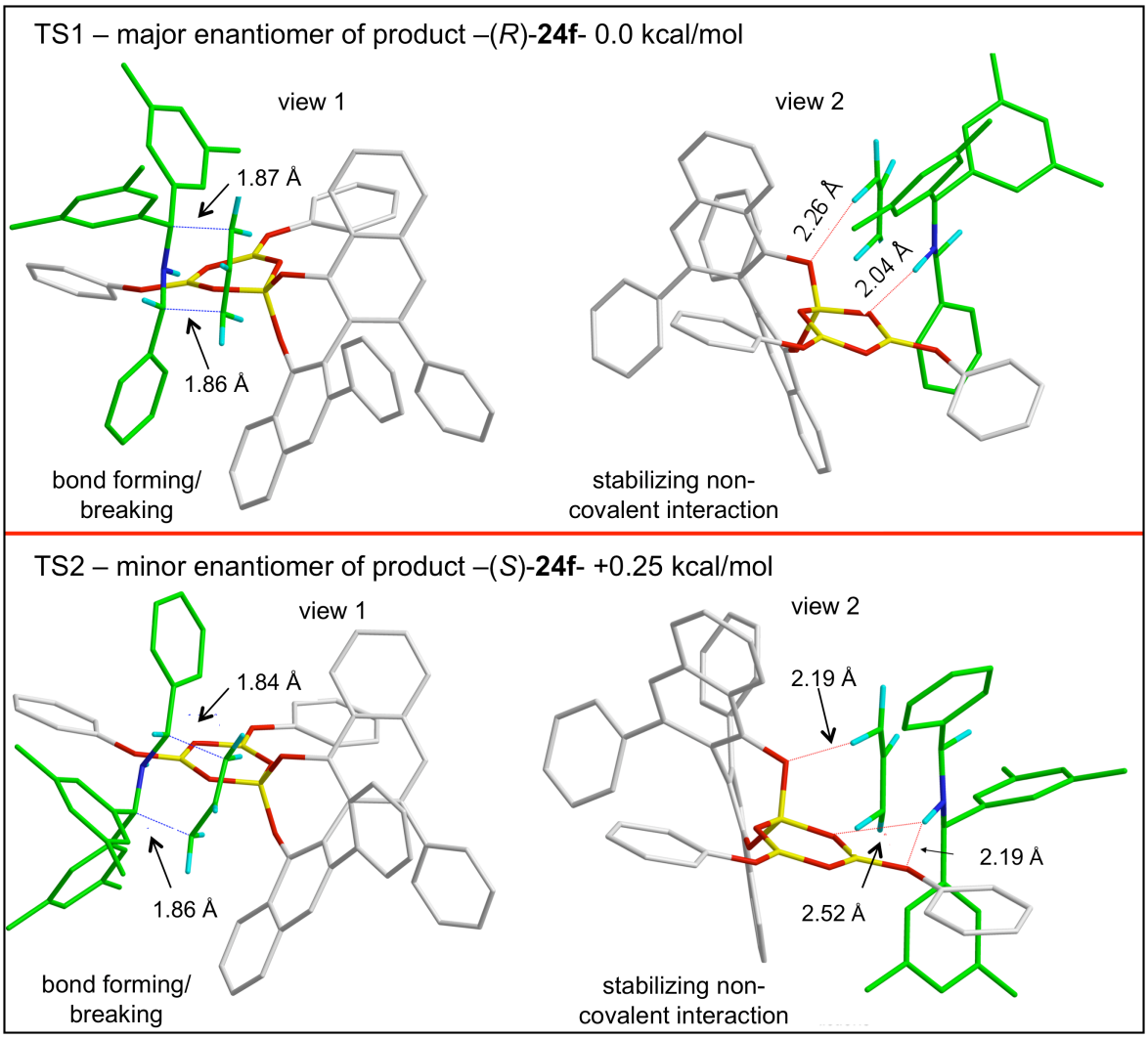
Scheme 3. 7 Division of layers for ONIOM (DFT:Semi-empirical) calculations



3.6.1 Transition structures without benzoic acid

Figure 3. 8 shows the lowest energy transition structures leading to (*R*)-**24f** and (*S*)-**24f** – the major and minor products – in the aza-Cope rearrangement catalyzed by (*S*)-VANOL-BOROX catalyst without the benzoic acid additive. The top panel in Figure 3. 8 presents two views of TS1, the transition state leading to the major enantiomer of **24f**.

Figure 3. 8 Transition state geometries for the aza-Cope rearrangement of **23f** catalyzed by (*S*)-VANOL-BOROX without benzoic acid additive computed using the ONIOM method described in Scheme 3.7B



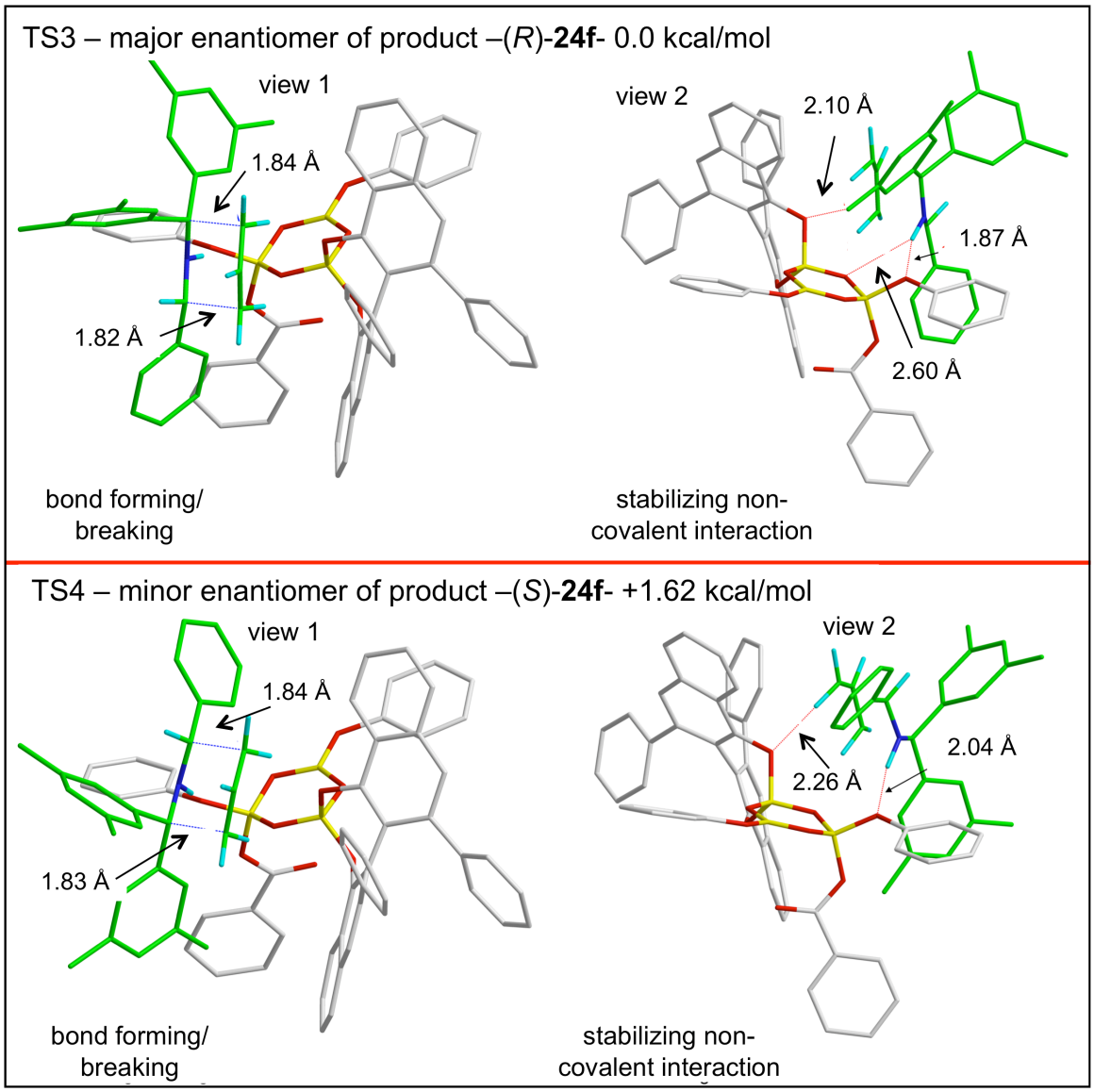
The key features of TS1 are (a) the protonated imine is bound to oxygen atom O2 via a short, strong hydrogen bond (2.04 Å, top panel view 2), (b) the bond-making and bond-breaking distances in the six membered chair-like transition state are almost identical (top panel view 1), (c) the intramolecular allyl nucleophile attacks the *re* face of the protonated iminum ion and (d) there is a stabilizing non-covalent –CH···O interaction between one of the polarized –CH bonds at the bond-breaking end of the allyl fragment

and O1 of the boroxinate anion (2.26 Å, top panel view 2). It is interesting to note that most of these features are also present in TS2 (see Figure 3. 8, bottom panel). The protonated imine is still bound to O2 (2.19 Å, bottom panel view 2), but the key difference between TS1 and TS2 is that it is bound 'upside down' relative to TS1. This binding mode of the imine in TS2 allows for the same stabilizing non-covalent –CH···O interaction seen in TS1, except that it is now between one of the polarized –CH bonds at the bond-*making* end of the allyl fragment and O1 of the boroxinate anion (2.19 Å, bottom panel view 2). The allyl nucleophile attacks the *si* face of the protonated imine. Since TS1 and TS2 have very similar interactions with the catalyst, it is no surprise that they are very close in energy (0.25 kcal/mol) – consistent with the low experimental ee of 25 %. Transition structures that lacked the stabilizing non-covalent –CH···O interaction present in TS1 and TS2 and transition structures with the protonated imine bound to O1, O2 and O4 were all found to be higher in energy.

3.6.2 Transition structures with benzoic acid

Figure 3.9 shows the lowest energy transition structures leading to (*R*)-**24f** and (*S*)-**24f** – the major and minor products – in the aza-Cope rearrangement catalyzed by the benzoic acid modified (*S*)-VANOL-BOROX catalyst described in Scheme 3.7. Several possibilities were explored before we arrived at TS3 and TS4 as the two lowest energy geometries for each enantiomer of the product. A systematic approach was followed in exploring the possibilities. For example, starting with the transition state geometry TS1, the transition state leading to the (*R*) product catalyzed by the (*S*)-VANOL-BOROX

Figure 3. 9 Transition state geometries for the aza-Cope rearrangement of **23f** catalyzed by (*S*)-VANOL-BOROX with benzoic acid additive computed using the ONIOM method described in Scheme 3.7B



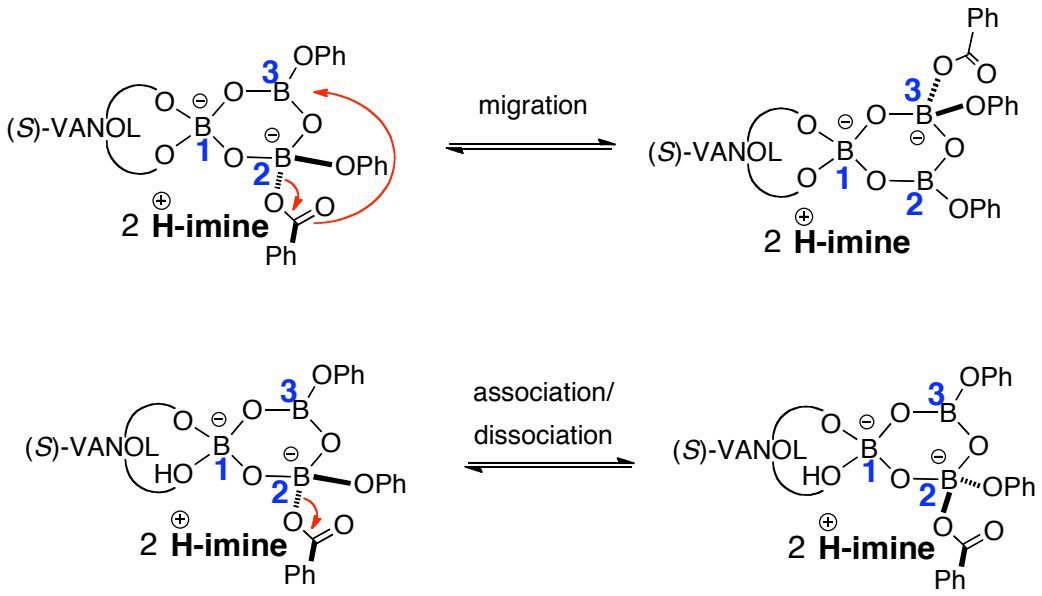
catalyst without the benzoic acid additive, eight different transition state geometries were explored by adding a benzoate anion to TS1- four from adding the benzoate anion to each face of the two tricoordinate boron atoms and an additional four by rotating the carbonyl of the resultant benzoate adduct in each case by 180° to either face toward or

away from the bound imine. The key findings from these explorations are detailed below.

Firstly, for both TS3 and TS4 the benzoate anion has added in a similar orientation to the same face of the boron atom B2. It is interesting that, of the four possible in-situ generated diastereomers of the 1:1 catalyst-imine complex and the two explored orientations for the benzoate in each diastereomer, the same orientation of the same diastereomer leads to the lowest energy transition structures for the formation of both enantiomers of the product. Secondly, the orientation of the imine with respect to the catalyst is almost identical when comparing TS1 versus TS3 and TS2 versus TS4. Intriguingly however, TS4 is 1.62 kcal/mol higher in energy that TS3 (as compared to TS2 which is only 0.25 kcal/mol higher in energy than TS1). These results are completely consistent with the increase in enantioselectivity upon addition of benzoic acid. Thirdly, there is no significant change in the bond-making and bond-breaking distance at the transition state, upon catalyst modification (compare the relevant distances in Figure 3. 8 and Figure 3.9). This again is consistent with the identical ^{13}C KIEs measured with and without added benzoic acid (since KIEs reflect the bond-making and bond-breaking distances at the transition state of the rate-limiting step).

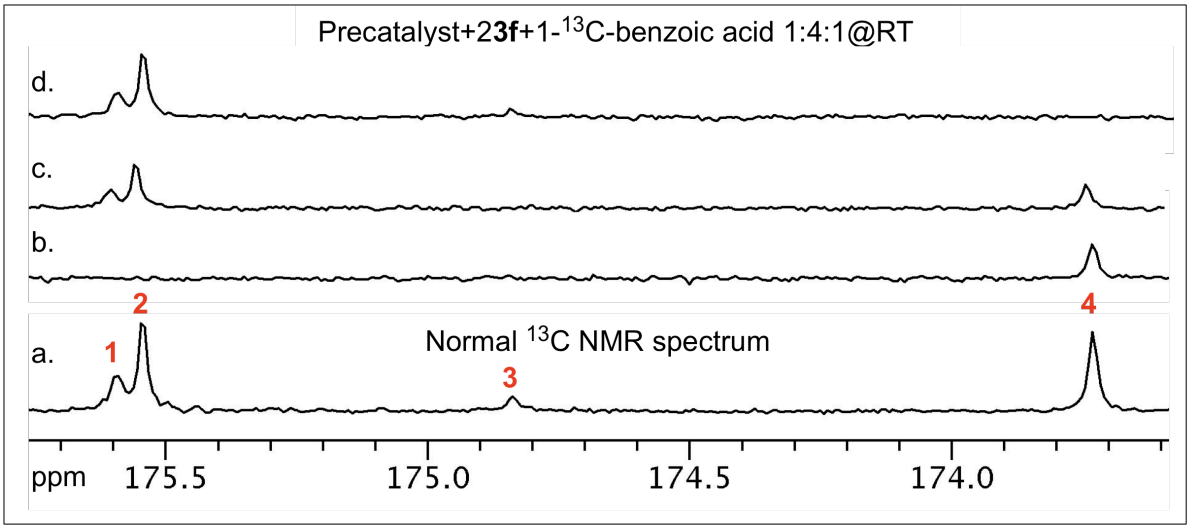
3.7 Spin saturation transfer experiment in support of the dynamic formation of diastereomers of catalyst upon the addition of benzoic acid

Figure 3. 10 Interconversion of diastereomeric catalyst species by migration of benzoate anion from B2 to B3



As discussed previously in section 3.5, the two diastereomeric catalyst species can also be interconverted by migration of benzoate anion from B2 to B3 (and vice versa) across the same face of the boroxinate ring (Figure 3.10). Next, we tried to find experimental evidence for the interconversion either via B2 to B3 migration or dissociation/association. NMR spin saturation transfer is a powerful tool to detect chemical exchange process on the NMR time scale. The NMR sample was prepared according to the procedure described in section 3.4.1, ~0.05 mmol of the precatalyst (0.7 mL of stock solution) was added to an NMR tube from the stock solution. This was followed by addition of 0.2 mmol of an imine (**23f** as a solid) at room temperature leading to the assembly of a catalyst-imine complex. Finally 0.05 mmol of 1-^{13}C benzoic acid was added to the NMR tube.

Figure 3. 11 Spin saturation transfer with imine **23f** (Precatalyst was prepared and regents were added in the sequence as shown in (Scheme 3.5)



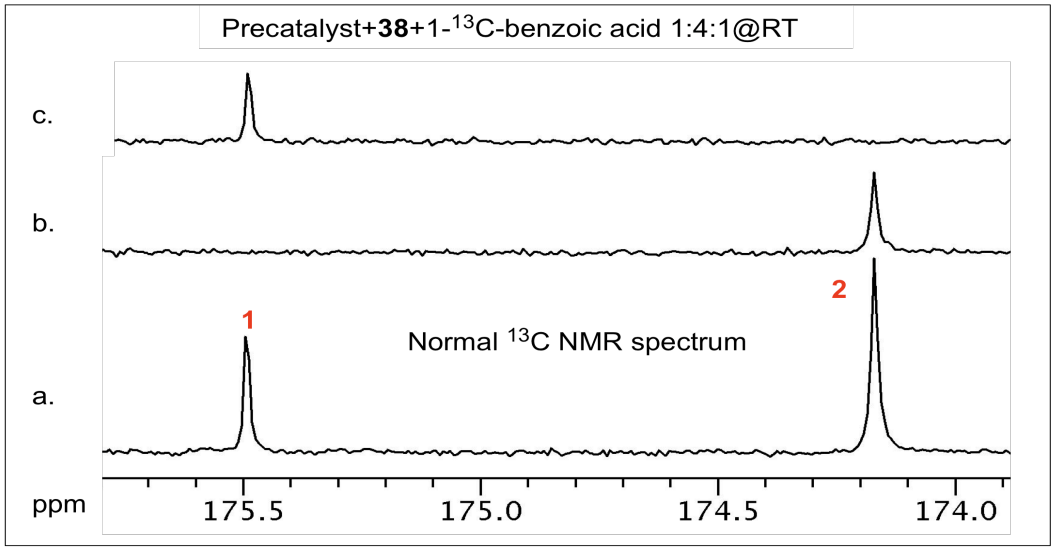
a. Normal ^{13}C NMR spectrum; b. irradiation of peaks 1 and 2;
c. irradiation of peak 3; d. irradiation of peak 4.

Pre-catalyst was prepared by heating 0.050 mmol VANOL ligand, 0.15 mmol BH_3•SMe_2, 0.10 mmol 2, 4, 6-trimethylphenol, and 0.15 mmol H_2O in 2 mL toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The resulting mixture was dissolved in 0.7 mL of d_8-toluene and transferred to a quartz NMR tube. 4 equiv. of imine **23f** was added to the NMR tube. Lastly, 1-^{13}C-labeled benzoic acid was added.

Figure 3.11 shows the spectra from spin saturation transfer experiments. Originally, there are four ^{13}C enriched peaks in the full ^{13}C NMR spectrum, two of which we propose correspond to the two diastereomers of the active catalysts upon the addition of benzoic acid. Since peak 1 and 2 are so close in chemical shift in the spectra, both peaks were saturated simultaneously, which resulted in the disappearance of peak 3 and decrease in the magnitude of peak 4. When peak 3 was irradiated, the magnitude of peaks 1,2 and 4 were reduced. Lastly, when peak 4 was saturated, the magnitude of peak 3 abated as well as that for peak 1 and 2. Although at this point, we could not

assign the peaks in the ^{13}C NMR spectra to the corresponding diasereomers of active catalyst, the presence of chemical exchange as detected by NMR spin saturation transfer clearly lends support to our proposal that the two diastereomeric catalyst species can also be interconverted either by migration of benzoate anion from B2 to B3 (and vice versa) across the same face of the boroxinate ring or by dissociation/association.

Figure 3. 12 NMR spin saturation transfer with imine **38** (Precatalyst was prepared and regents were added in the sequence as shown in Scheme 3.5)



a. Normal ^{13}C NMR spectrum; b. irradiation of peak 1;
c. irradiation of peak 2;

Pre-catalyst was prepared by heating 0.050 mmol VANOL ligand, 0.15 mmol BH_3•SMe_2, 0.10 mmol 2, 4, 6-trimethylphenol, and 0.15 mmol H_2O in 2 mL toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg. The resulting mixture was dissolved in 0.7 mL of d_8-toluene and transferred to a quartz NMR tube. 4 equiv. of imine **23f** was added to the NMR tube. Lastly, 1-^{13}C-labeled benzoic acid was added.

An NMR spin saturation transfer experiment was also conducted with imine **38**. The results were shown in Figure 3. 12. There are two peaks formed upon the addition of

benzoic acid to the precatalyst mixture, which we propose correspond to the two diastereomers of the active catalysts. When either peak 1 or peak 2 was saturated during the experiment, the other peak disappeared immediately, indicating the existence of a chemical exchange process between the two diastereomers.

We believe that a combination of factors is responsible for the observed increase in enantioselectivity,

(a) *Charge of the counter-ion* – Upon addition of benzoate to the boroxinate core, the net charge of the modified counter-ion is -2. As a result, the substrate should be 'bound' tighter in the transition state to the chiral pocket of the catalyst as evidenced by (i) the stronger hydrogen bonds between the protonated imine and the catalyst (1.87 Å and 1.86 Å in TS3 and TS4 versus 2.04 Å and 2.19 Å in TS1 and TS2) and (ii) stronger CH···O interactions between the –CHs of allyl fragment and the dianionic counter-ion (2.10 Å and 2.06 Å in TS3 and TS4 versus 2.26 Å and 2.19 Å in TS1 and TS2). This tighter binding of the transition states to the catalyst core could, in principle, amplify the energy difference between the enantiomeric transition states since these structures now experience a greater interaction with the chiral space of the catalyst.

(b) *Additional non-covalent interactions* – In the (*S*)-VANOL-BOROX catalyst-imine complex, due to the trigonal planar orientation of substituents on the boron atom B2, there is minimal interaction between the phenol substituent on B2 and the imine substrate (See Figure 3. 8). Addition of a benzoate anion to this boron generates a tetrahedral boron center, which thrusts the phenol moiety into a geometry that can now interact with the aromatic groups on the imine substrate via a CH-π interaction. This in-situ generation of a tetrahedral boron center in the catalyst and the resulting altered

interactions between the phenol moiety and the imine substrate possibly contributes to the increase in enantioselectivity observed upon addition of benzoic acid.

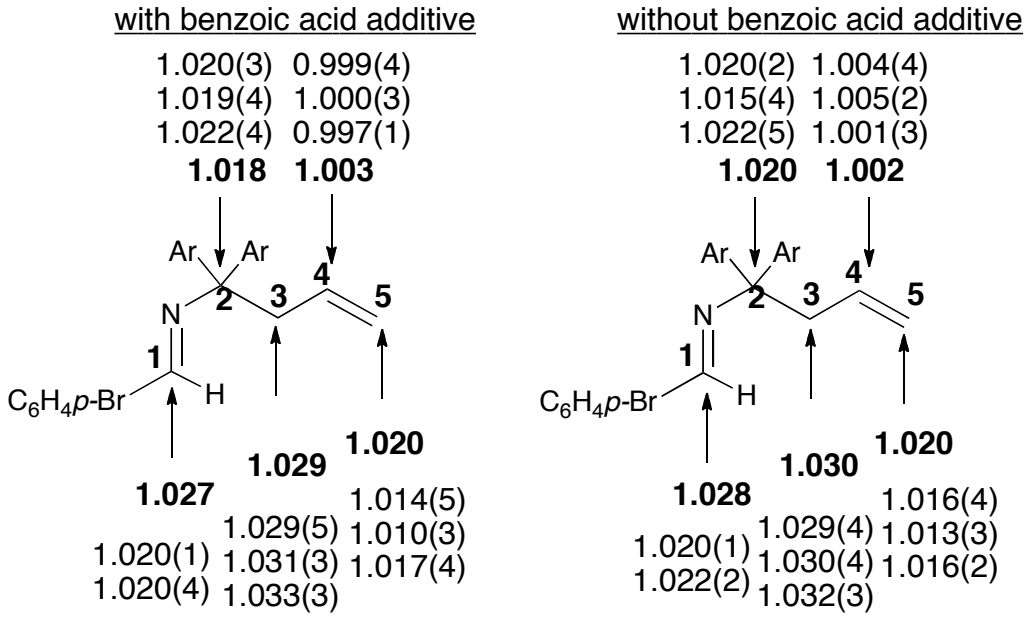
(c) *Stereodifferentiation by newly generated chiral center* – From our NMR studies, it is clear that there are at least two distinct diastereomers of the catalyst that are formed upon addition of benzoic acid to (*S*)-VANOL-BOROX catalyst-imine complex. Calculations suggest that one of these in-situ formed diastereomers catalyzes the formation of both enantiomers of product faster than the other diastereomer (both TS3 and TS4, the lowest energy transition structures for formation of (*R*) and (*S*) enantiomers of product, engage the same diastereomer of the catalyst). These results lead to the conclusion that even though more than one catalyst species might be formed upon addition of benzoic acid to the (*S*)-VANOL-BOROX catalyst-imine complex, only one of these catalyst species might be relevant to catalysis. Therefore, it is likely that the chirality of this lone catalytically active species helps differentiate the enantiomeric transition states better than the catalyst without benzoic acid which has only one chiral center. This is a novel idea in asymmetric catalysis and can be imagined to be complementary to double-stereodifferentiation obtained by using substrate with chiral centers, which prefer one chirality of the catalyst to the other.

3.8 Predicted KIEs and interpretation

Finally, for the quantitative interpretation of the experimental KIEs, transition structures were located for the aza-Cope rearrangement of **36**, the *p*-bromobenzaldehyde derived imine used for the determination of experimental KIEs, catalyzed by the (*S*)-VANOL-BOROX catalyst, both with and without benzoic acid additive. In order to obtain the highest accuracy in the theoretical prediction of KIEs,

transition structures corresponding to TS1 and TS3 (leading to major enantiomer of product, with and without benzoic acid) were recalculated using the ONIOM scheme outlined in Scheme 3.6 and Scheme 3.7C where all atoms in **36** were calculated using the high-level DFT method (B3LYP/6-31+G**). The KIEs for the resultant structures were computed from their scaled theoretical vibrational frequencies based on conventional transition state theory using the program ISOEFF 98.[25] Tunneling corrections were applied to the predicted KIEs using a one-dimensional infinite parabolic barrier model.[26] The results from these predictions are shown in Figure 3.13.

Figure 3. 13 Predicted ^{13}C NMR KIEs for the aza-Cope rearrangement of **36** (Calculated KIEs are shown in bold; Ar = 3,5-dimethylphenyl)



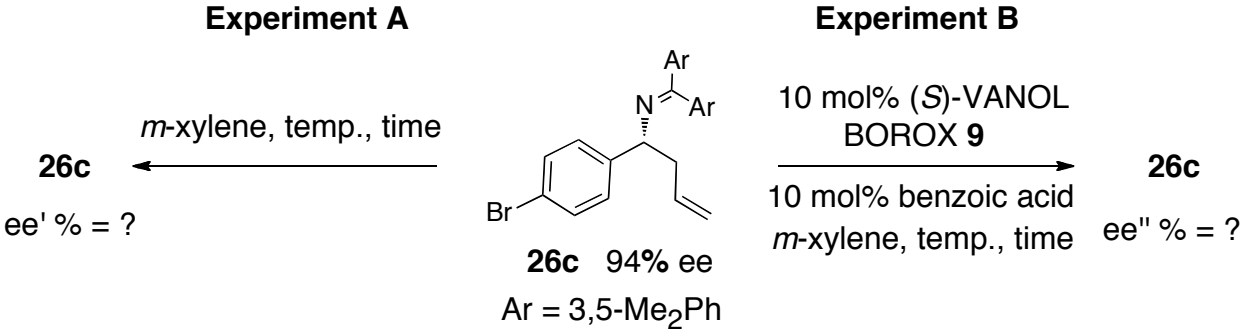
Overall, the theoretical KIE predictions are remarkably close to the experimentally determined values. For carbon atoms C2, C3 and C4 the predicted values are almost identical to the experimental measurement. The KIE predictions for the bond-forming carbon atoms C1 and C5, though slightly higher than the experiment, is well within the

acceptable limits to validate the transition state model. The key observation here is that the predicted KIE values are nearly identical for each carbon atom (C1-C5 in Figure 3.13) in both cases – models with and without the benzoic acid additive. This matches the trend observed in the experiments where KIEs measured with and without benzoic acid are almost identical at every carbon.

3.9 Equilibrium study of the aza-Cope rearrangement with BOROX catalyst 9 and benzoic acid

Compound **26c** was obtained from aza-Cope rearrangement catalyzed by BOROX catalyst **9** (see supporting information for chapter 2) with 94% ee. Although the presence of the two aryl groups (Ar) could stablize this product **26c**, it has the tendency to undergo a retro-aza-Cope rearrangement, which results in diminishing the enantioselectivity of the aza-Cope rearrangement. Hence, compound **26c** with 94% ee was subjected to the equilibrium study as shown in Scheme 3. 8. In experiment B, where **26c** was stirred under standard aza-Cope rearrangent with imines (**26c** obtained from imine **36** or aldehyde **25c** provided the same enantioselectivity) as described in chapter 2 with the exception that the temperature was elevated to 100°C, the ee'' dropped slightly to 92% after 24 h (entry 3). Futhermore, the ee'' diminished to 60% after another 24 h at 150°C. Meanwhile, a control experiment A was also carried out, where compound **26c** was heated to 100°C at the absence of BOROX catalyst 9 and benzoic acid. The enantioselectivity (ee') remained 94% after 24 h at 100°C (entry 1) and slightly dropped to 91% after stirring at 150°C for another 24 h (entry 2). As noted, when experiment A and B were carried out at 60°C for 24 h, we did not observe a decrease in enantioselectivity of compound **26c**.

Scheme 3. 8 Equilibrium study of the aza-Cope rearrangement



Entry	Experiment No.	Temp. (°C)	Time (h)	ee' %	ee'' %
1	A	100	24	94	ND
2	A	150	24	91	ND
3	B	100	24	ND	92
4	B	150	24	ND	60

3.10 Conclusion

We have presented here a mechanistic study of the chiral Brønsted acid catalyzed aza-Cope rearrangement and the role of an achiral acid (benzoic acid) in increasing the enantioselectivity of the reaction. The observation of significant ^{13}C KIE on all bond-making and bond-breaking carbon atoms supports a concerted mechanism proceeding via a six-membered pericyclic transition state. The identical ^{13}C KIEs measured with and without the benzoic acid additive suggest that the key features of the transition state geometry remain unchanged upon addition of benzoic acid. ^{11}B and ^{13}C NMR studies are used to probe the nature of catalyst modification that occurs upon addition of benzoic acid. It is proposed that the benzoate anion adds to a tri-coordinated boron atom to generate diastereomeric catalyst structures with a di-anionic counter ion. A theoretical model is developed, which accurately predicts the experimental KIEs and the observed enantioselectivity. The newly formed tetra-coordinated chiral boron center and

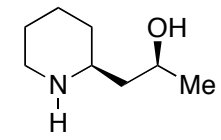
the increased charge of the counter-ion are likely instrumental in increasing asymmetric induction.

CHAPTER FOUR
TOTAL SYNTHESIS OF SEDAM ALKALOIDS VIA CATALYST CONTROLLED AZA – COPE REARRANGEMENT AND HYDROFORMYLATION WITH FORMALDEHYDE

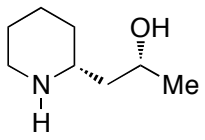
4.1 Introduction

The sedum alkaloids exist widely in nature and these types of alkaloids have memory-enhancing properties and are effective in the treatment of cognitive disorders.[27] The most commonly occurring members of this alkaloid family are 2-substituted piperidines with various combinations of hydroxyl functionalities in the side chains, featuring the 1,3-amino alcohol moiety and a select set are shown in Scheme 4. 1.[28] A review of the syntheses of sedium alkaloids has appeared in 2002[28] and the field has remained very active.[29]

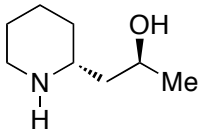
Scheme 4. 1 Sedum and related alkaloid natural products



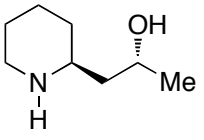
(+)-Sedridine



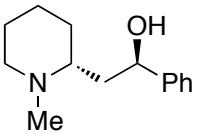
(-)-Sedridine



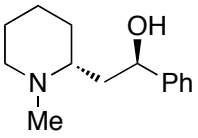
(+)-Allosedridine



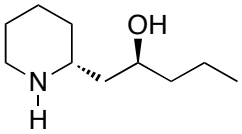
(-)-Allosedridine



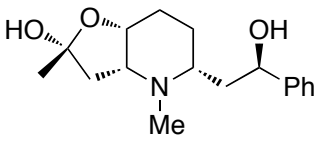
(+)-Sedamine



(-)-Sedamine



(-)-Halosaline

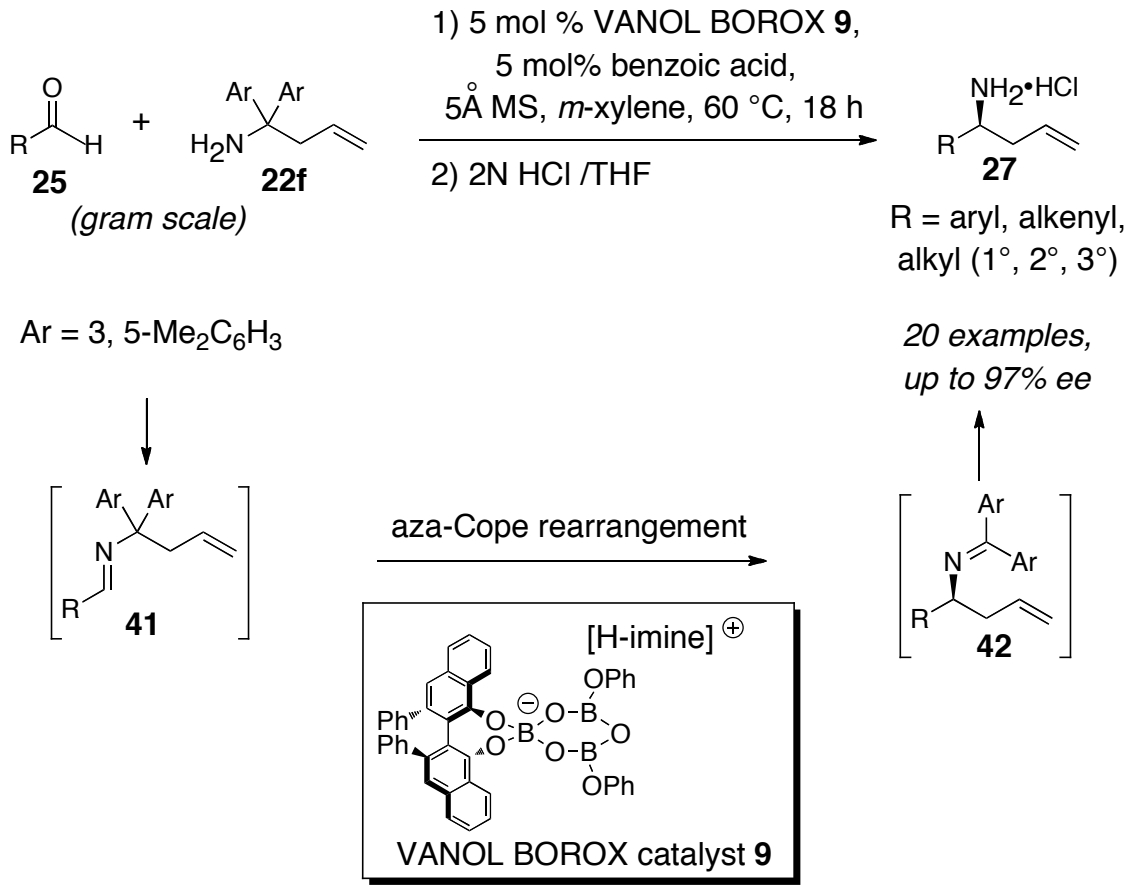


(-)-Sedacryptine

We have recently discovered a catalytic asymmetric method for the preparation of homo-allylic amines[22] directly from aldehydes (Scheme 4. 2). The key transformation involves an aza-Cope rearrangement of an in-situ generated imine **41** to give imine **42**

which upon hydrolysis provides homoallylic amines with excellent asymmetric inductions over a broad range of aromatic, alkenyl and aliphatic achiral substrates. The successful catalyst system results from the synergistic interplay between the boroxinate species **9** and benzoic acid.

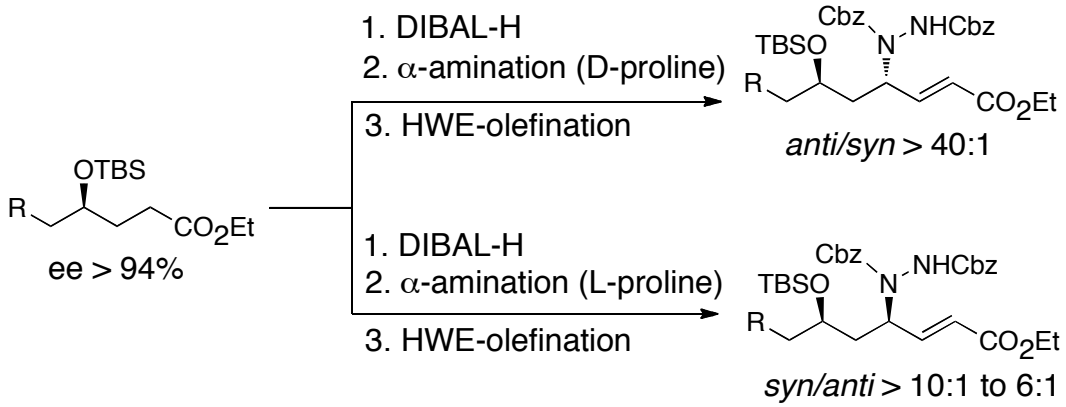
Scheme 4. 2 Direct aminoallylation of non-chiral aldehydes



Our interests for the present study were directed toward the catalytic asymmetric direct aminoallylation of chiral aldehydes especially to those that would allow for the highly diastereoselective introduction of homo-allylic amino alcohol moiety. Our goals are three-fold. 1) Define a new facile method for the controlled syntheses of *syn*-1,3-amino alcohols and *anti*-1,3-aminoalcohols. The controlled synthesis of both *syn*- and

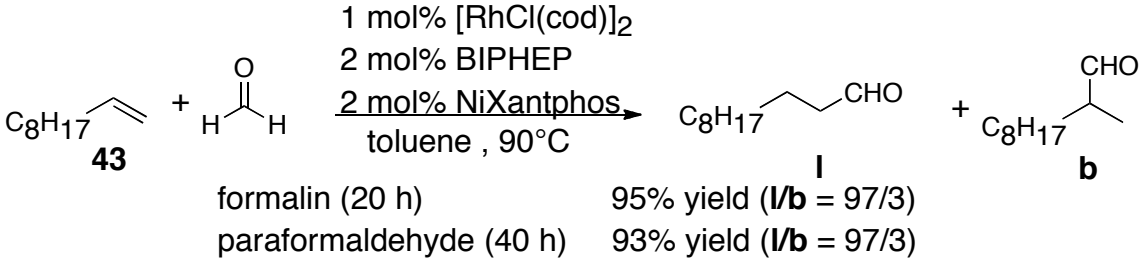
anti-1,3-aminoalcohols from a single substrate have been reported from β-aminoketones[30] and β-borylamines.[31] We only know of a single example where a catalyst controlled process can be used to access *syn*- or *anti*-1,3-aminoalcohols from a single substrate (Scheme 4. 3).[32] 2) Determine the interplay of the synergistic chiral VANOL-boroxinate/non-chiral benzoic acid catalyst system with an existing chiral center. 3) Total synthesis of sedum alkaloids with a divergent synthesis of syn- and anti-1,3-aminoalcohols.

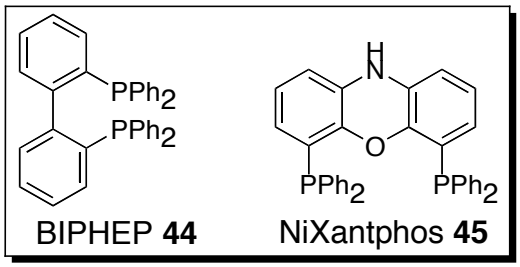
Scheme 4. 3 Kumar's catalyst controlled synthesis of syn/anti-1,3-aminoalcohols from a single substrate



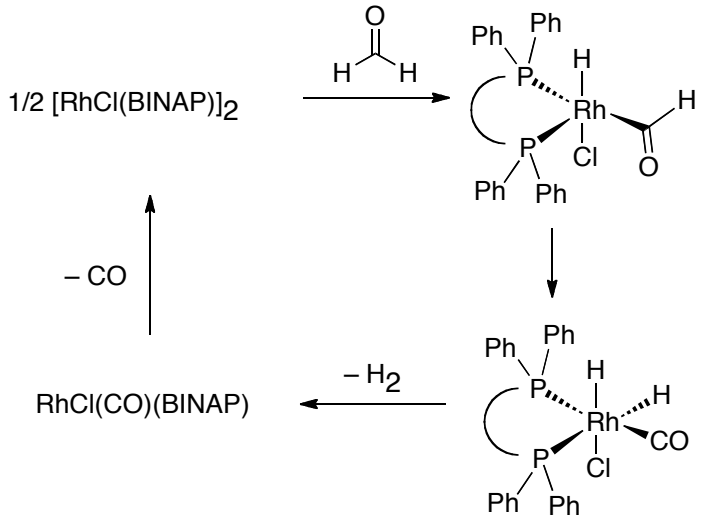
Hydroformylation is an important process for the production of aldehydes from olefins in industry. Conventionally, hydroformylation utilizes syngas (CO/H_2) in the presence of a transition metal catalyst to give homologous linear and/or branched aldehydes. A recent innovation in hydroformylation chemistry features an experimentally convenient alternative using formaldehyde as a syngas substitute. This synthetically useful method was first described by Morimoto and coworkers when they smartly applied two types of catalysts to the two cooperative catalytic processes simultaneously involved in the hydroformylation with formaldehyde (Scheme 4.4).[33]

Scheme 4. 4 Hydroformylation with formaldehyde

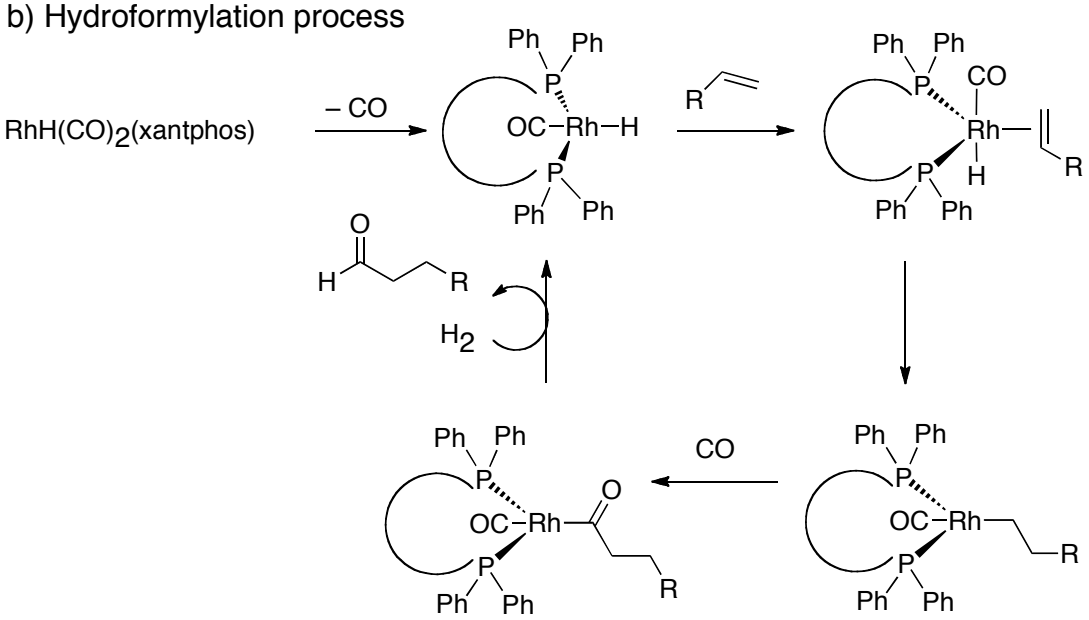




a) Decarbonylation process



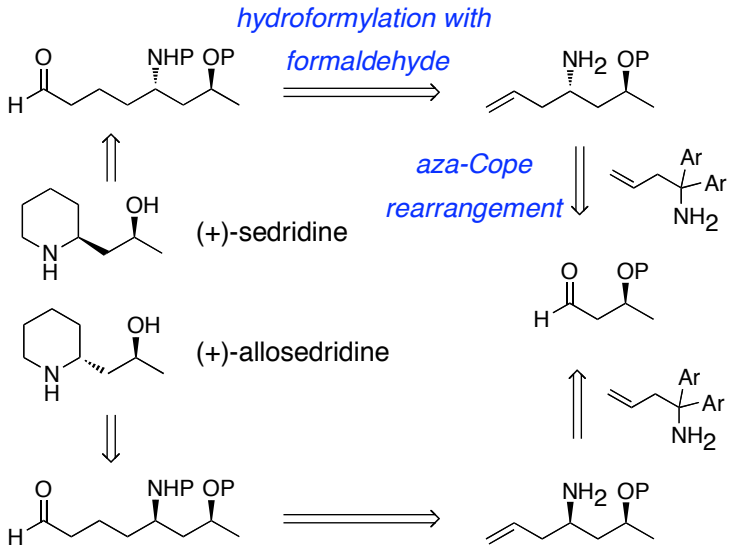
b) Hydroformylation process



4.2 Retrosynthetic analysis of (+)-allosedridine

We were attracted to the potential that hydroformylation presents for realization of the total synthesis of sedum alkaloids when coupled with diastereoselective aza-Cope rearrangement as illustrated in Scheme 4. 5 for synthesis of (+)-allosedridine. The key intramolecular amidocarbonylation[34] involves hydroformylation of homo-allylic amino alcohols with formaldehyde and was inspired by Morimoto's work with simple alkenes.

Scheme 4. 5 Retrosynthesis of (+)-sedridine and (+)-allosedridine



4.3 Direct aminoallylation of chiral β-alkoxy aldehydes

The initial screen of chiral aldehydes was carried out with the TBS protected aldehyde (*R*)-**46a** derived from the commercially available methyl (*R*)-3-hydroxybutyrate (Table 4. 1). The diastereoselectivity is nearly equal and opposite with the (*R*)- and (*S*)-ligands of VANOL (33:1 vs 1:23) and thus this is a case of catalyst control (entries 1 & 2). The total yield of **47a** and **48a** was low and the elimination product **49** was observed as a by-product. The reaction of the benzyl protected aldehyde **46b** with amine **25** gave a 4:1 mixture of aza-Cope product (**47b**+**48b**) and by-product **49**. Incorporation of a larger protecting group (TBDPS) lead to a mixture largely consisting of the eliminated imine **49**. However, when the sterically less hindered triethylsilyl protecting group (TES) was installed, the formation of **49** was completely shut down (Table 4. 1, entry 5) giving an 87% yield and a 1:20 diastereoselectivity in favor of **48** with (*R*)-VANOL and a 74% yield and a 26:1 diastereoselectivity in favor of **47** with (S)-VANOL.

Table 4. 1 Direct aminoallylation of chiral *β*-alkoxy aldehydes

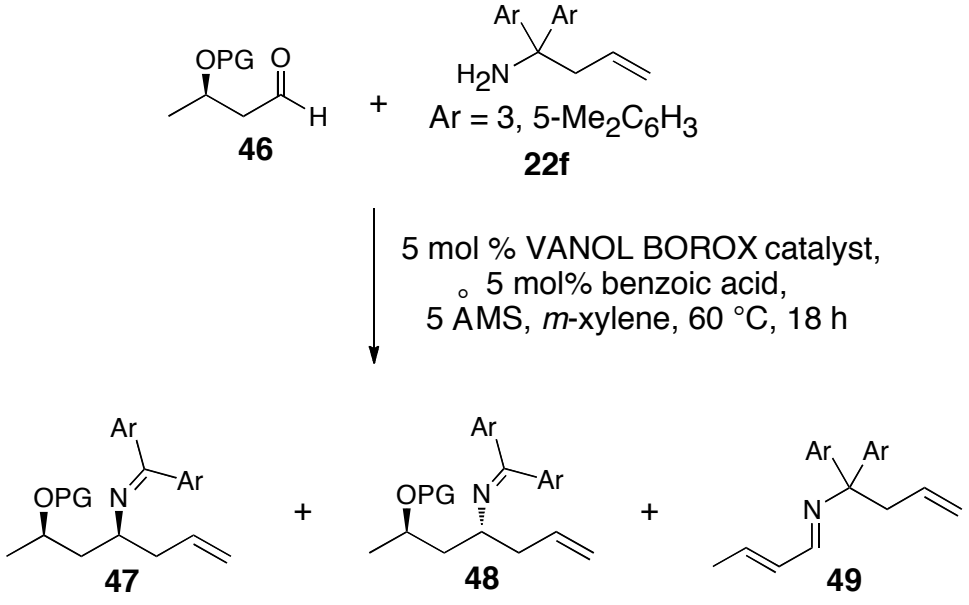


Table 4.1 (cont'd)

entry[a]	series	ligand	PG	Conv (%)[b]	(**47**+**48**) : **49**[c]	**47** : **48**[d]	%Yield (**47**+**48**)[e]
1[d]	a	(*R*)-VANOL	TBS	73(70)	3:1	33:1	48
2	a	(*S*)-VANOL	TBS	72(67)	4:1	1:23	44
3	b	(*R*)-VANOL	Bn	(80)	4:1	nd	nd
4	c	(*R*)-VANOL	TBDPS	(52)	1:10	nd	nd
5[f]	d	(*R*)-VANOL	TES	100	100:0	1:20	87
6[f]	d	(*S*)-VANOL	TES	100	100:0	26:1	74

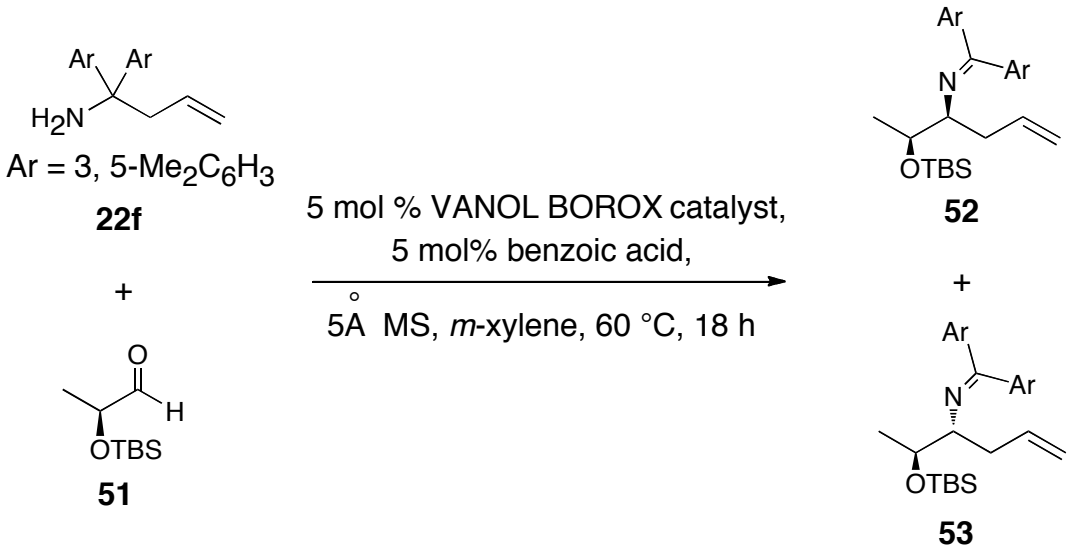
[a.] Unless otherwise specified all reactions were run at 0.2 M in amine **22f** with 1.1 equiv **46**. The catalyst was prepared from 1 equiv of the ligand, 2 equiv of 2,4,6-trimethylphenol, 3 equiv of H_2O and 3 equiv of $BH_3 \bullet SMe_2$. [b.] Calculated from the ^1H NMR spectrum of the crude reaction mixture from the ratio of (**47**+**48**):**22f** (or **22f**+imine) and the isolated yield of **47**+**48**. The value in parentheses based on the ratios of **22f** (or **22f**+imine **50**), **47**, **48** and **49** and assumption no other products are formed. In most cases, the unreacted material is in the form of amine **22f**, but in some cases a small amount of imine **50** formed from **46** and **22f** is present. [c.] Determined from the ^1H NMR spectrum of the crude reaction mixture. [d.] Isolated ratio. [e.] Isolated yield of a mixture of **47**+**48** after chromatography on silica gel. [f.] Reaction performed on (*S*)-**46** also of 98% ee. This reaction gives the enantiomer of **47** and **48**.

4.4 Direct aminoallylation of chiral *α*-alkoxy aldehydes

The interplay of the catalyst with a pre-existing α-chiral center in the aldehyde was also investigated. As shown in Table 4. 2, the reaction of the chiral aldehyde (*S*)-**51** is not under catalyst control but rather displays a match and mis-matched relationship. A 12:1 selectivity was observed for the matched case with the (*S*)-VANOL catalyst resulting in a 71% isolated yield. The same diasteromer predominated in the mis-matched case with the (*R*)-VANOL catalyst but the selectivity dropped to 2.5:1. The stereochemistry of **52** was assigned as anti since the matched case would be expected

to be with the *Re*-face addition to the imine with the (*S*)-VANOL catalyst since this is the preference with non-chiral aldehydes.[22]

Table 4. 2. Direct aminoallylation of a chiral α-alkoxy aldehyde



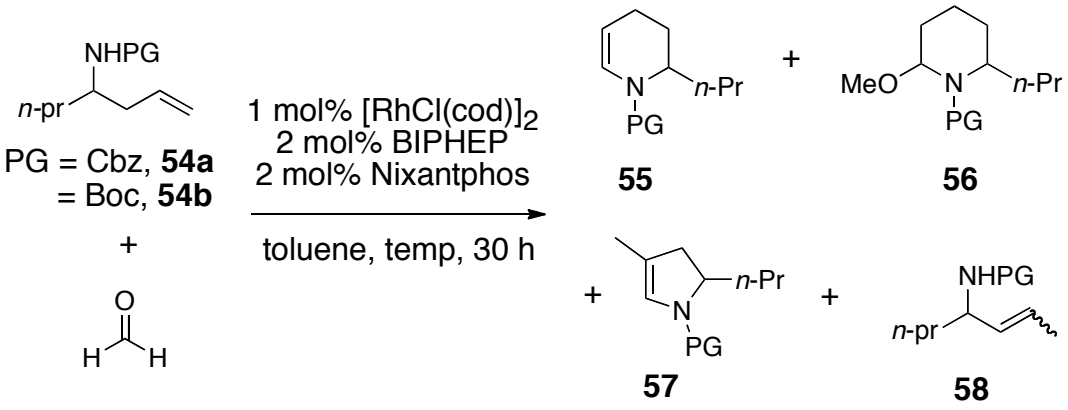
(*R*)-VANOL **52**:**53** = 2.5:1 %yield (**52**+**53**) = 71
(*S*)-VANOL **52**:**53** = 12:1 %yield (**52**+**53**) = 71

4.5 Optimization of the intramolecular amidocarbonylation with formaldehyde

In Morimoto's hydryformylation protocol, extremely high regioselectivity was obtained for simple alkenes. However, when this approach was first applied to an intramolecular amidocarbonylation with homo-allylic amine, a disappointling low yield was obtained. As indicated in Table 4. 3, Further studies show that the yield relies on the formaldehyde source; when formalin was utilized, in the presence of methanol as a stabilizer, a significant amount of the 2-alkoxypiperidine **56** was observed in the ^{1}H NMR spectrum of the crude reaction mixture (Table 4. 3, entry 1). *para*-Formaldehyde gave didehydropiperidine **55** and its five-membered analog **57** along with some of the

olefin isomerization product **58**. Therefore, paraformaldehyde was used instead, and with the proper control of conditions the didehydropiperidine **55** could be obtained in 73% isolated yield (Table 4. 3, entry 3).

Table 4. 3 Optimization of the intramolecular amidocarbonylation with formaldehyde



entry[a]	PG	formaldehyde source	temp (°C)	yield **55**(%)[b]	**55**:**57**:**58**[c]
1	Cbz	formalin	90	46	-[d]
2	Cbz	paraformaldehyde	90	69	6:1:1
3	Boc	paraformaldehyde	90	73	6:1:1
4[e]	Boc	paraformaldehyde	90	nd	2:3:0
5	Boc	paraformaldehyde	120	nd	15:20:7
6	Boc	paraformaldehyde	70	nd	0:100:0

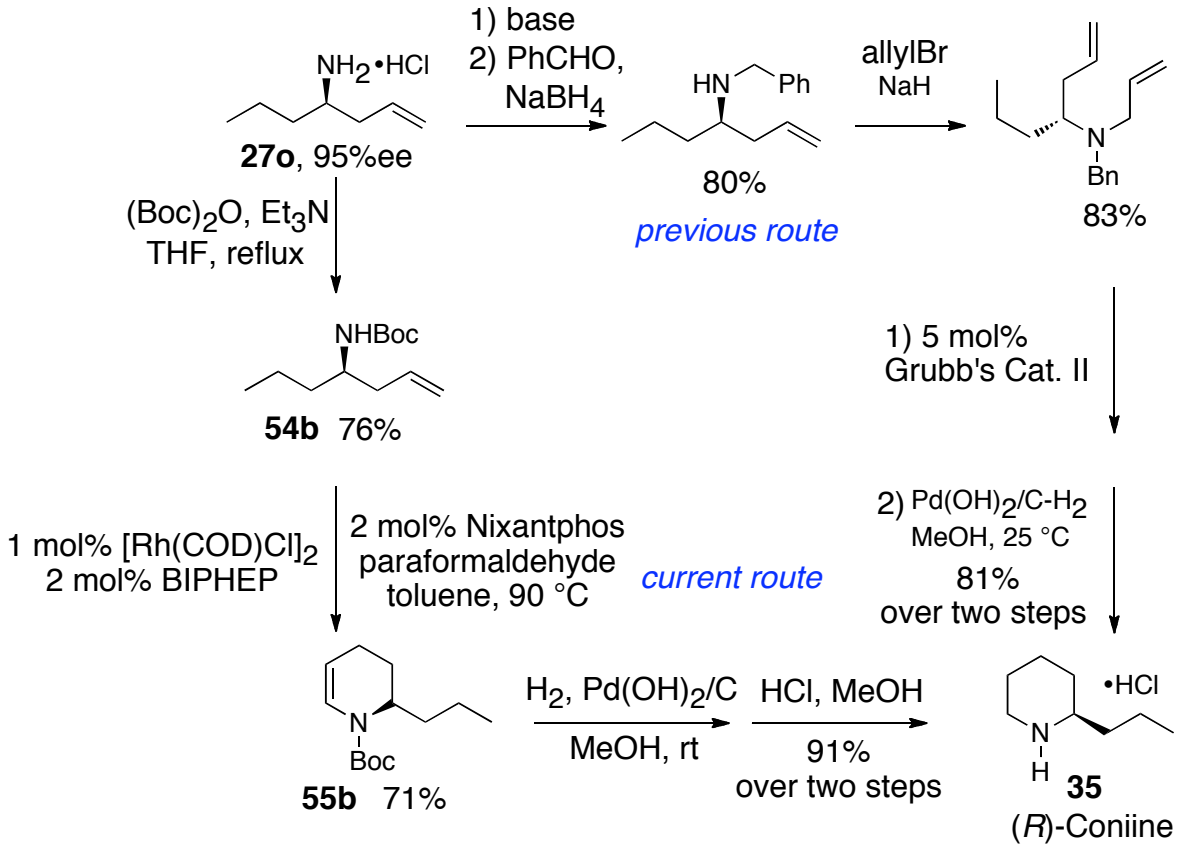
[a.] Unless otherwise specified all reactions were run at 0.15 M in **54** with 5.0 equiv formaldehyde. nd = not determined. [b.] Isolated yield after chromatography on silica gel. [c.] Calculated from the ^{1}H NMR spectrum of the crude reaction mixture. [d.] A 38% yield of **56** also formed in this reaction. [e.] 5 mol% PPTS was added to this reaction.

4.6 Synthesis of (-)-Coniine

The intramolecular amidocarbonylation was then applied to the synthesis of (-)-Coniine **35**. Previously, we have developed a concise total synthesis of (-)-Coniine. which involved two key reactions – asymmetric catalytic amino-allylation of *n*-butanal

and an RCM reaction.[22] Alternatively, for the current study, we are able to synthesize this natural product by coupling the catalytic asymmetric aza-Cope rearrangement of non-chiral aldehyde **27o** with the intramolecular amidocarbonylation as illustrated in Scheme 4. 6. The chiral center is installed in acyclic amine **27o** in 83% yield and 95% ee with catalytic asymmetric direct aminoallylation of *n*-butanal as shown in Scheme 2. 6, and the piperidine ring is closed using an intra-amidocarbonylation in 71% yield. Subsequent reduction of the double bond and cleavage of Boc give the target compound **35** in 91% yield over two steps.

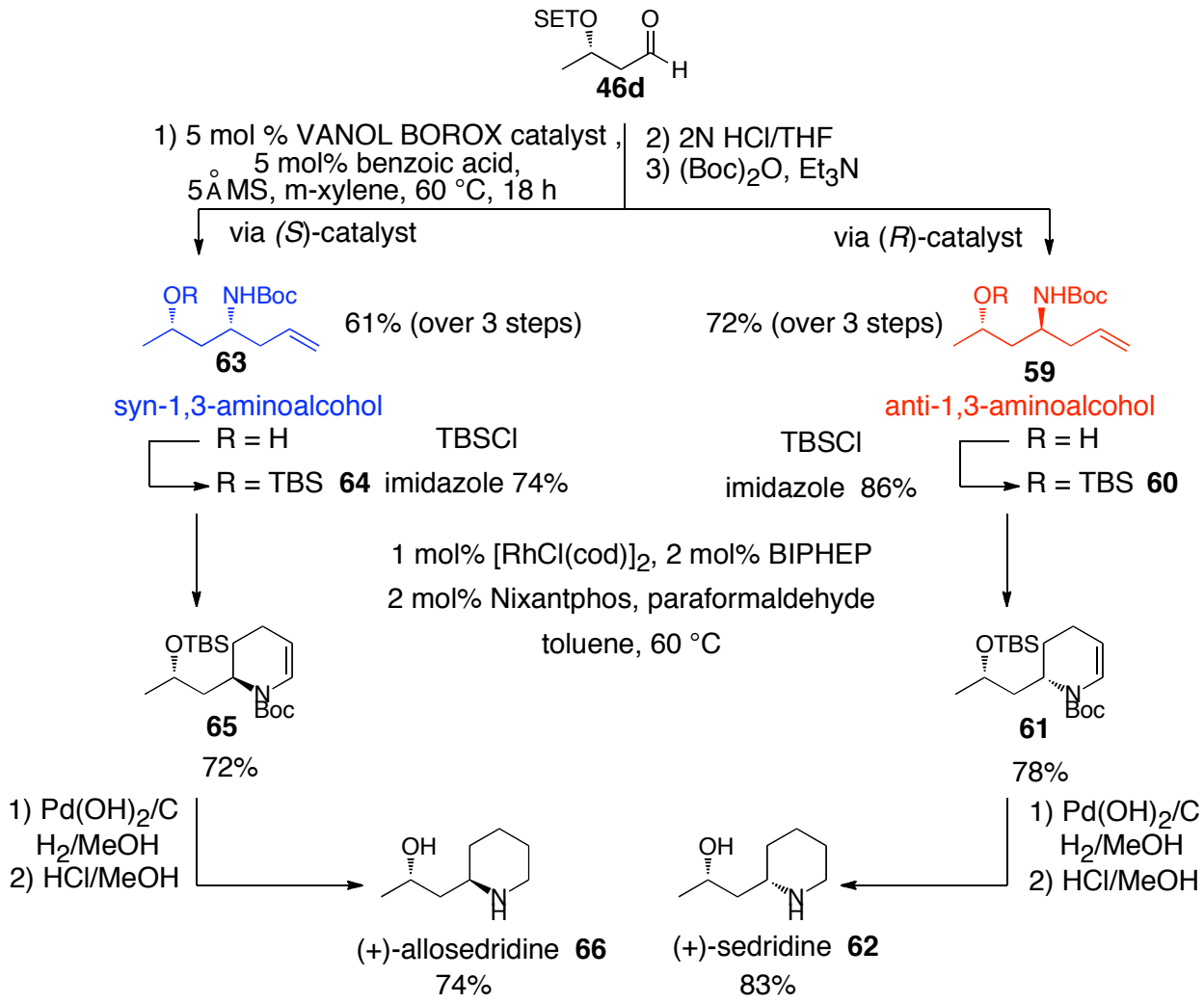
Scheme 4. 6 Total synthesis of (-)-Coniine



4.7 Total synthesis of (+)-Sedridine and (+)-allosedridine

Finally, we coupled the diastereoselective aza-Cope rearrangement and the intramolecular amidocarbonylation reactions in the total synthesis of (+)-Sedridine and (+)-Allosedridine. Chiral aldehyde **46d** was subjected to a diastereoselective aza-Cope

Scheme 4. 7 Synthesis of (+)-Sedridine and (+)-Allosedridine



rearrangement catalyzed by the BOROX catalyst derived from (*R*)-VANOL. Following hydrolysis and protection with Boc the anti-amino alcohol **59** was obtained in 72% yield with good diastereoslectivity over three steps in a one-pot fashion. Compound **59** was

then protected with TBS and subjected to an intramolecular amidocarbonylation reaction to afford **61** in 78% yield. Subsequent reduction and deprotection gave (+)-sedridine **62** in 83% yield. (+)-allosedridine **66** was obtained with a similar route with BOROX catalyst from (*S*)-VANOL. Presumably, we are able to access all four stereoisomers of sedridine by combining the two enantiomers of aldehyde **46d** with (*R*)- or (*S*)-VANOL derived BOROX catalysts.

4.8 Conclusion

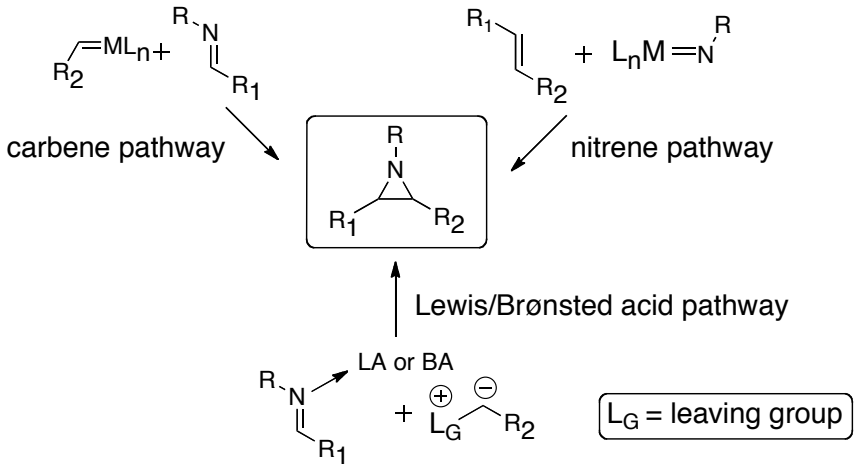
This work has demonstrated that the aldehydes bearing a chiral β–hydroxyl group will undergo the aza-Cope rearrangement to give good yields of homo-allylic amino alcohols with where there is a strong catalyst control case between the chiral aldehyde and (*S*)-VANOL or (*R*)-VANOL derived catalysts. It is important to note that the very high asymmetric inductions of the boroxinate catalyst/benzoic acid for the catalytic asymmetric aza-Cope rearrangement were essentially unaffected by the nature of the chiral group in the substrate. The highly diastereoselective aza-Cope rearrangement can be coupled to the intramolecular amidocarbonylation with paraformaldehyde. The coupling of these methods led to a direct and highly diastereoselective method for the rapid introduction of substituted piperidine units, which was demonstrated in the stereocontrolled synthesis of (+)-sedridine and (+)-allosedridine.

CHAPTER FIVE
TRIMETHYLSILYLDIAZOMETHANE AS A VERSATILE STITCHING AGENT FOR THE INTRODUCTION OF AZIRIDINES INTO FUNCTIONALIZED ORGANIC MOLECULES

5.1 Introduction

Aziridines are attractive synthetic building blocks. As with their epoxide analogs, the highly strained ring structures of aziridines provide access to a wide range of important nitrogen-containing products by undergoing several highly regio- and stereoselective cycloadditions and ring opening reactions.[35] Aziridines also play a very important role, through ring expansion reactions, in the formation of five membered heterocycles such as oxazoline-2-ones and imidazolidin-2-ones.[36]

Scheme 5. 1 Three approaches towards catalytic asymmetric aziridination



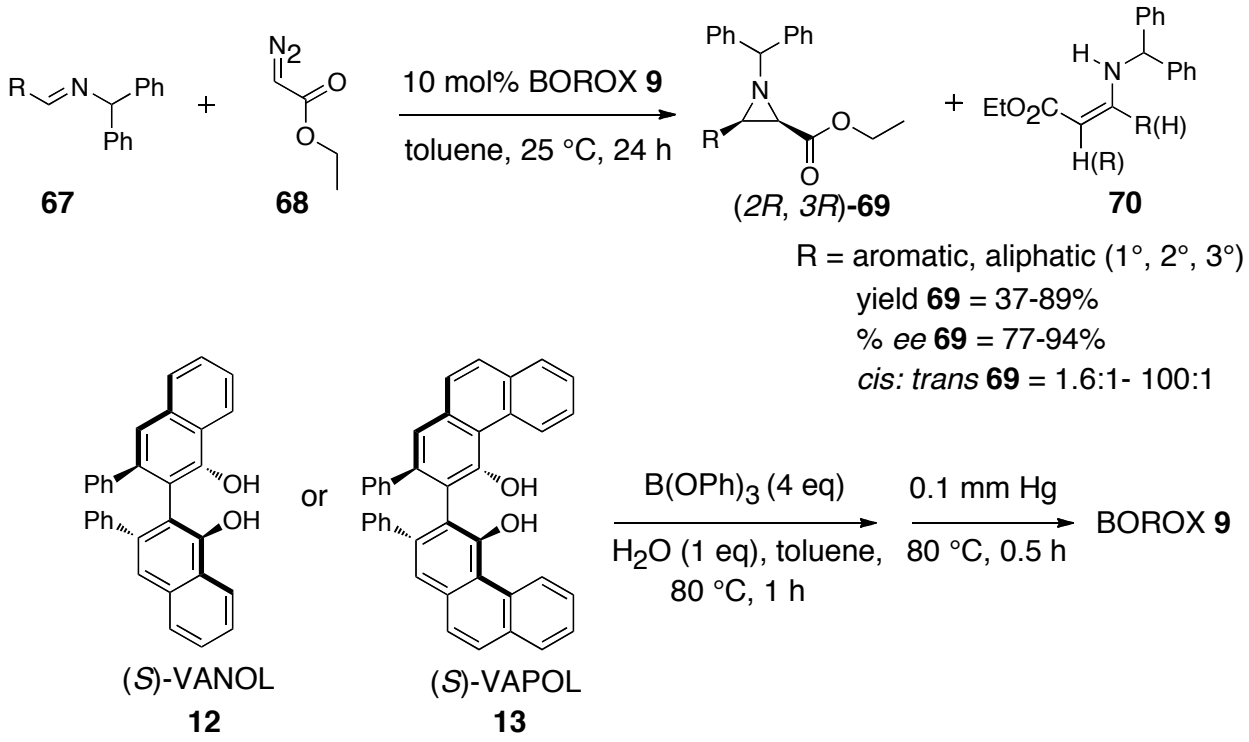
In the last two decades, a lot of effort has been put forth to develop effective asymmetric catalytic aziridination protocols. Although quite a few successful systems have been reported since then,[37] none of them are particularly general over a broad

range of substrates. So it is of great importance to develop a catalytic enantioselective aziridination which could be applied to a wide range of substrates.

To date, there have mainly been three different approaches towards catalytic asymmetric aziridinations. These are depicted in Scheme 5. 1.

Since 1999, our group has developed a catalytic asymmetric aziridination protocol which involves a Brønsted acid mediated addition of a diazo compound to an imine (Scheme 5. 2).[38] This aziridination protocol represents the most general and the most diastereo- and enantioselective catalytic asymmetric aziridination system to date.

Scheme 5. 2 The Antilla-Wulff catalytic asymmetric aziridination



An enormous amount of work[39] has been carried out in our group towards developing this aziridination protocol in the ten years since its discovery. Efforts towards

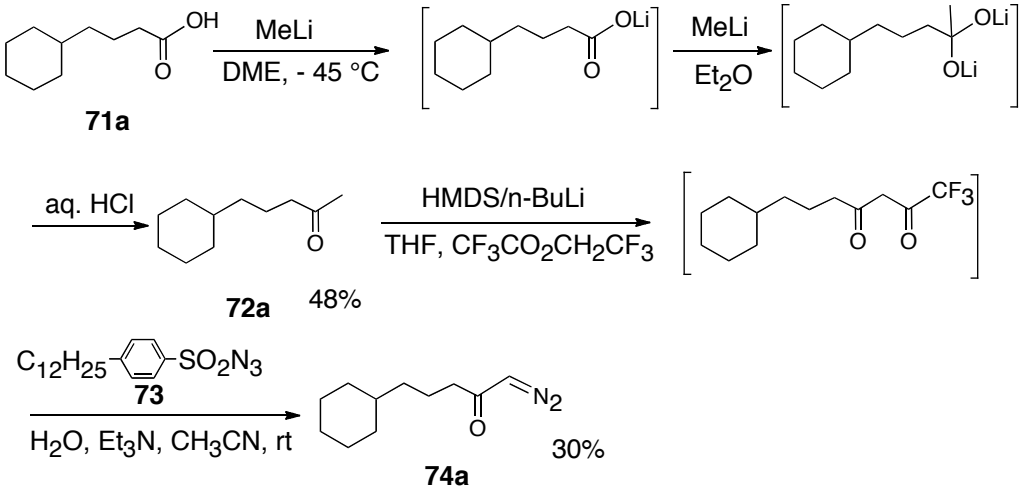
fine-tuning numerous aspects of the reaction,[39a-e] expanding its scope,[39f-i] elucidating the mechanism[39j-m] and applying it in a synthetic sense[39n-p] have been undertaken.

However, with the exception of one study,[39f] commercially available ethyl diazoacetate (EDA) has been the only diazo source used in all the *cis*-aziridination work reported by our group. Our interest for the present study was directed towards the development of the catalytic asymmetric *cis*-aziridination reaction with alternative diazo sources especially to those that would allow for the straightforward introduction of a variety of functional groups into the aziridine core. The goals are two-fold: define a facile catalytic asymmetric method for the introduction of aziridine units into functionalized organic molecules and determine the tolerance of the VAPOL/VANOL chiral polyborate catalyst **9** to various common organic functional groups.

5.2 Synthesis of diazo ketone via the diazo transfer method

As a first step, a mild, simple and general approach for the synthesis of the diazo compounds from precursors bearing the desired remote functional groups was required. The diazo transfer method[40] (Scheme 5.3) was tried initially, but that route did not give satisfactory results. The overall yield of **74a** was only 13% after four steps, and the purification of the final diazo ketone was extremely tedious, requiring at least three purifications by column chromatography to obtain the pure product.

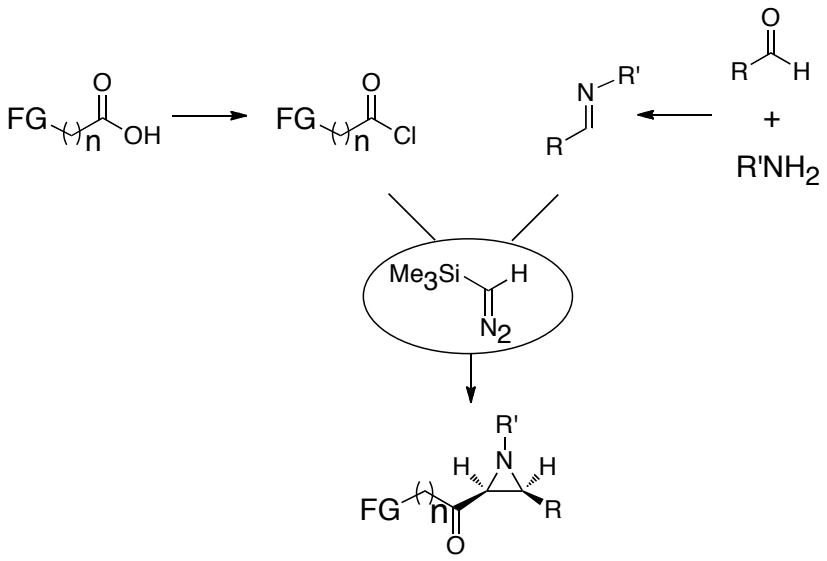
Scheme 5. 3 Synthesis of diazo ketone **74** via the diazo transfer method



Another well-known reagent for the synthesis of diazo compounds is diazomethane. However, it is notorious because of its high toxicity, thermal lability and potentially explosive nature. Diazomethane was thus decided to be avoided in our protocol.

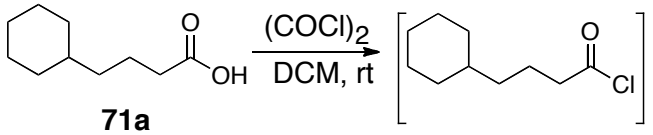
5.3 Synthesis of diazo ketones with $TMSCHN_2$

Scheme 5. 4 Tandem acylation/aziridination of $TMSCHN_2$

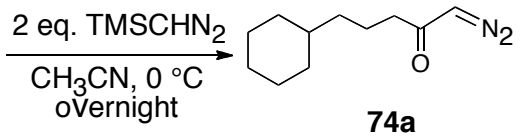


In 1981, Shioiri and co-workers reported trimethylsilyldiazomethane ($TMSCHN_2$) as a stable and safe substitute for the hazardous diazomethane in the Arndt-Eistert synthesis. [41] They also reported the preparation and isolation of 1-(diazoacetyl)naphthalene from $TMSCHN_2$ and the acid chloride of 1-naphthalene carboxylic acid, but it was the only isolated diazo ketone mentioned. This made us wonder if the same $TMSCHN_2$ protocol could be used to prepare other aromatic diazo ketones required for our study, and maybe aliphatic diazo ketones as well. If successful, this method would be much easier than the azide transfer method in terms of the reaction manipulation and product purification, and would also be much safer than the diazomethane option. Surprisingly, however, accessing diazo ketones via the use of $TMSCHN_2$ has never been explored to date, despite the wide spread use of diazo compounds in organic synthesis. We were attracted to the potential that trimethylsilyldiazomethane ($TMSCHN_2$) presents for introduction of aziridine units into functionalized organic molecules in a synthetically convergent manner (Scheme 5. 4).

Scheme 5. 5 Synthesis of diazo ketone **74a** by $TMSCHN_2$



71a



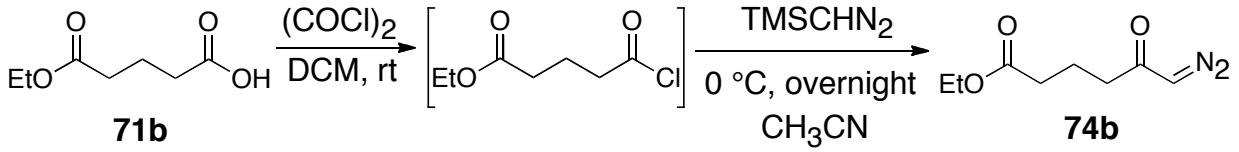
74a

73% (overall from **71a**)

We thus re-examines the synthesis of the diazo ketone **74a** via $TMSCHN_2$ (Scheme 5.5). We were delighted to discover that it worked very well with an overall yield of 73% for **74a**.

5.3.1 Optimization of the number of equivalents of $TMSCHN_2$

Table 5. 1 Optimization of the number of equivalents of $TMSCHN_2$



71b **74b**

Entry[a]	Equiv. of $TMSCHN_2$	Yield **74b** (%)[b]
1	1.1	70
2	1.5	74
3	2.0	73
4	2.5	77

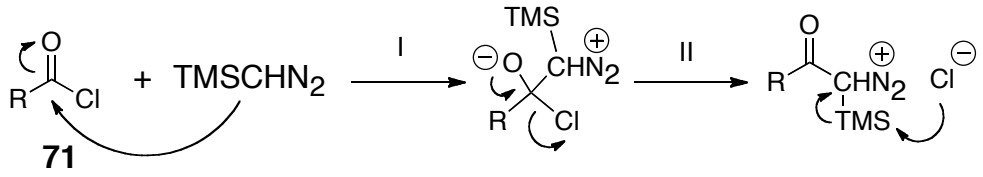
[a.] The acid **71** was reacted with oxalyl chloride for 1 h and then after volatiles were removed, the acid chloride was reacted with $TMSCHN_2$ at 0°C for 12 h at 0.2 M in CH_3CN. [b.] Isolated yield after purification by column chromatography on silica gel.

Considering the high cost of $TMSCHN_2$, it was then decided to optimize the number of equivalents of $TMSCHN_2$ needed for this reaction (Table 5. 1). It was found that the number of equivalents could be lowered from 2.5 to 1.1, while still providing a satisfactory yield of the diazo ketone **74b**. For the synthesis of diazo ketones from acyl chlorides. All reported examples required at least 2 equivalent of diazomethane to furnish good yield.[42] However, with $TMSCHN_2$, 1.1 equivalent is sufficient to provide

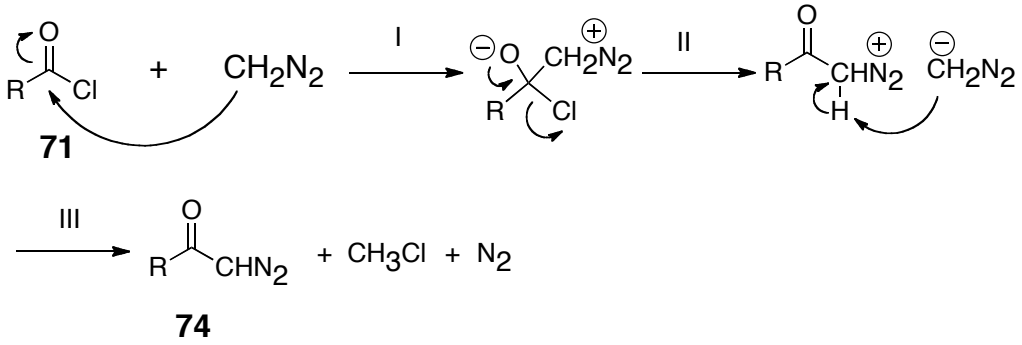
satisfactory yield. Scheme 5. 6 depicts a proposed mechanism for the diazo ketone formation with diazomethane and $TMSCHN_2$, respectively, that explains the origin of the difference. With $TMSCHN_2$, in the second step of the proposed mechanism, chloride anion serves as a nucleophile to attack TMS group, which furnishes the diazo ketone. While with CH_2N_2, after the nucleophilic attack to the acyl chloride in the first step, another equivalent of CH_2N_2 is required for deprotonation in the second step to afford the diazo ketone.

Scheme 5. 6 Proposed mechanism for the formation of diazo ketone with $TMSCHN_2$ and CH_2N_2

Diazo ketone formation with 1 equivalent of $TMSCHN_2$



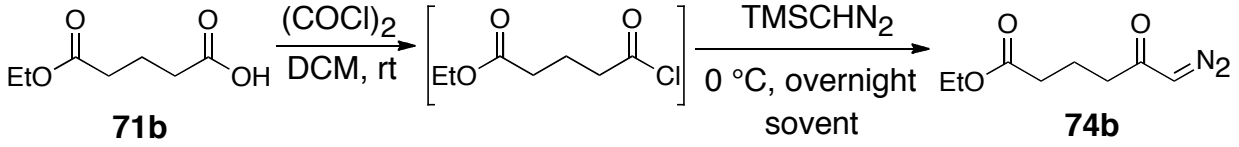
Diazo ketone formation with 2 equivalent of CH_2N_2



5.3.2 Sovent study for the synthesis of diazo ketone 74b

Subsequently, a variety of solvents were screened for diazo ketone formation with $TMSCHN_2$ and CH_3CN was determined to be the optimum solvent (Table 5. 2).

Table 5. 2 Solvent study for the synthesis of diazo ketone **74b**



71b **74b**

Entry[a]	Solvent	Yield **74b** (%)[b]
1	Hexane	20
2	CH_3CN	70
3	Et_2O	13
4	Toluene	21
5	CH_2Cl_2	27
6	EtOH	0
7[c]	DMF	68

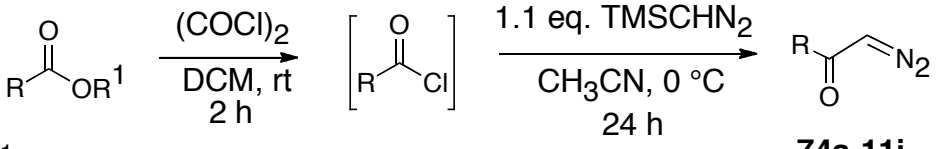
[a.] The acid 71 was reacted with oxalyl chloride for 1 h and then after volatiles were removed, the acid chloride was reacted with $TMSCHN_2$ at 0°C for 12 h at 0.2 M in CH_3CN. [b.] Isolated yield after purification by column chromatography on silica gel. [c.] No quench with satd $NAHCO_3$.

5.3.3 Substrate scope for the synthesis of diazo ketones with $TMSCHN_2$

We then examined the substrate scope of the reaction for the formation of various diazo ketones (Table 5. 3). To our pleasure, this protocol worked very well for the formation of aliphatic diazo ketones (entry 1-6 and 10). However the results for the reaction of aromatic carboxylic acids were disappointing, giving no desired products at all (Table 5. 3, entry 7-9). Triethylamine as an addictive was found to be necessary to

afford the diazo ketones from benzoic acid in acceptable yield (Table 5. 3, entry 7). The reactions of *trans*-cinnamic acid and phenylpropiolic acid failed even with the addition of triethylamine (Table 5. 3, entry 8 and 9).

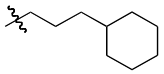
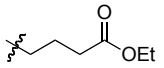
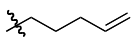
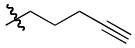
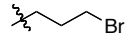
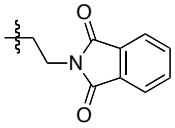
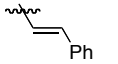
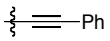
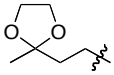
Table 5. 3 Substrate scope for the synthesis of diazo ketones **74** via $TMSCHN_2$



R^1 = H **71a-i,**

R^1 = TBDMS **71j**

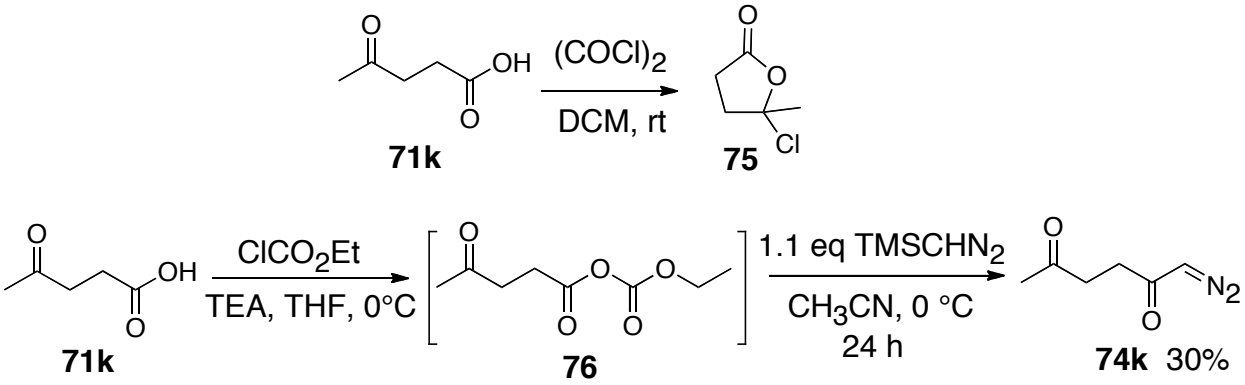
74a-11j

Entry	Series	R	Yield **11** (%)[a]
1	a		73
2	b		70
3[c]	c		69
4	d		66
5	e		78
6[d]	f		82
7[c,e]	g		52
8[c]	h		0
9[c]	i		15
10[d]	j		52

[a.] The acid **71** was reacted with oxalyl chloride for 1 h and then after volatiles were removed, the acid chloride was reacted with $TMSCHN_2$ at 0°C for 12 h at 0.2 M in CH_3CN. [b.] Isolated yield after purification by column chromatography on silica gel. [c.] 1.2 eq of Et_3N was added. [d.] The starting acids/ester were prepared according to reported procedures.[43] [e.] The product **74g** was not observed without Et_3N.

The application of $TMSCHN_2$ in the synthesis of diazo ketones starting from the corresponding acyl chloride is efficient in practice. However, in the case of substrate **71k**, other methods for acid activation, like forming the corresponding acid anhydrides instead of the acid chlorides, are preferred. This is due to the predominant formation of cyclic ester[44] of the type **75** (Scheme 5). Indeed, when acid **71k** was subjected to the standard acid chloride reaction, the undesired product **75** was obtained in quantitative yield. Thus, we turned our attention towards forming the acid anhydride **76** to get to the diazo ketone **74k** (Scheme 5). However, the overall yield was disappointing and the reaction was sluggish. We then tried to synthesize some relatively more active acid anhydrides, such as the (4-nitrophenylcarbonic)-4-oxopentanoic anhydride and (2,2,2-trichloroethylcarbonic)-4-oxopentanoic anhydride. But none of these anhydrides could be made successfully, and the ^1H NMR analysis of the crude reaction mixtures did not match the desired anhydride products.

Scheme 5. 7 Preparation of the diazo ketone **74k** via the corresponding acid anhydride

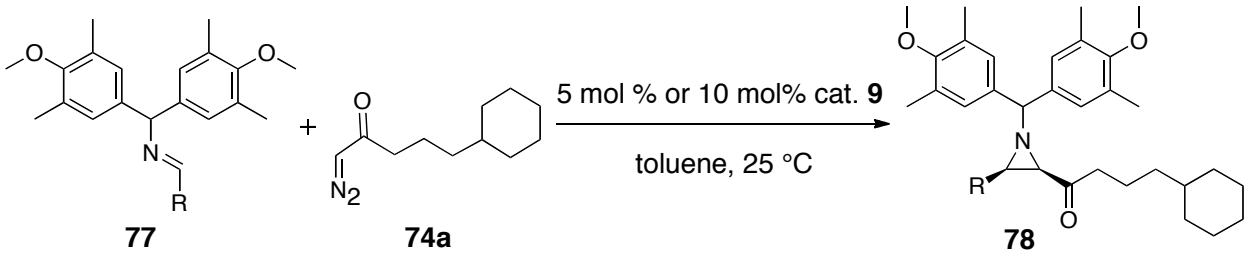


5.4 Introduction of aziridines into functionalized organic molecules

Thus, with the requisite diazo ketones bearing the remote functional groups in hand, the catalytic asymmetric aziridinations with the VAPOL and VANOL-borate catalysts were then examined, using the optimal conditions previously developed in our group.[39b]

5.4.1 Optimization of the aziridination reaction with diazo ketone 74a

Table 5. 4 Optimization of the aziridination reaction[a]



77 **74a** **78**

Entry	Series	R	Ligand	Time (h)	Cat. Loading **9** (%)	Conv. (%)[b]
1	a	Phenyl	*(S)*-VAPOL	24	5	100
2		Phenyl	*(R)*-VANOL	24	5	100
3	b	Cyclohexyl	*(S)*-VAPOL	96	5	67
4		Cyclohexyl	*(R)*-VANOL	96	5	68
5		Cyclohexyl	*(S)*-VAPOL	24	10	100
6		Cyclohexyl	*(R)*-VANOL	24	10	100
7	o	*t*-butyl	*(S)*-VAPOL	96	5	66
8		*t*-butyl	*(R)*-VANOL	96	5	64

[a.] Unless specified, all reactions were run in toluene at 25 °C containing 1 mmol imine **77** with 1.2 eq of diazo ketone **74a** and 5 mol% or 10 mol% of the catalyst **9** which was prepared according to procedure presented in Scheme 5. 2. *Ent*-**78** was obtained with (*R*)-VANOL. [b.] Determined form crude reaction mixture by ^{1}H NMR.

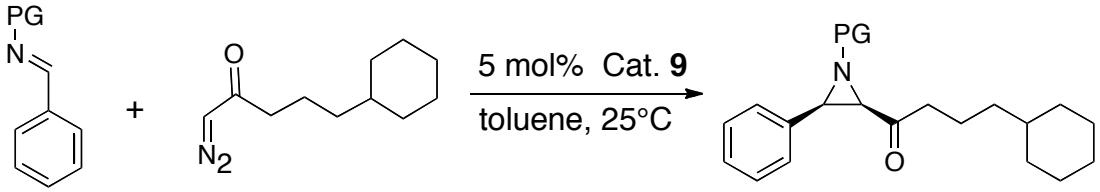
The catalytic asymmetric aziridination with remotely functionalized diazo ketones was optimized successively in three steps. First, we tried to optimize the representative imines to be used in the study. The *N*-MEDAM (bis(4-methoxy-3,5-dimethylphenyl)methanamine) phenyl imine **77a** and the *N*-MEDAM *t*-butyl imine **77c**

were selected at the beginning and the corresponding conversions were initially checked (Table 5. 4). The phenyl imine **77a** gave full conversion in 24 h with 5 mol% catalyst loading (Table 5. 4, entry 1 and 2). The conversions for the *N*-MEDAM *t*-butyl imine however were disappointing (Table 5. 4, entry 7 and 8). This might be due to the steric interactions between the bulky *t*-butyl group and the aliphatic chain of the diazo compounds. The less hindered *N*-MEDAM cyclohexyl imine **77b** was then used to replace the *N*-MEDAM *t*-butyl imine. But the conversions were still disappointing (Table 5. 4, entry 3 and 4). It was then decided to increase the catalyst loading in the second step of the optimization. The catalyst loading was increased to 10 mol%, which led to the complete conversion of the cyclohexyl imine **77b** (Table 5. 4, entry 5 and 6).

5.4.2 Optimization of the *N*-protecting group

In the last optimization step, we looked at the *N*-protection group in the imine (Table 5.5). The initial aziridination studies in our group were done with the benzhydryl group as the *N* protection group for the imine. However, recently, it has been shown that the *N*-MEDAM group is far superior for the aziridination reaction, especially for aliphatic imines. [39d] The benzhydryl amine was commercially available, while the MEDAM amine has to be synthesized in 4 steps.[39d] Thus, both the *N*-MEDAM phenyl imine **77a** and *N*-benzhydryl phenyl imine **78** were evaluated for the aziridination reactions with diazo ketone **74a**. From the results obtained (Table 5.5), it was evident that the *N*-MEDAM protection group was the protecting group of choice for this study.

Table 5. 5 Optimization of the N-protecting group[a]



PG = MEDAM **77a** **74a** PG = MEDAM **78a**

PG = benzhydryl **79** PG = benzhydryl **80**

Entry	PG	Ligand	Yield *cis* (%)[b]	*ee cis* (%)[c]
1	MEDAM	*(S)*-VAPOL	72	99
2	MEDAM	*(R)*-VANOL	85	94
3	Benzhydryl	*(S)*-VAPOL	66	92
4	Benzhydryl	*(R)*-VANOL	58	85

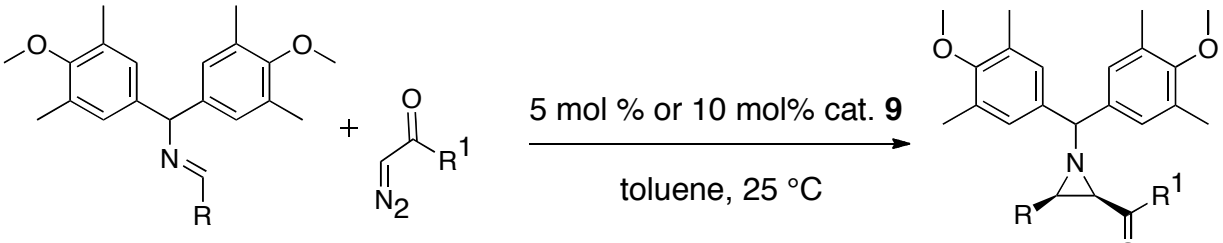
[a.] Unless specified, all reactions were run in toluene at 25 °C containing 1 mmol imine **77a** or **79** with 1.2 equiv of diazo ketone **74a.** [b.] Isolated yield after purification by column chromatography on silica gel. [c.] Determined by HPLC analysis.

5.4.3 Substrate scope for tandem acylation/aziridination of $TMSCHN_2$

Applying the optimized conditions, the aziridination reactions of the functionalized diazo ketones **74a-f** and **74j** with the imine **77a** and **77b** were examined in toluene and the results are presented in Table 5. 6. All reactions gave excellent asymmetric inductions for all aziridines with both VANOL and VAPOL catalysts and with both imines. The cis-aziridines were obtained with ≥ 50:1 selectivity in all cases. Higher asymmetric inductions were observed with the VAPOL catalysts for both imines in all cases with the curious exception of 5-bromo-1-diazopentan-2-one **74e** (entries 19 and 20). With the diazoketone **74a** as the control, it can be seen that the boroxinate catalyst **9** is remarkably tolerant of the presence of a variety of functional groups with essentially

no change in the asymmetric induction over the entire range of functional groups in the diazo ketones.

Table 5. 6 Aziridination of functionalized diazo ketones **74a-f,j** with imine **77a** and **77b**



77a R = Ph
77b R = Cy

74

78

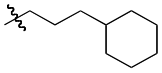
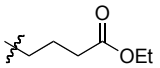
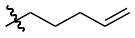
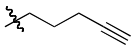
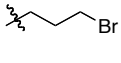
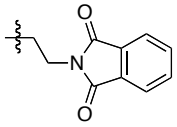
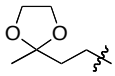
Entry	Prod. **78** Series	R	R^1	Ligand[b]	Time (h)	Conv (%)	Yield[c] *cis* **78** (%)	*ee*[d] *cis* **78** *(%)*
1	a	Ph		(S)-VAPOL	24	91	72	99
2		Ph		*(R)*-VANOL	24	100	85	94
3	b	Cy	**74a**	*(S)*-VAPOL	24	100	82	95
4		Cy		*(R)*-VANOL	36	93	65	91
5	c	Ph		*(S)*-VAPOL	24	98	76	99
6		Ph		*(R)*-VANOL	28	83	78	96
7	d	Cy	**74b**	*(S)*-VAPOL	24	100	92	97
8		Cy		*(R)*-VANOL	24	100	90	94
9	e	Ph		*(S)*-VAPOL	24	100	77	99
10		Ph		*(R)*-VANOL	24	100	82	96
11	f	Cy	**74c**	*(S)*-VAPOL	24	100	72	95
12		Cy		*(R)*-VANOL	24	100	79	91
13	g	Ph		*(S)*-VAPOL	24	100	89	99
14		Ph		*(R)*-VANOL	24	100	95	99
15	h	Cy	**74d**	*(S)*-VAPOL	24	100	79	96
16		Cy		*(R)*-VANOL	24	100	73	91

Table 5.6 (cont'd)

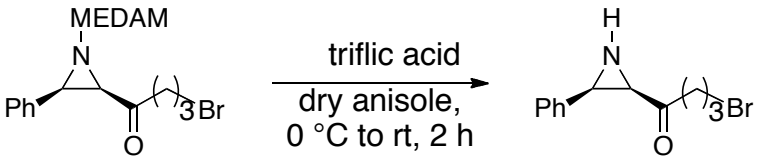
17	i	Ph	 **74e**	*(S)*-VAPOL	24	100	85	95
18		Ph		*(R)*-VANOL	24	100	78	98
19	j	Cy		*(S)*-VAPOL	28	93	61	92
20		Cy		*(R)*-VANOL	24	100	71	89
21	k	Ph	 **74f**	*(S)*-VAPOL	28	88	80	98
22		Ph		*(R)*-VANOL	28	87	85	93
23	l	Cy		*(S)*-VAPOL	36	70	63	88
24		Cy		*(R)*-VANOL	36	68	64	87
25	m	Ph	 **74j**	*(S)*-VAPOL	24	100	88	97
26		Ph		*(R)*-VANOL	24	100	85	93
27	n	Cy		*(S)*-VAPOL	24	100	62	93
28		Cy		*(R)*-VANOL	24	100	64	91

[a.] Unless specified, all reactions were run in toluene at 25 °C containing imine **77a** and **77b** with 1.2 eq of diazo ketone **74a-f** and **74j.** [b.] Catalyst loading was 5 mol% for **77a** and 10 mol% for **77b** which was prepared according to procedure presented in Scheme 5. 2. [c.] Isolated yield after purification by column chromatography on silica gel. [d.] Determined by chiral HPLC analysis. [e.] Calculated from ^{1}H NMR of crude reaction mixture.

5.5 Deprotection of MEDAM group

The most efficient method for the deprotection of MEDAM-aziridines is treatment with triflic acid in anisole. [39c,d] However, this method was optimized for simple aziridines sans functionality. It was not clear if the functionalized aziridines generated in the present study would be tolerant of these conditions. As a test, aziridine **78i**, was subjected to 5 equivalents of triflic acid in anisole for 2 h and, to our delight, cleavage of the MEDAM group could be achieved to give the N-H aziridine **81i** in excellent yield (Scheme 5. 8). It was interesting to note that this molecule could be isolated and purified on silica gel with no evidence for intramolecular alkylation on nitrogen.

Scheme 5. 8 Deprotection of MEDAM group from (2*R*, 3*R*)-**78i**



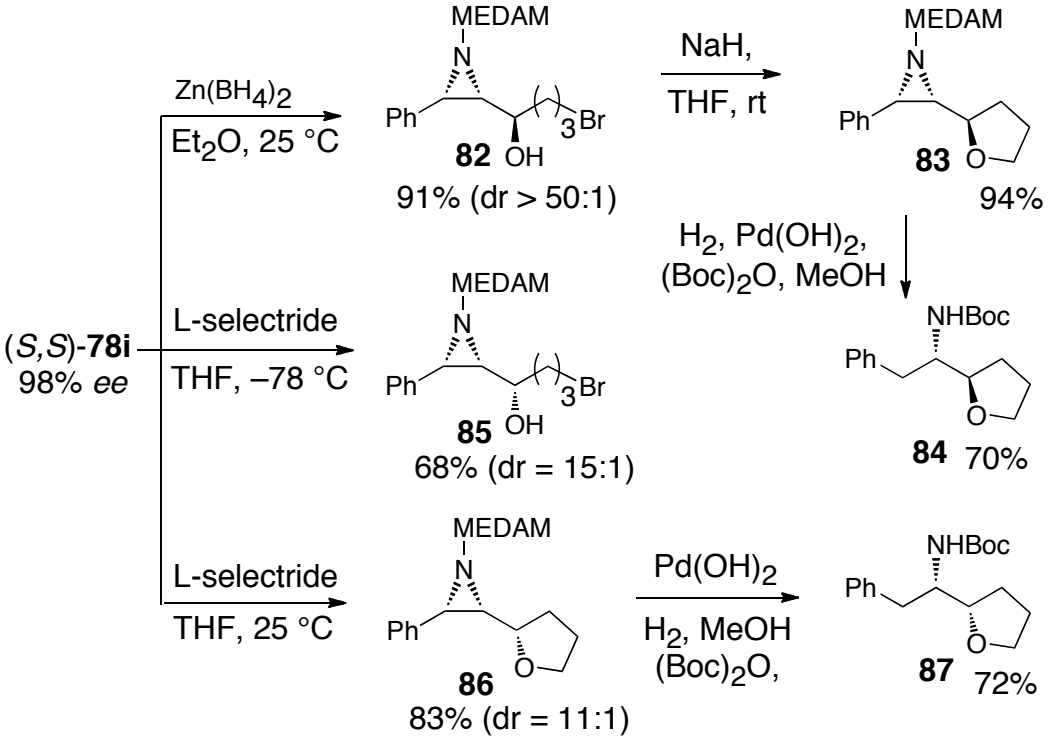
(2*R*,3*R*)-**78i** **81i**, 84% yield

5.6 Diastereoselective synthesis of tetrahydrofurylamines

Tetrahydrofurylamines are widely used in the synthesis of various medical agents such as ion channel modulators,[45] enzyme inhibitors,[46] analgesics,[47] antibiotics[48] and neuotropics,[49] anticarcinogenic drugs[50] and antifungal agents.[51] These types of compounds are also of particular interest with regard to ligands for asymmetric alkylation.[52] Despite the broad use and importance of tetrahydrofurylamines, a search of the literature produced few reports for the asymmetric preparation of tetrahydrofurylamines, especially those bearing two contiguous chiral centers. Key to the general access to all the stereoisomers of tetrahydrofurylamines from the aziridinyl ketone **78i** is the ability to control the stereochemistry in the reduction of the ketone function. The reduction was first examined with zinc borohydride, a well-known chelation-controlled reducing agent.[39f] Despite our concerns with the presence of the large MEDAM group on the nitrogen which might prevent the coordination of zinc, it proved possible to reduce the ketone moiety with >50:1 selectivity for diastereomer **82** (Scheme 5. 9). Non-chelation-controlled reduction of the ketone functionality in **78i** could be effected with L-selectride at –78 °C in 68% yield and with a 15:1 selectivity for diastereomer **85**. When the reduction with L-selectride was conducted at room

temperature, the stereochemistry of the reduction only dropped to 11:1 and the resulting lithium alkoxide cyclized to give the tetrahydrofurylaziridine **86**. Reductive opening of the aziridine and reductive cleavage of the MEDAM group in the presence of $(Boc)_2O$ afforded the tetrahydrofurylamine **87**. After cyclization of **82** with NaH, the diastereomeric tetrahydrofurylamine **84** could be obtained from **83** with the same protocol used in the conversion of **86** to **87**.

Scheme 5. 9 Diastereoselective access to enantiomeric tetrahydrofurylamines



5.7 Conclusion

This work has demonstrated that the Shioiri acylation of trimethylsilyldiazomethane with aliphatic acid chlorides can be coupled to the catalytic asymmetric aziridination of aldimines with a chiral polyborate Brønsted acid catalyst derived from the vaulted biaryl ligands VANOL and VAPOL. The coupling of these methods led to a direct and highly

enantioselective method for the rapid introduction of aziridine units into functionalized organic molecules. It is important to note that the very high asymmetric inductions of the boroxinate catalyst for the catalytic asymmetric aziridination were essentially unaffected by the nature of the functional group in the diazo component. The products of these tandem reactions are synthetically useful intermediates and this was demonstrated in the stereocontrolled synthesis of tetrahydrofuryl amines.

CHAPTER SIX EXPERIMENTAL SECTION

6.1 Supporting information for chapter two

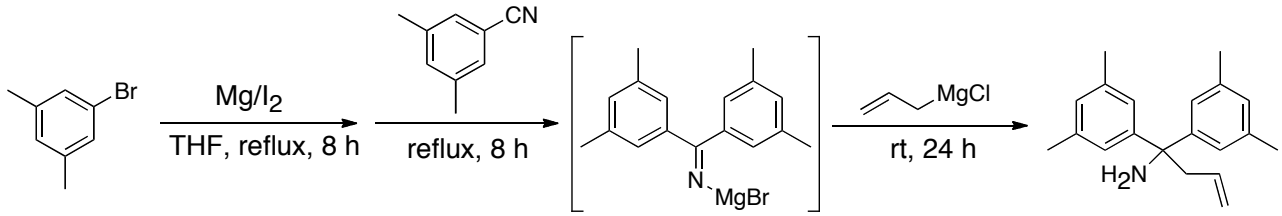
6.1.1 General information

All experiments were performed under an argon atmosphere. Flasks were flame-dried and cooled under argon before use. All solvents were dried appropriately if used in the reaction. Both VAPOL and VANOL ligands are commercially available from Aldrich as well as Strem Chemicals. If desired, they could be purified using column chromatography on regular silica gel with 2:1 dichloromethane/hexanes. Phenol was sublimed and stored in a dry desiccator. Solid aldehydes were either used as purchased from Aldrich or sublimed before use. Liquid aldehydes were either used as purchased from Aldrich or distilled before use.

Melting points were measured on a Thomas Hoover capillary melting point apparatus. ^{1}H NMR and ^{13}C NMR were recorded on a Varian 300 MHz, VXR-500 MHz or VXR-600 MHz instrument in $CDCl_3$ unless otherwise noted. $CHCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.24) and ^{13}C NMR (δ = 77.0). 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 m^2/g surface area and 0.4 g/mL bulk density. 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.

HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotation was 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.

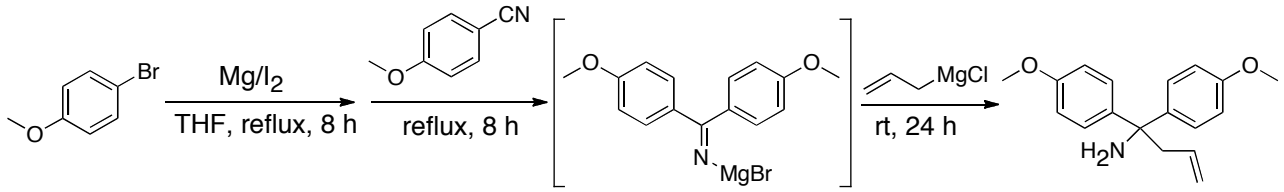
6.1.2 General procedure for the preparation of the amines – Illustrated for the synthesis of 1,1-bis(3,5-dimethylphenyl)but-3-en-1-amine 22f



22f

To a flame-dried 100 mL three-necked round bottomed flask filled with Nitrogen and equipped with a refluxing condenser was added 1-bromo-3,5-dimethylbenzene (3.7 g, 20 mmol), magnesium (1.2 g, 50 mmol), THF (45 mL) and a few crystals of I_2. The mixture was slowly heated to reflux and kept at reflux for 8 h. The resulting light brown solution was allowed to cool down to room temperature. At the same time, to a flame-dried 250 mL three-necked round-bottomed flask filled with nitrogen was added 3,5-dimethylbenzonitrile[53] (2.4 g, 18 mmol) and THF (45 mL). Then the freshly prepared Grignard reagent was transferred at room temperature via syringe to the 250 mL flask containing the nitrile compound over 5 min. The resulting mixture was heated to reflux for 8 h under an nitrogen atmosphere, and then allowed to cool down to room temperature, and then 0 °C. To this mixture was transferred a solution of allyl magnesium chloride in THF (2.0 M, 44 mmol, 22 mL). The ice-bath was then removed and the reaction mixture was stirred at room temperature for 24 h. The mixture was then

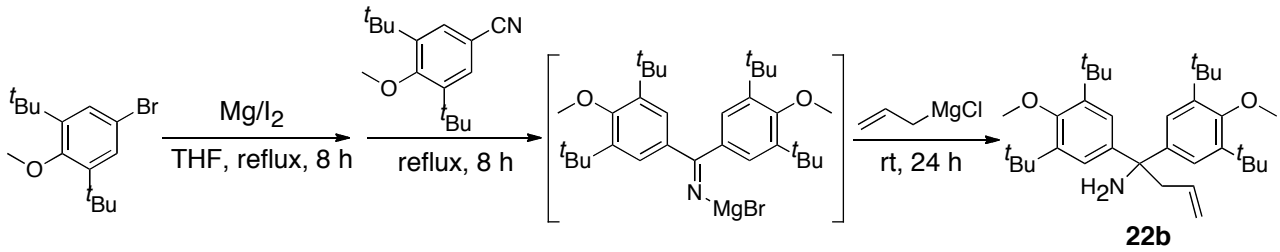
cooled down to 0 °C and carefully quenched by the slow addition of 1 N aqueous NaOH (20 mL). THF was removed under reduced pressure and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product as a yellow solid, which was purified by silica gel chromatography (8:1 hexanes/EtOAc as elute) to afford amine **22f** as a white solid (mp 85-86 °C) in 24% yield after three steps (1.2 g, 4.3 mmol). *Spectral data for **22f**:* R_f = 0.2 (8:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.72 (bs, 2H), 2.26 (s, 12H), 2.95 (d, 2H, *J* = 6.9 Hz), 5.04-5.16 (m, 2H), 5.44-5.53 (m, 1H), 6.82 (s, 2H), 6.97 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.75, 47.98, 60.12, 119.04, 124.59, 128.18, 134.83, 137.60, 148.45; IR (thin film) 3410m, 3390m, 3072m, 2976m, 1604m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 278 (1.04) (1.04), 238 (100), 110 (70), 41 (53); Anal calcd for $C_{20}H_{25}N$: C, 85.97; H, 9.02; N, 5.01. Found: C, 86.10; H, 8.95; N, 4.97.



22a

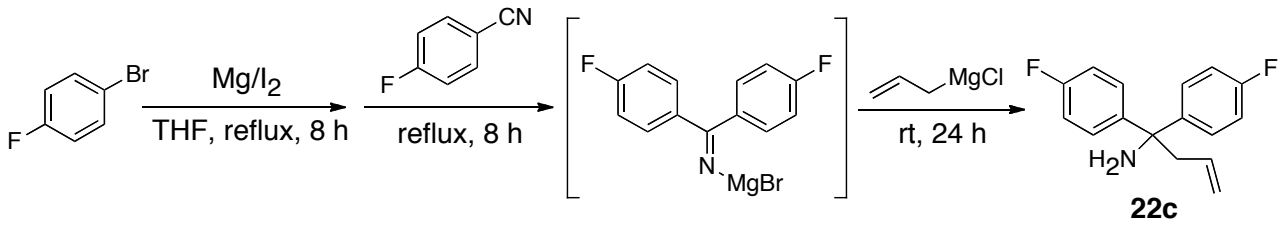
*1,1-bis(4-methoxyphenyl)but-3-en-1-amine **22a**.* The general procedure described above for the preparation and purification of amine **22f** was followed for the synthesis of **22a**, starting from 1-bromo-4-methoxybenzene (3.7 g, 20 mmol). Purification by column chromatography on silica gel (1:15 ether/pentane) gave the pure amine **22a** as an oil in

20% yield (1.0 g, 3.6 mmol). *Spectral data for **22a**:* R_f = 0.2 (1:15 ether/pentane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (bs, 2H), 2.94 (d, 2H, *J* = 6.5 Hz), 3.76 (s, 6H), 5.06-5.15 (m, 2H), 5.48-5.55 (m, 1H), 6.79-6.82 (m, 4H), 7.26-7.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.16, 55.45, 59.66, 113.59, 119.20, 127.90, 134.65, 140.92, 158.21; IR (thin film) 3372m, 3071m, 2934m, 1608m, 1248m, 1035m cm-1; HRMS (ES+) calcd for $C_{18}H_{22}NO_2$ *m/z* 284.1651 (M^++1), meas 284.1665.



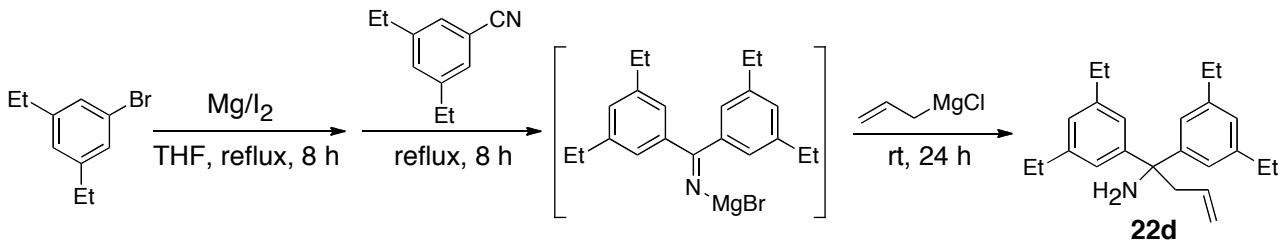
*1,1-bis(3,5-di-tert-butyl-4-methoxyphenyl)but-3-en-1-amine **22b**.* The general procedure described above for the preparation and purification of amine **22f** was followed for the synthesis of **22b**, starting from 5-bromo-1,3-di-*tert*-butyl-2-methoxybenzene (4.5 g, 21 mmol). Purification by column chromatography on silica gel (1:16:0.17 acetone/hexanes/TEA) gave the pure amine **22b** as an oil in 22% yield (2.1 g, 4.2 mmol). *Spectral data for **22b**:* R_f = 0.2 (1:16:0.17 acetone/hexanes/TEA). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (s, 36 H), 1.79 (bs, 2H), 2.94 (d, 2H, *J* = 7.0 Hz), 3.64 (s, 6H), 5.07-5.19 (m, 2H), 5.61-5.65 (m, 1H), 7.15 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.38, 36.09, 48.29, 60.91, 64.30, 118.71, 125.36, 135.33, 142.15, 142.63, 157.88; IR (thin film) 2959m, 1653m, 1224, 1014m cm-1; HRMS (ES+) calcd for $C_{34}H_{54}NO_2$ *m/z* 508.4155

(M^++1), meas 508.4158.



22c

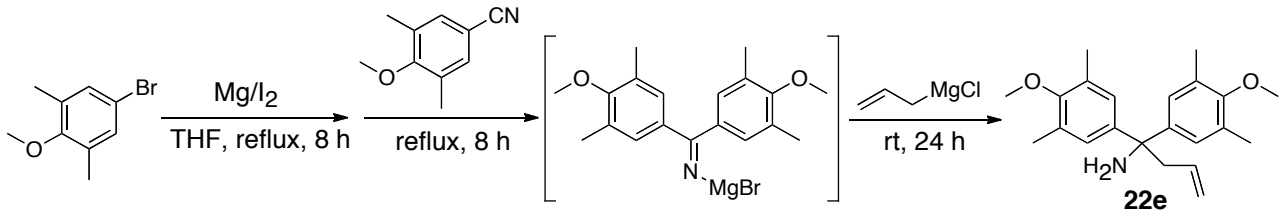
1,1-bis(4-fluorophenyl)but-3-en-1-amine ***22c***. The general procedure described above for the preparation and purification of amine **22f** was followed for the synthesis of **22c**, starting from 1-bromo-4-fluorobenzene (1.9 g, 11 mmol). Purification by column chromatography on silica gel (1:2:0.1 DCM/hexanes/TEA) gave the pure amine **22c** as an oil in 21% yield (0.54 g, 2.1 mmol). *Spectral data for* ***22c****:* R_f = 0.2 (1:2:0.1 DCM/hexanes/TEA). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (bs, 2H), 2.95 (d, 2H, *J* = 7.0 Hz), 5.08-5.15 (m, 2H), 5.43-5.50 (m, 1H), 6.94-6.98 (m, 4H), 7.30-7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.07, 59.83, 115.04-115.21 (d, *J* = 21.0 Hz), 119.84, 128.40-128.46 (d, *J* = 8.0 Hz), 133.86, 144.03-144.05 (d, *J* = 3.0 Hz), 160.70-162.65 (d, *J* = 244 Hz); IR (thin film) 3400m, 3300m, 3076m, 2924m, 1601m, 1226m, 1014m cm-1; HRMS (ES+) calcd for $C_{16}H_{16}NF_2$ *m/z* 260.1251 (M^++1), meas 260.1238.



22d

1,1-bis(3,5-diethylphenyl)but-3-en-1-amine ***22d****.* The general procedure described

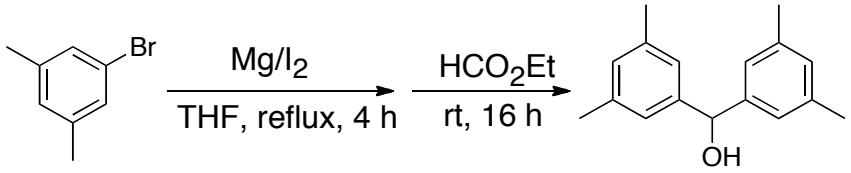
above for the preparation and purification of amine **22f** was followed for the synthesis of **22d**, starting from 1-bromo-3,5-diethylbenzene[54] (1.3 g, 6 mmol). Purification by column chromatography on silica gel (1:24:0.25 acetone/hexanes/TEA) gave the pure amine **22d** as an oil in 22% yield (0.40 g, 1.2 mmol). *Spectral data for **22d**:* R_f = 0.2 (1:24:0.25 acetone/hexanes/TEA). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.21 (t, 12H, *J* = 8.0 Hz), 1.81 (bs, 2H), 2.62 (q, 8H, *J* = 7.5 Hz), 3.00-3.02 (d, 2H, *J* = 7.0 Hz), 5.08-5.19 (m, 2H), 5.54-5.58 (m, 1H), 6.90 (s, 2H), 7.06 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.96, 29.29, 48.23, 60.63, 118.95, 123.91, 125.60, 135.01, 144.05, 148.50; IR (thin film) 3072m, 2984m, 1599m, 1458m cm-1; HRMS (ES+) calcd for $C_{24}H_{34}N$ *m/z* 336.2691 (M^++1), meas 336.2682.



*1,1-bis(4-methoxy-3,5-dimethylphenyl)but-3-en-1-amine **22e**.* The general procedure described above for the preparation and purification of amine **22f** was followed for the synthesis of **22e**, starting from 5-bromo-2-methoxy-1,3-dimethylbenzene (4.5 g, 21 mmol). Purification by column chromatography on silica gel (1:2 ether/pentane) gave the pure amine **22e** as an oil in 27% yield (1.7 g, 5.1 mmol). *Spectral data for **22e**:* R_f = 0.2 (1:2 ether/pentane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (bs, 2H), 2.23 (s, 12H), 2.91 (d, 2H, *J* = 7.5 Hz), 3.68 (s, 6H), 5.05-5.15 (m, 2H), 5.45-5.52 (m, 1H), 6.99 (s, 4H); ^{13}C

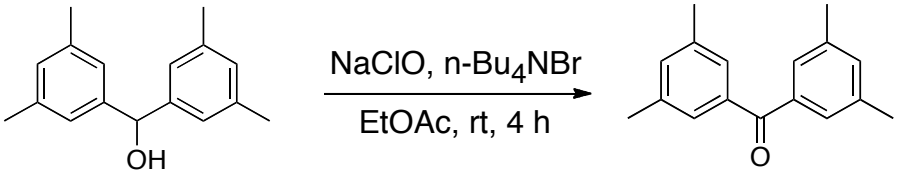
NMR (125 MHz, $CDCl_3$) δ 16.60,48.16, 59.55, 59.83, 119.09, 127.16, 130.25, 134.88, 143.64, 155.53; IR (thin film) 2932m, 1653m cm-1; HRMS (ES+) calcd for $C_{22}H_{30}NO_2$ *m/z* 340.2277 (M^++1), meas 340.2264.

6.1.3 Large scale preparation of 1,1-bis(3,5-dimethylphenyl)but-3-en-1-amine 22f



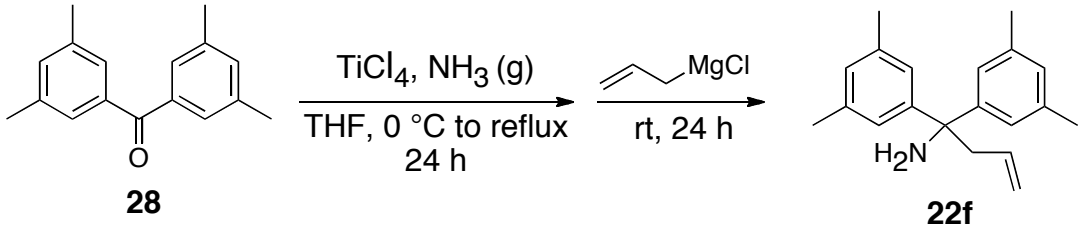
To a flame-dried 2 L three-necked round-bottomed flask filled with Nitrogen and equipped with a refluxing condenser was added 1-bromo-3,5-dimethylbenzene (100 g, 540 mmol), magnesium (32.5 g, 1.35 mol), THF (1.08 L) and a few crystals of I_2. The mixture was slowly heated to reflux and kept at reflux for 4 h. The resulting light brown solution was allowed to cool down to room temperature and then 0 °C. Then ethyl formate (18.6 g, 20.4 mL, 250 mmol) was slowly added to the freshly prepared Grignard reagent and the mixture was stirred at room temperature for 16 h. The reaction was quenched at 0 °C by addition of H_2O (18 mL + 36 mL). The resulting slurry was filtered through a Celite pad and washed with THF until no alcohol was left (as monitored by TLC). The mixture was then concentrated under reduced pressure to afford an orange solid. This solid was dissolved in dichloromethane (360 mL) and washed with water (60 mL x 2). The organic phase was then dried over Na_2SO_4, filtered and stripped of solvent to give an off-white solid (60 g) which could be used in the next step without further purification. *Spectral data:* ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.10 (s, 1H), 2.29 (s,

12H), 5.67-5.68 (d, 1H, *J* = 3.0 Hz), 6.89 (s, 2H), 6.98 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.34, 76.37, 124.22, 129.14, 137.99, 143.89.



28

To a 2 L round-bottomed flask was sequentially added the unpurified alcohol (60 g, 250 mmol), n-BuN_4Br (15 g, 47 mmol) and EtOAc (800 mL). Bleach (6% commercially available Clorox regular bleach) (720 mL) was then added to the reaction mixture at room temperature slowly to give a yellow solution.[55] Upon completion after 4 h, the mixture turned colorless and the organic phase was separated. The aqueous phase was then extracted with EtOAc (150 mL x 3). The combined organic phase was washed with H_2O (150 mL) and brine (150 mL), drided over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow solid. The crude product was purified by crystallization with hexanes to give ketone **28** as an off-white solid (mp 110-112 °C) in 64 % yield over two steps (38 g, 160 mmol). *Spectral data for **28**:* ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.35 (s, 12H), 7.19 (s, 2H), 7.37 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.16, 127.66, 133.85, 137.77,138.00, 197.55.

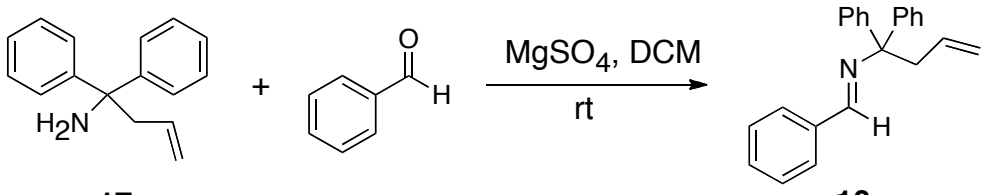


28 **22f**

To a flame-dried 2 L three-necked round bottomed flask filled with Nitrogen and equipped with a refluxing condenser was added ketone **28** (25.7 g, 108 mmol) and THF (500 mL). The resulting mixture was cooled down to 0 °C. Then $TiCl_4$ (22 mL, 173 mmol) was quickly added to the cold solution and a yellow slurry was formed.[56] The yellow slurry then turned dark green after gaseous ammonia was bubbled into the stirred mixture for 5 min. With a continuous supply of gaseous ammonia, the dark green slurry turned orange and NH_3 (g) was kept for another 20 min and then the NH_3 flow was stopped. The resulting mixture was warmed up to room temperature and then slowly heated to reflux for 24 h. Allyl magnesium chloride (2 M in THF, 864 mmol, 432 mL) was added at 0 °C. Stirring was continued at room temperature for 24 h. Upon completion, the reaction mixture was merged into an ice-water bath and carefully quenched with sat. Na_2CO_3 (400 mL). The white slurry was filtered through a Celite pad and washed with EtOAc (600 mL). The organic phase was separated and washed with water (100 mL x 2) and brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford an off-white solid. The crude product was purified by crystallization with hexanes to give amine **22f** as a white solid in 86% yield (25.6 g, 93

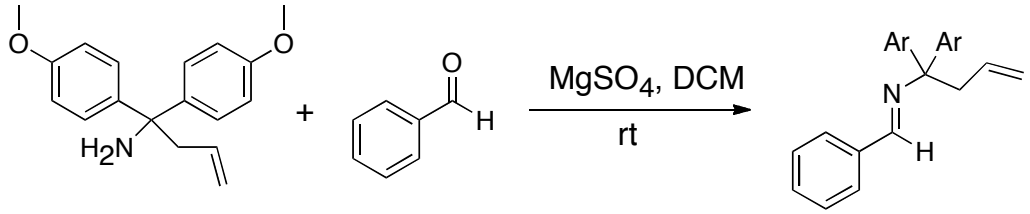
mmol) (1st crop, 55%, mp 85-87°C; 2nd crop, 16%, mp 86-87°C; 3rd crop, 15%, mp 85-86°C).

6.1.4 General procedure for the preparation of the imines – Illustrated for the synthesis of (E)-N-benzylidene-1,1-diphenylbut-3-en-1-amine 10



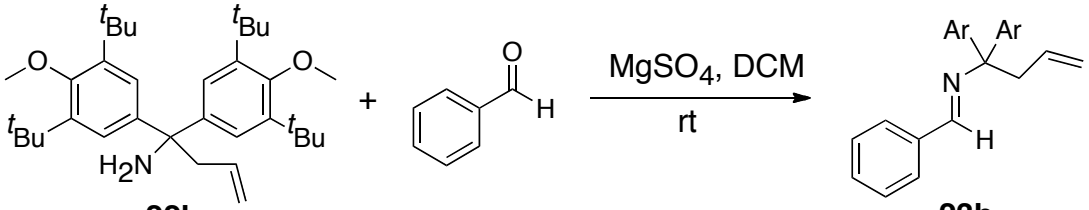
17 **10**

To a flame-dried 50 mL round bottomed flask filled with argon was added $MgSO_4$ (1.50 g, 12.5 mmol) and 10.0 mL dry CH_2Cl_2. This was followed by the addition of 1,1-diphenylbut-3-en-1-amine **17**[54] (0.670 g, 3.00 mmol, 1 equiv). After stirring for 5 minutes, benzaldehyde (0.350 g, 3.30 mmol, 1.1 equiv) was added.[57] The reaction mixture was stirred for 48 h at room temperature. Thereafter, the reaction mixture was filtered through a Celite bed and the Celite bed was washed with CH_2Cl_2. The filtrate was then concentrated by rotary evaporation and placed under high vacuum (0.05 mm Hg) for 1 h to give the crude imine **10** as a light yellow oil which could be used in the next step without further purification. *Spectral data for **10**:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.17 (d, 2H, *J* = 7.0 Hz), 4.95-5.00 (m, 2H), 5.80-5.88 (m, 1H), 7.24-7.45 (m, 13H), 7.81-7.86 (m, 2H), 7.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.02, 72.29, 117.73, 126.78, 128.17, 128.58, 128.74, 128.76, 130.80, 134.78, 137.20, 146.58, 159.99.



22a **23a**

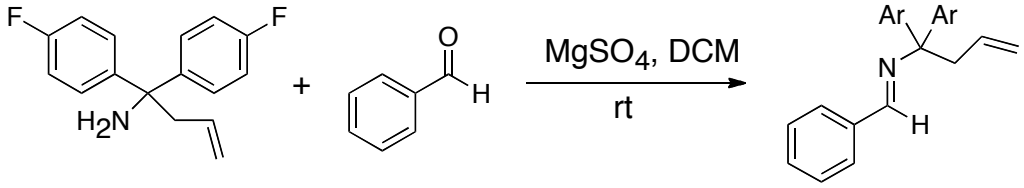
(E)-N-benzylidene-1,1-bis(4-methoxyphenyl)but-3-en-1-amine ***23a****.* 1,1-bis(4-methoxyphenyl)but-3-en-1-amine **22a** (0.43 g, 1.5 mmol) was reacted according to the general procedure described above to afford the crude imine **23a** as a light yellow oil which was used in the next step without further purification. *Spectral data for* ***23a****:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.09 (d, 2H, *J* = 7.0 Hz), 3.82 (s, 6H), 4.99-4.99 (m, 2H), 5.81-5.87 (m, 1H), 6.87 (d, 4H, *J* = 8.5 Hz), 7.28 (d, 4H, *J* = 9.0 Hz), 7.41-7.43 (m, 3H), 7.79-7.81 (m, 2H), 7.83 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.06, 55.14, 55.16, 71.25, 113.16, 113.35, 117.24, 127.64, 128.28, 128.45, 129.72, 130.43, 134.80, 138.56, 158.00, 159.21.



22b **23b**

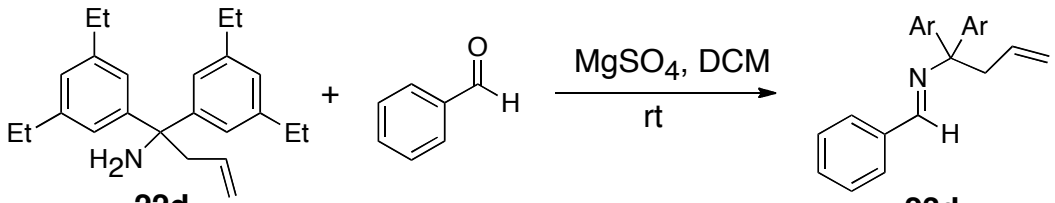
(E)-N-benzylidene-1,1-bis(3,5-di-tert-butyl-4-methoxyphenyl)but-3-en-1-amine ***23b***. 1,1-bis(3,5-di-*tert*-butyl-4-methoxyphenyl)but-3-en-1-amine **22b** (1.3 g, 2.5 mmol) was reacted according to the general procedure described above to afford the crude imine **23b** as a yellow solid. Crystallization (hexanes) afforded **23b** in 77% isolated yield (1.14 g, 1.93 mmol) as white crystals (mp 99–101 °C). *Spectral data for* ***23b****:* ^{1}H NMR

($CDCl_3$, 500 MHz) δ 1.37 (s, 36H), 3.10 (d, 2H, *J* = 6.5 Hz), 3.68 (s, 6H), 4.99-5.06 (m, 2H), 5.85-5.91 (m, 1H), 7.11 (s, 4H), 7.42 (t, 3H, *J* = 6.5, 3.5 Hz), 7.78-7.80 (m, 2H), 7.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.38, 36.04, 46.83, 64.32, 73.18, 117.17, 127.39, 128.41, 128.72, 130.51, 135.83, 137.42, 139.54, 142.34, 157.86, 159.20.



22c **23c**

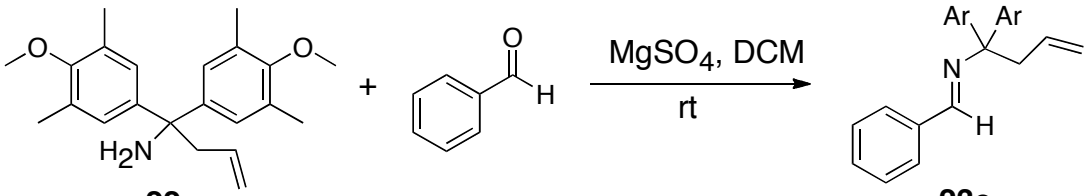
(E)-N-benzylidene-1,1-bis(4-fluorophenyl)but-3-en-1-amine ***23c***. 1,1-bis(4-fluorophenyl)but-3-en-1-amine **22c** (0.26 g, 1.0 mmol) was reacted according to the general procedure described above to afford the crude imine **23c** as a light yellow oil which was used in the next step without further purification. *Spectral data for **23c**:* ^1H NMR ($CDCl_3$, 500 MHz) δ 3.06-3.07 (m, 2H), 4.91-4.95 (m, 2H), 5.72-5.77 (m, 1H), 6.99-7.02 (m, 4H), 7.29-7.33 (m, 4H), 7.40-7.43 (m, 3H), 7.76-7.79 (m, 3H).



22d **23d**

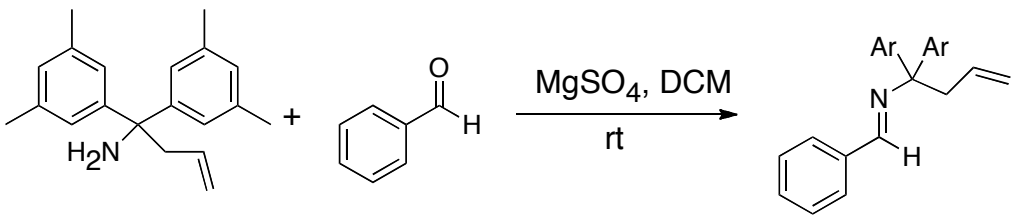
(E)-N-benzylidene-1,1-bis(3,5-diethylphenyl)but-3-en-1-amine ***23d***. 1,1-bis(3,5-diethylphenyl)but-3-en-1-amine **22d** (84 mg, 0.25 mmol) was reacted according to the general procedure described above to afford the crude imine **23d** as a light yellow oil

which was used in the next step without further purification. *Spectral data for **23d**:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (t, 12H, *J* = 7.5 Hz), 2.61 (q, 8H, *J* = 7.0 Hz), 3.13 (d, 2H, *J* = 7.5 Hz), 4.93-4.99 (m, 2H), 5.80-5.86 (m 1H), 6.92 (s, 2H), 7.01 (s, 4H), 7.40-7.42 (m, 3H), 7.79-7.81 (m, 2H), 7.84 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.72, 29.00, 46.86, 72.39, 117.01, 125.41, 125.59, 128.28, 128.41, 130.29, 135.13, 137.19, 143.45, 146.04, 159.28.



22e **23e**

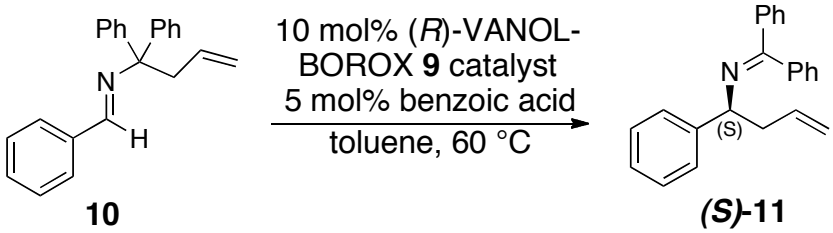
*(E)-N-benzylidene-1,1-bis(4-methoxy-3,5-dimethylphenyl)but-3-en-1-amine **23e***. 1,1-bis(4-methoxy-3,5-dimethylphenyl)but-3-en-1-amine **22e** (170 mg, 0.500 mmol) was reacted according to the general procedure described above to afford the crude imine **23e** as a light yellow oil which was used in the next step without further purification. *Spectral data for **23e:*** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 12H), 3.02 (d, 2H, *J* = 6.5 Hz), 3.70 (s, 6H), 4.90-4.95 (m, 2H), 5.71-5.76 (m, 1H), 6.98 (s, 2H), 7.38-7.40 (m, 4H), 7.75-7.77 (m, 3H), 7.80 (s, 1H).



22f **23f**

(E)-N-benzylidene-1,1-bis(3,5-dimethylphenyl)but-3-en-1-amine ***23f****.* 1,1-bis(3,5-dimethylphenyl)but-3-en-1-amine **22f** (0.56 g, 2.0 mmol) was reacted according to the general procedure described above to afford the crude imine **23f** as a yellow solid. Crystallization with hexanes afforded **23f** in 80% isolated yield (0.59 g, 1.6 mmol) as white crystals (mp 117-118 °C). *Spectral data for* ***23f****:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.31 (s, 12H), 3.12 (d, 2H, *J* = 6.0 Hz), 4.94-4.99 (m, 2H), 5.78-5.83 (m, 1H), 6.88 (s, 2H), 6.99 (s, 4H), 7.42 (s, 3H), 7.82-7.86 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.57, 46.79, 71.74, 117.10, 126.21, 128.07, 128.32, 128.42, 130.36, 134.93, 137.06, 137.12, 146.34, 159.57; IR (thin film) 3007m, 2916m, 1640m, 1450m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 367 (M)+ (18.04), 326 (100), 180 (90), 140 (100); Anal calcd for $C_{20}H_{25}N$: C, 88.24; H, 7.95; N, 3.81. Found: C, 88.24; H, 8.07; N, 3.78.

6.1.5 Optimization of diarylmethyl group for catalytic asymmetric Aza-cope rearrangement with imines – Illustrated for the synthesis of (S)-N-(diphenylmethylene)-1-phenylbut-3-en-1-amine 11



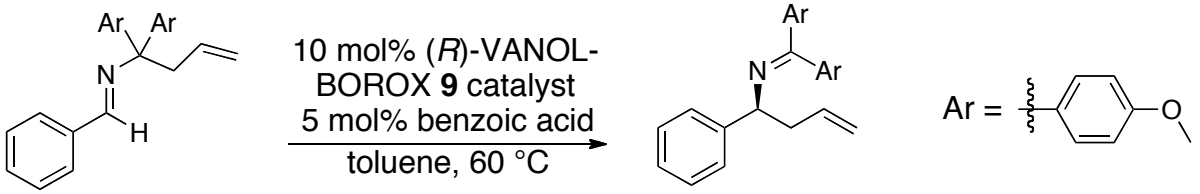
10 ***(S)*-11**

Preparation of catalyst stock solution.[58] A 50 mL Schlenk flask was flame dried under high vacuum and cooled under a low flow of Argon. To the flask was added sequentially (*R*)-VANOL (44 mg, 0.1 mmol), phenol (19 mg, 0.2 mmol), dry toluene (2.0 mL), BH_3•SMe_2 (2 *M* solution in toluene, 150 μL, 0.3 mmol) and water (5.4 μL, 0.3 mmol) under a low flow of Argon. The threaded Teflon valve on the Schlenk flask was

then closed, and the mixture heated at 100 °C for 1 h. The valve was carefully and slowly opened to gradually apply high vacuum (0.1 mm Hg) and the solvent was removed. The vacuum was maintained for a period of 30 min at 100 °C. The flask was then removed from the oil bath and allowed to cool to room temperature under a low flow of Argon. This was then completely dissolved in 2 mL of dry toluene to afford the stock solution of the catalyst.

The Aza-cope rearrangement. A 5 mL Schlenk test tube fitted with a threaded Teflon valve and a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Argon. To the test tube was then added imine **10** (31 mg, 0.10 mmol, 1 equiv), toluene (0.1 mL) and 0.20 mL of the catalyst stock solution (10 mol% catalyst) via a plastic syringe fitted with a metallic needle. At the same time, to an oven-dried 5 mL vial was added benzoic acid (12 mg, 0.1 mmol) and toluene (1 mL). Then 50 μL of the benzoic acid stock solution (5 mol%) was transferred to the above catalyst-imine complex via a plastic syringe fitted with a metallic needle. After addition of the rest of the toluene (0.15 mL), the Schlenk test tube was closed and the reaction was stirred at 60 °C for 18 h. Upon completion, the reaction mixture was directly loaded to a silica gel column (2 cm x 20 cm) with a pipette. Purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min and gave the rearrangement product **11** as a white solid (mp 81-82 °C) in 76% yield (24 mg, 0.076 mmol). *Spectral data for* **11***:* R_f = 0.2 (1:12 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.59-2.62 (m, 1H), 2.69-2.73 (m, 1H), 4.46 (dd, 1H, *J* = 5.5 Hz, 8.0 Hz), 4.96-5.03 (m, 2H), 5.65-5.70 (m, 1H), 7.08-7.10 (m, 2H), 7.23-7.26 (m, 1H), 7.30-7.41 (m, 7H), 7.44-7.46 (m, 3H), 7.69-7.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.21, 66.74, 116.96, 126.97, 127.41, 128.16,

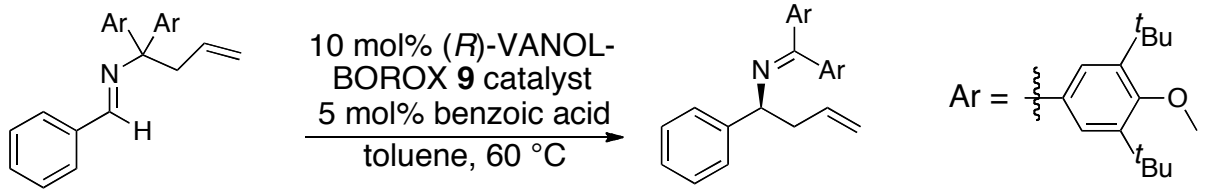
128.24, 128.53, 128.55, 128.56, 128.85, 130.12, 136.03, 137.36, 140.30, 144.75, 166.93; IR (thin film) 3078m, 2929m, 1601m cm^{-1}; The optical purity of **11** was determined to be 42% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.6 mL min^{-1}). Retention times were 5.3 min (major enantiomer, (*S*)-**11**) and 6.8 min (minor enantiomer, (*R*)-**11**).



23a ***(S)*-24a**

(S)-N-(bis(4-methoxyphenyl)methylene)-1-phenylbut-3-en-1-amine ***24a****.* (*E*)-N-benzylidene-1,1-bis(4-methoxyphenyl)but-3-en-1-amine **23a** (37 mg, 0.10 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:6 ether/pentane) was complete in 5 min to afford the rearrangement product **24a** as a viscous oil in 54% yield (20 mg, 0.054 mmol). *Spectral data for* ***24a****:* R_f = 0.2 (1:6 ether/pentane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.54-2.58 (m, 1H), 2.62-2.66 (m, 1H), 3.79 (s, 3H), 3.85 (s, 3H), 4.43 (dd, 1H, *J* = 5.5 Hz, 7.5 Hz), 4.91-4.97 (m, 2H), 5.59-5.68 (m, 1H), 6.82 (d, 2H, *J* = 8.5 Hz), 6.92 (d, 2H, *J* = 9.0 Hz), 6.97 (d, 2H, *J* = 8.5 Hz), 7.19-7.20 (m, 1H), 7.26-7.32 (m, 4H), 7.60 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.05, 55.25, 55.32, 66.25, 113.23, 113.57, 116.45, 126.55, 127.13, 128.21, 129.36, 129.46, 130.15, 133.43, 135.97, 144.89, 159.36, 161.01, 165.91; IR (thin film) 3003m, 2932m, 1606m, 1248m cm^{-1}; mass spectrum, *m/z*

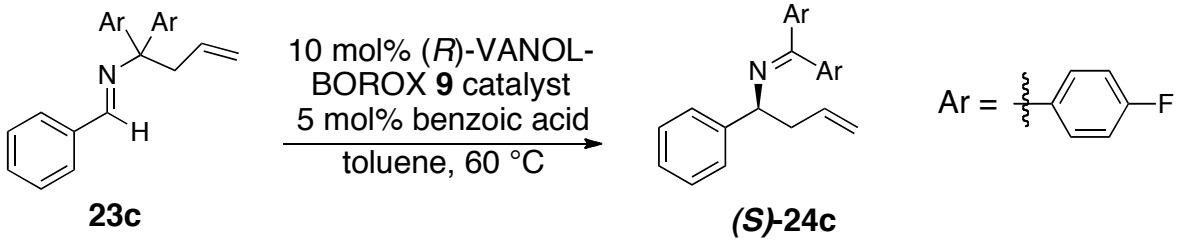
(% rel intensity) 371 (M+) (1.3), 330 (100), 165 (50), 91 (37); HRMS (ES+) calcd for $C_{25}H_{26}NO_2$ *m/z* 372.1964 (M^++1), meas 372.1949. The optical purity of **24a** was determined to be 20% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.6:0.4, 222 nm, flow rate 0.3 mL min^{-1}). Retention times were 21.2 min (major enantiomer, (*S*)-**24a**) and 22.8 min (minor enantiomer, (*R*)-**24a**).



23b ***(S)*-24b**

(S)-N-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methylene)-1-phenylbut-3-en-1-amine ***24b***. (*E*)-N-benzylidene-1,1-bis(3,5-di-tert-butyl-4-methoxyphenyl)but-3-en-1-amine **23b** (60 mg, 0.1 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:40 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **24b** as a foamy solid (mp 42-44 °C) in 67% yield (40 mg, 0.067 mmol). *Spectral data for **24b**:* R_f = 0.2 (1:40 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (s, 36H), 2.52-2.56 (m, 1H), 2.65-2.70 (m, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 4.41 (dd, 1H, *J* = 5.0 Hz, 8.0 Hz), 4.90-4.97 (m, 2H), 5.63-5.70 (m, 1H), 6.85 (s, 2H), 7.14-7.17 (m, 1H), 7.23-7.29 (m, 4H), 7.59 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (1 sp^2 Carbon missing) δ 32.18, 32.34, 36.03, 36.05, 44.35, 64.42, 64.64, 66.87, 116.44, 126.50, 126.73, 127.51, 128.38, 131.96, 134.44, 136.58, 143.15, 143.56, 145.35, 159.24, 161.47, 167.31; IR (thin film) 2961m, 1653m, 1223m cm^{-1}; mass

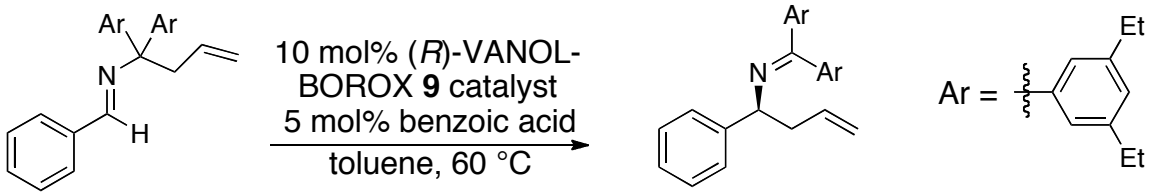
spectrum, *m/z* (% rel intensity) 367 (M+) (4.0), 554 (100), 269 (32), 234 (14); Anal calcd for $C_{41}H_{57}NO_2$: C, 82.64; H, 9.64; N, 2.35. Found: C, 82.07; H, 9.84; N, 2.25. To measure the optical purity of **24b,** the imine **24b** was hydrolyzed with 18% aq. HCl in THF and then protected with $(Boc)_2O$. The optical purity was determined to be 39% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.9:0.1, 222 nm, flow rate 0.6 mL min^{-1}). Retention times were 64.2 min (major enantiomer) and 81.2 min (minor enantiomer).



23c ***(S)*-24c**

(S)-N-(bis(4-fluorophenyl)methylene)-1-phenylbut-3-en-1-amine ***24c****.* (*E*)-N-benzylidene-1,1-bis(4-fluorophenyl)but-3-en-1-amine **23c** (33 mg, 0.10 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **24c** as a viscous oil in 75% yield (25 mg, 0.075 mmol). *Spectral data for **24c**:* R_f = 0.2 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.52-2.54 (m, 1H), 2.59-2.64 (m, 1H), 4.31 (dd, 1H, *J* = 5.5 Hz, 8.0 Hz), 4.89-4.95 (m, 2H), 5.54-5.60 (m, 1H), 6.94 (m, 4H), 7.07 (t, 2H, *J* = 9.0 Hz), 7.16-7.19 (m, 1H), 7.23-7.26 (m, 4H), 7.57-7.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.96, 66.64, 114.96 (d, *J* = 21.5 Hz), 115.53 (d, *J* =21.0 Hz), 116.85, 126.85, 127.02, 128.38, 129.76 (d, *J* = 7.9 Hz), 130.47,

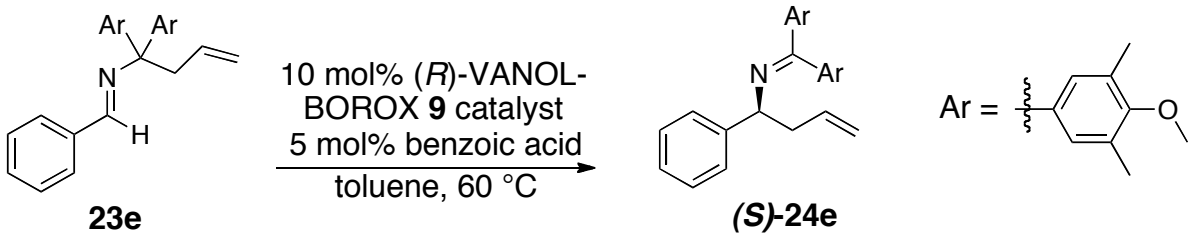
(d, *J* = 9.0 Hz), 132.62 (d, *J* = 3.0 Hz), 135.57, 136.11 (d, *J* = 3.0 Hz), 144.26, 161.60, 163.32 (d, *J* = 64 Hz), 164.79 (d, *J* = 63 Hz); IR (thin film) 3010m, 2938m, 1603m, 1224m cm^{-1}; HRMS (ES+) calcd for $C_{23}H_{20}NF_2$ *m/z* 348.1564 (M^++1), meas 348.1551. The optical purity of **24c** was determined to be 41% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.3 mL min^{-1}). Retention times were 10.3 min (major enantiomer, (*S*)-**24c**) and 12.0 min (minor enantiomer, (*R*)-**24c**).



23d ***(S)*-24d**

(S)-N-(bis(3,5-diethylphenyl)methylene)-1-phenylbut-3-en-1-amine ***24d****.* (*E*)-*N*-benzylidene-1,1-bis(3,5-diethylphenyl)but-3-en-1-amine **23d** (26 mg, 0.060 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:20 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **24d** as a viscous oil in 70% yield (18 mg, 0.042 mmol). *Spectral data for* ***24d****:* R_f = 0.2 (1:20 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11-1.14 (m, 12H), 2.52-2.66 (m, 10H), 4.33 (dd, 1H, *J* = 8.0 Hz, 5.5 Hz), 4.85-4.92 (m, 2H), 5.56-5.62 (m, 1H), 6.61 (s, 2H), 6.98 (s, 2H), 6.98-7.14 (m, 1H), 7.17-7.26 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.52, 15.63, 28.73, 28.79, 43.98, 66.54, 116.30, 124.65, 125.67, 127.04, 127.26, 128.14, 128.96, 136.10, 137.44, 140.32, 143.82, 144.01, 144.25,

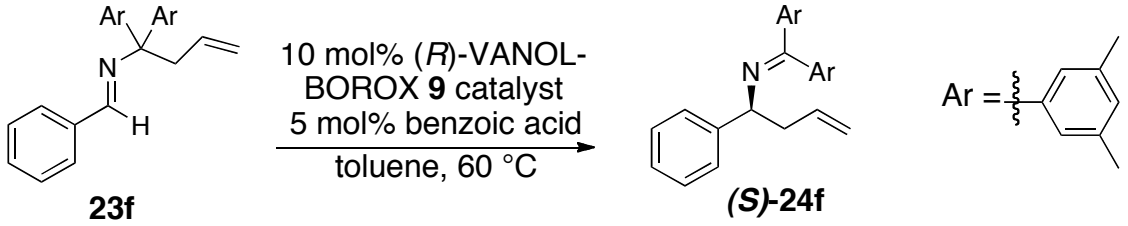
144.90, 167.67; To determine the optical purity of compound **24d**, the compound was hydrolyzed with 18% aq. HCl in THF and then protected with $(Boc)_2O$. *Spectral data for the N-Boc amine*: ^{1}H NMR (CDCl3, 500 MHz) δ 1.34 (s, 9H), 2.45 (bs, 2H), 4.73 (d, 2H), 4.99-5.05 (m, 2H), 5.58-5.64 (m, 1H), 7.15-7.20 (m, 3H), 7.24-7.27 (m, 2H); IR (thin film) 2980m, 1604m, 1522m, 1176m cm^{-1}; Anal calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.66; H, 8.99; N, 5.53; The optical purity was determined to be 40% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.9:0.1, 222 nm, flow rate 0.6 mL min^{-1}). Retention times were 64.5 min (major enantiomer) and 82.2 min (minor enantiomer).



23e ***(S)*-24e**

*(S)-N-(bis(4-methoxy-3,5-dimethylphenyl)methylene)-1-phenylbut-3-en-1-amine **24e**.* *(E)*-N-benzylidene-1,1-bis(4-methoxy-3,5-dimethylphenyl)but-3-en-1-amine **23e** (43 mg, 0.10 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:15 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **24e** as a viscous oil in 70% yield (30 mg, 0.07 mmol). *Spectral data for **24e**:* R_f = 0.2 (1:15 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 6H), 2.30 (s, 6H), 2.54-2.56 (m, 1H), 2.67-2.71 (m, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 4.39 (dd, 1H, *J* = 5.0 Hz, 8.0 Hz), 4.91-4.96 (m, 2H), 5.61-5.69 (m, 1H),

6.87 (s, 2H), 7.11-7.15 (m, 1H), 7.21-7.27 (m, 4H), 7.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (1 sp^2 carbon missing) δ 21.27, 21.32, 64.44, 64.60, 66.85, 116.42, 126.52, 126.71, 127.54, 128.41, 131.95, 134.41, 136.62, 143.15, 143.54, 145.37, 159.21, 161.45, 167.28; IR (thin film) 3036m, 2924m, 1652m cm^{-1}. The optical purity of **24e** was determined to be 63% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.6 mL min^{-1}). Retention times were 7.3 min (major enantiomer, (*S*)-**24e**) and 9.1 min (minor enantiomer, (*R*)-**24e**).

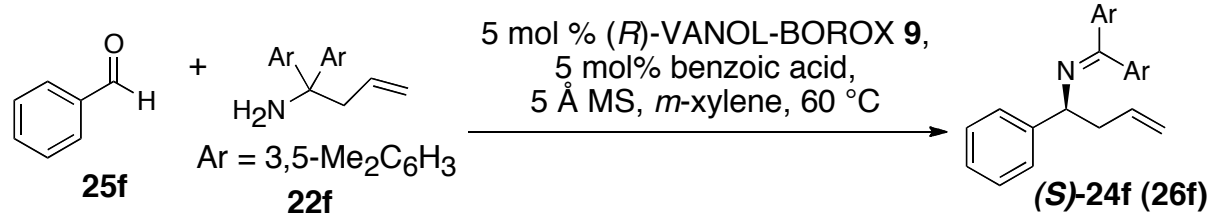


23f ***(S)*-24f**

(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-phenylbut-3-en-1-amine ***24f****.* (*E*)-N-benzylidene-1,1-bis(3,5-dimethylphenyl)but-3-en-1-amine **23f** (37 mg, 0.1 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **24f** as a viscous oil in 85% yield (31 mg, 0.085 mmol). *Spectral data for* ***24f****:* R_f = 0.2 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.27 (s, 6H), 2.28 (s, 6H), 2.55-2.59 (m, 1H), 2.63-2.68 (m, 1H), 4.37 (dd, 1H, *J* = 7.5 Hz, 5.5 Hz), 4.91-4.97 (m, 2H), 5.61-5.67 (m, 1H), 6.61 (s, 2H), 6.99 (d, 2H, *J* = 11 Hz), 7.16-7.21 (m, 1H), 7.25-7.29 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) (1 sp^2 carbon missing) δ 21.29, 21.31, 44.17, 66.44, 116.37, 125.50, 126.36, 126.53, 127.24, 128.14, 129.65,

131.47, 135.99, 137.37, 137.59, 140.36, 144.82, 167.61; IR (thin film) 3024m, 2916m, 1959m, 1599m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 367 (M)+ (7.65), 326 (100), 180 (29), 103 (14); HRMS (ES+) calcd for $C_{27}H_{30}N$ *m/z* 368.2378 (M^++1), meas 368.2374. The optical purity of **24f** was determined to be 69% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.3 mL min^{-1}). Retention times were 11.4 min (major enantiomer, (*S*)-**24f**) and 14.3 min (minor enantiomer, (*R*)-**24f**).

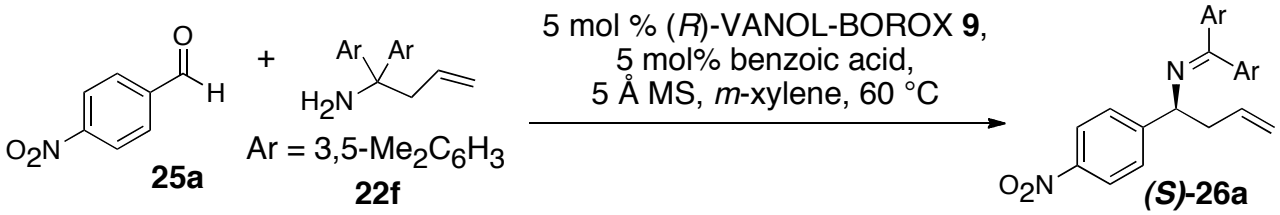
6.1.6 General procedure for catalytic asymmetric aminoallylation of aldehydes – Illustrated for the synthesis of (S)-N-(bis(3,5-dimethylphenyl)methylene)-1-phenylbut-3-en-1-amine 24f (24f = 26f)



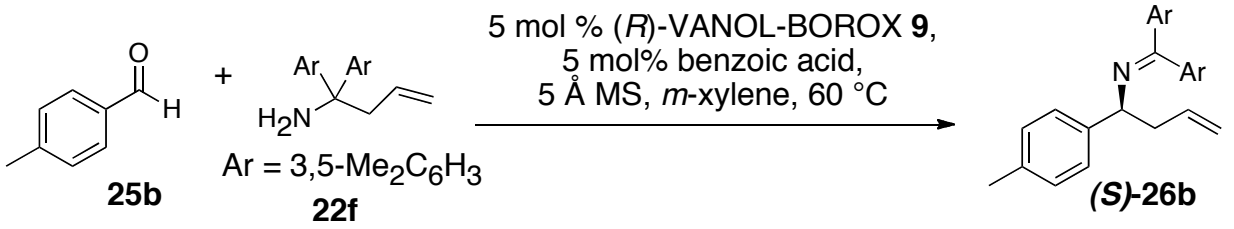
Preparation of catalyst stock solution. A 50 mL Schlenk flask was flame dried under high vacuum and cooled under a low flow of Argon. To the flask was added sequentially (*R*)-VANOL (44 mg, 0.1 mmol), 2,4,6-trimethylphenol (28 mg, 0.2 mmol), dry toluene (2.0 mL), BH_3•SMe_2 (2 *M* solution in toluene, 150 μL, 0.3 mmol) and water (5.4 μL, 0.3 mmol) under a low flow of Argon. The threaded Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. The valve was carefully opened to gradually apply high vacuum (0.1 mm Hg) and the solvent was removed. The vacuum was maintained for a period of 30 min at 100 °C. The flask was then removed from the oil bath and allowed to cool to room temperature under a low flow of Argon. This was

then completely dissolved in 2 mL of dry *m*-xylene to afford the stock solution of the catalyst.

The aminoallylation of aldehydes. A 5 mL Schlenk test tube charged with 5Å powdered molecular sieves (50 mg) and fitted with a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Argon. To the test tube was then added amine **22f** (28 mg, 0.10 mmol, 1.0 equiv), 0.10 mL of the catalyst stock solution (5 mol% catalyst) and *m*-xylene (0.35 mL) via a plastic syringe fitted with a metallic needle. The mixture was stirred for 30 min at 60 °C. At the same time, to an oven-dried 5 mL vial was added benzoic acid (12 mg, 0.1 mmol) and *m*-xylene (1 mL). Then benzaldehyde **25f** (12 mg, 11 μL) and 50 μL of the benzoic acid stock solution (5 mol%) were transferred to the above catalyst-amine complex under a high flow of Argon via a plastic syringe fitted with a metallic needle. The test tube was closed and the reaction was stirred at 60 °C for 18 h. Upon completion, the reaction mixture was directly loaded to a silica gel column (2 cm x 20 cm) with a pipette. Purification by flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min and gave the rearrangement product **24f** as a white solid in 92% yield. Spectral data matches that given in section E. The optical purity of **24f** was determined to be 80% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.3 mL min^{-1}). Retention times were 11.4 min (major enantiomer, (*S*)-**13a**) and 14.3 min (minor enantiomer, (*R*)-**24f**). $[\alpha]^{23}_{D}$ = -2.9 (*c* = 3.0, CH_2Cl_2) on 80% ee *S*-**24f.**

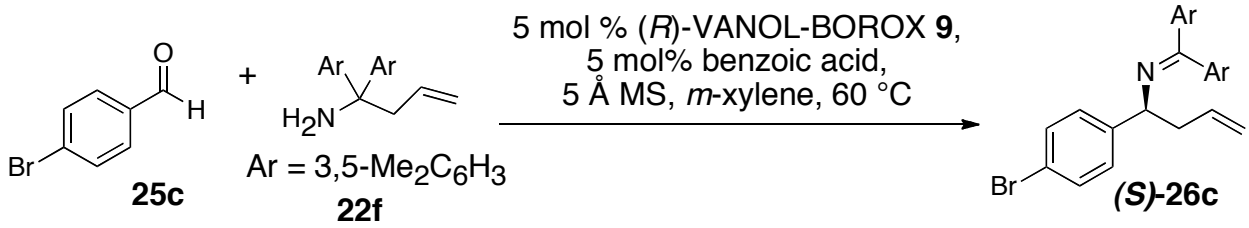


(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(4-nitrophenyl)but-3-en-1-amine ***26a***. *p*-Nitrobenzaldehyde **25a** (17 mg, 0.11 mmol, 1.1 equiv) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26a** as a viscous oil in 85% yield (35 mg, 0.085 mmol). *Spectral data for* ***26a****:* R_f = 0.18 (1:15 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 6H), 2.29 (s, 6H), 2.53-2.57 (m, 1H), 2.61-2.65 (m, 1H), 4.46 (t, 1H, *J* = 6.0 Hz), 4.92-4.96 (m, 2H), 5.60-5.65 (m, 1H), 6.57 (s, 2H), 7.02 (d, 2H, *J* = 6.0 Hz), 7.23 (m, 2H), 7.45 (dd, 2H, *J* = 9.0 Hz, 2.5 Hz), 8.13 (dd, 2H, *J* = 7.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.30, 21.34, 43.76, 65.85, 117.37, 123.48, 125.16, 126.38, 128.02, 129.99, 131.94, 134.74, 136.92, 137.57, 137.93, 139.78, 146.76, 152.33, 168.94; IR (thin film) 3004m, 2917m, 1596m, 1521m, 1200m cm^{-1}; HRMS (ES+) calcd for $C_{27}H_{29}NO_2$ *m/z* 413.2229 (M^++1), meas 413.2239. The optical purity of **26a** was determined to be 97% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.6:0.4, 222 nm, flow rate 0.6 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26a** with 95% ee. Retention times were 5.2 min (major enantiomer, (*S*)-**26a**) and 6.0 min (minor enantiomer, (*R*)-**26a**). $[\alpha]^{23}_D$ = +51.2 (*c* = 1.0, CH_2Cl_2) on 95% ee *R* -**26a**.



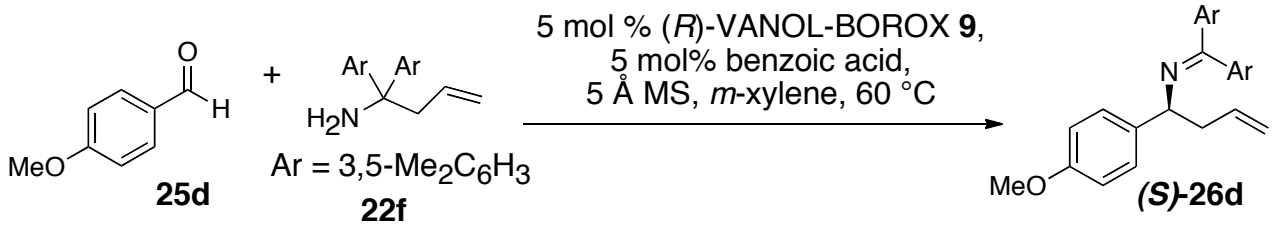
(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(p-tolyl)but-3-en-1-amine ***26b****.* *p*-tolualdehyde **25b** (15 mg, 0.11 mmol, 1.1 equiv) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26b** as a viscous oil in 92% yield (35 mg, 0.092 mmol). *Spectral data for* ***26b****:* R_f = 0.25 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29 (t, 15H), 2.55-2.59 (m, 1H), 2.63-2.67 (m, 1H), 4.35 (dd, 1H, *J* = 7.5 Hz, 6.0 Hz), 4.92-4.98 (m, 2H), 5.62-5.68 (m, 1H), 6.64 (s, 2H), 6.98 (s, 1H), 7.01 (s, 1H), 7.09 (d, 2H, *J* = 7.5 Hz), 7.18-7.24 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.08, 21.29, 21.32, 43.87, 66.18, 116.29, 125.53, 126.35, 127.11, 128.86, 129.62, 131.41, 136.00, 136.10, 137.33, 137.40, 137.56, 140.41, 141.79, 167.36; IR (thin film) 3004m, 2917m, 1596m, 1511m, 1198m cm^{-1}; HRMS (ES+) calcd for $C_{28}H_{32}N$ *m/z* 382.2535 (M^++1), meas 385.2522. To determine the optical purity, the product **26b** was hydrolyzed with NH_2OH•HCl (31 mg, 0.45 mmol) in THF (2 mL) and water (1 mL) to afford the homoallylic amine. The optical purity was determined to be 87% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol:diethylamine 95:5:0.05, 222 nm, flow rate 1.0 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26b** with 87% ee. Retention times were 5.0 min (major

enantiomer) and 4.0 min (minor enantiomer). $[\alpha]^{23}_{D}$ = +32.1 (*c* = 1.0, CH_2Cl_2) on 87% ee *R*-**26b**.



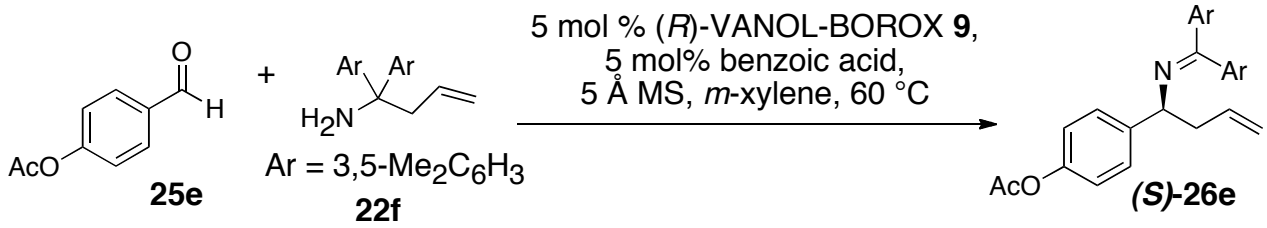
(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(4-bromophenyl)but-3-en-1-amine ***26c***. *p*-Bromobenzaldehyde **25c** (21 mg, 0.11 mmol, 1.1 equiv) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26c** as a viscous oil in 83% yield (38 mg, 0.083 mmol). *Spectral data for* ***26c****:* R_f = 0.20 (1:15 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29 (s, 6H), 2.31 (s, 6H), 2.52-2.57 (m, 1H), 2.61-2.67 (m, 1H), 4.35 (dd, 1H, *J* = 7.0 Hz, 6.0 Hz), 4.94-4.99 (m, 2H), 5.60-5.69 (m, 1H), 6.62 (s, 2H), 7.02 (d, 2H, *J* = 7.5 Hz), 7.18 (d, 2H, *J* = 6.5 Hz), 7.25 (s, 2H), 7.41 (d, 2H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.28, 21.32, 43.79, 65.79, 116.75, 120.26, 125.33, 126.35, 128.98, 129.77, 131.22, 131.64, 135.46, 137.18, 137.43, 137.72, 140.10, 143.79, 168.03; IR (thin film) 3005m, 2918m, 1595m, 1485m, 1235m cm^{-1}; HRMS (ES+) calcd for $C_{27}H_{29}NBr$ *m/z* 446.1483 (M^++1), meas 446.1471. The optical purity of **26c** was determined to be 95% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.3 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26c** with 93% ee. Retention times were 10.0 min (major

enantiomer, (*S*)-**26c**) and 12.0 min (minor enantiomer, (*R*)-**26c**). $[\alpha]^{23}_{D}$ = +53.3 (*c* = 1.0, CH_2Cl_2) on 93% ee *R* -**26c**.



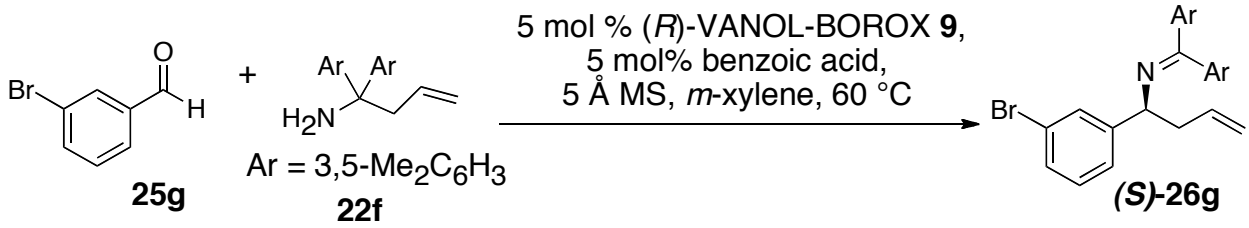
(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(4-methoxyphenyl)but-3-en-1-amine ***26d****. p*-Methoxybenzaldehyde **25d** (15 mg, 0.11 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26d** as a viscous oil in 88% yield (35 mg, 0.088 mmol). *Spectral data for* ***26d****:* R_f = 0.20 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.11 (s, 6H), 2.14 (s, 6H), 2.39-2.42 (m, 1H), 2.45-2.49 (m, 1H), 3.61 (s, 3H), 4.17 (dd, 1H, *J* = 8.0 Hz, 6.5 Hz), 4.75-4.82 (m, 2H), 5.45-5.51 (m, 1H), 6.47 (s, 2H), 6.60 (d, 2H, *J* = 9.0 Hz), 6.82 (s, 1H), 6.85 (s, 1H), 7.03-7.08 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.29, 21.33, 43.90, 55.19, 65.80, 113.55, 116.30, 125.50, 126.34, 128.18, 129.62, 131.43, 136.08, 137.01, 137.35, 137.41, 137.58, 140.39, 158.25, 167.27; IR (thin film) 3001m, 2916m, 1597m, 1324m, 1037m cm^{-1}; HRMS (ES+) calcd for $C_{28}H_{32}NO$ *m/z* 398.2484 (M^++1), meas 398.2498. The optical purity was determined to be 86% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 97.7:0.3, 222 nm, flow rate 0.6 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26d** with 83% ee. Retention times were 5.7 min (major

enantiomer, (*S*)-**26d**) and 6.4 min (minor enantiomer, (*R*)-**26d**). $[\alpha]^{23}_{D}$ = +24.1 (*c* = 1.0, CH_2Cl_2) on 83% ee *R*-**26d**.



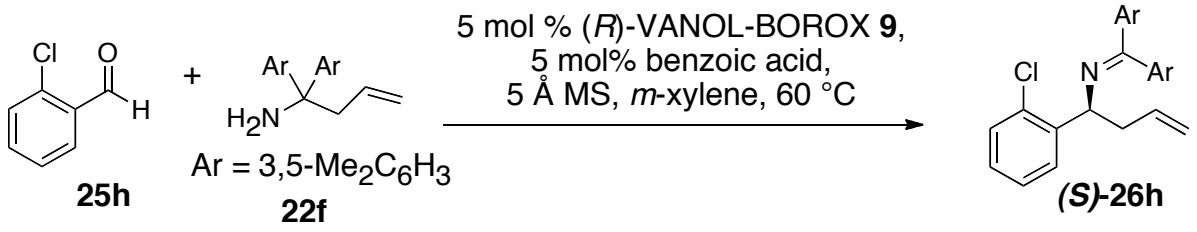
(S)-4-(1-((bis(3,5-dimethylphenyl)methylene)amino)but-3-en-1-yl)phenyl acetate ***26e****. p*-Acetoxybenzaldehyde **25e** (18 mg, 0.11 mmol, 1.1 equiv) was reacted according to the general procedure described above and purification with flash column chromatography (1:15 acetone/hexanes) was complete in 5 min to afford the rearrangement product **26e** as a viscous oil in 85% yield (37 mg, 0.085 mmol). *Spectral data for* ***26e****:* R_f = 0.18 (1:15 acetone/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29 (t, 15H), 2.54-2.56 (m, 1H), 2.63-2.66 (m, 1H), 4.38 (dd, 1H, *J* = 8.0 Hz, 6.0 Hz), 4.93-4.98 (m, 2H), 5.62-5.67 (m, 1H), 6.62 (s, 2H), 6.99 (d, 4H, *J* = 8.5 Hz), 7.25 (s, 2H), 7.29 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.12, 21.28, 21.31, 43.91, 65.81, 116.57, 121.10, 125.41, 126.34, 128.13, 129.70, 131.55, 135.75, 137.24, 137.38, 137.65, 140.21, 142.31, 149.22, 167.76, 169.50; IR (thin film) 2918m, 1763m, 1504m, 1164m cm^{-1}; HRMS (ES+) calcd for $C_{29}H_{32}NO_2$ *m/z* 426.2433 (M^++1), meas 426.2419. The optical purity of **26e** was determined to be 94% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.6:0.4, 222 nm, flow rate 0.6 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26e** with 92% ee. Retention times were 5.7 min (major

enantiomer, (*S*)-**26e**) and 6.7 min (minor enantiomer, (*R*)-**26e**). $[\alpha]^{23}_{D}$ = +16.8 (*c* = 1.0, CH_2Cl_2) on 92% ee *R*-**26e**.



(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(3-bromophenyl)but-3-en-1-amine ***26g****.* *m*-Bromobenzaldehyde **25g** (21 mg, 0.11 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:50 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26g** as a viscous oil in 87% yield (39 mg, 0.087 mmol). *Spectral data for* ***26g****:* R_f = 0.18 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 6H), 2.30 (s, 6H), 2.51-2.55 (m, 1H), 2.61-2.65 (m, 1H), 4.32 (dd, 1H, *J* = 8.0 Hz, 6.0 Hz), 4.93-4.97 (m, 2H), 5.59-5.65 (m, 1H), 6.59 (s, 2H), 7.01 (d, 2H, *J* = 9.5 Hz), 7.14 (t, 1H, *J* = 7.5 Hz), 7.20-7.22 (m, 3H), 7.30-7.32 (m, 1H), 7.41 (t, 1H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.30, 21.33, 43.79, 65.96, 116.81, 122.24, 125.36, 125.88, 126.39, 129.66, 129.77, 129.81, 130.40, 131.69, 135.43, 137.18, 137.45, 137.75, 140.05, 147.13, 168.29; IR (thin film) 3004m, 2916m, 1619m, 1472m, 1199m cm^{-1}; HRMS (ES+) calcd for $C_{27}H_{29}NBr$ *m/z* 446.1483 (M^++1), meas 446.1481. The optical purity was determined to be 90% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.3 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26g** with 90% ee. Retention

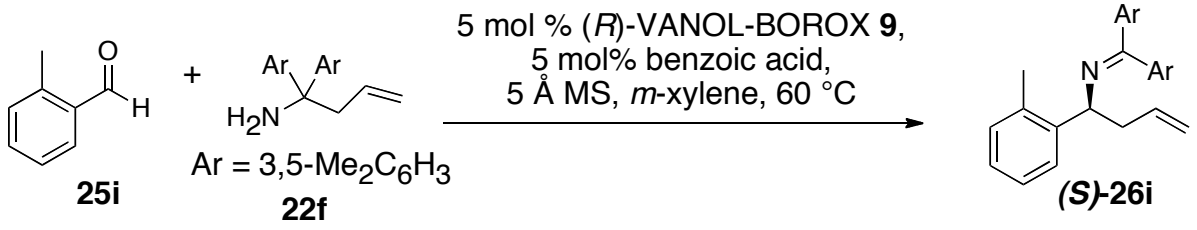
times were 8.8 min (major enantiomer, (*S*)-**26g**) and 10.5 min (minor enantiomer, (*R*)-**26g**). $[\alpha]^{23}_{D}$ = +2.9 (*c* = 3.0, CH_2Cl_2) on 90% ee *R*-**26g.**



25h **22f** ***(S)*-26h**

(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(2-chlorophenyl)but-3-en-1-amine ***26h***. 2-Chlorobenzaldehyde **25h** (30 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26h** as a viscous oil in 88% yield (35 mg, 0.18 mmol). *Spectral data for **26h**:* R_f = 0.18 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.32 (s, 6H), 2.34 (s, 6H), 2.59-2.66 (m, 2H), 4.95-5.03 (m, 3H), 5.72-5.78 (m, 1H), 6.60 (s, 2H), 7.05 (d, 2H, *J* = 8.0 Hz), 7.15-7.18 (m, 1H), 7.27-7.34 (m, 4H), 7.86 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.32, 42.95, 61.98, 116.51, 125.44, 126.46, 126.86, 127.38, 128.96, 129.55, 129.73, 131.60, 131.97, 135.60, 137.13, 137.40, 137.66, 140.31, 142.76, 168.72; IR (thin film) 3070m, 2916m, 1594m, 1470m, 1033m cm^{-1}; HRMS (ES+) calcd for $C_{27}H_{29}NCl$ *m/z* 402.1989 (M^++1), meas 402.1994. To determine the optical purity, the product **26h** was hydrolyzed with NH_2OH•HCl (62 mg, 0.9 mmol) in THF (4 mL) and water (2 mL) to afford the homoallylic amine. The optical purity was determined to be

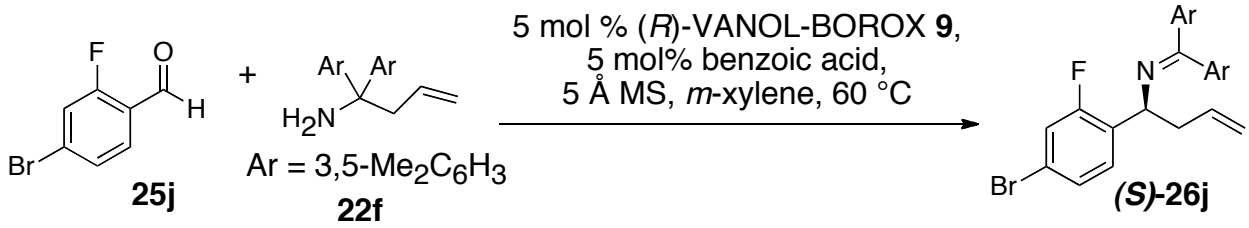
92% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol:diethylamine 95:5:0.05, 222 nm, flow rate 0.4 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26h** with 94% ee. Retention times were 10.1 min (major enantiomer) and 9.3 min (minor enantiomer). $[\alpha]^{23}_{D}$ = -156.2 (*c* = 1.0, CH_2Cl_2) on 94% ee *R*-**26h**.



25i **22f** ***(S)*-26i**

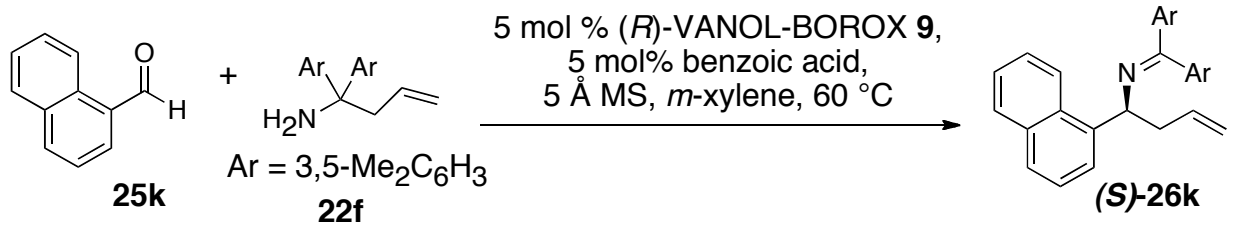
(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(o-tolyl)but-3-en-1-amine ***26i****.* *o*-Tolualdehyde **25i** (26 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26i** as a viscous oil in 84% yield (64 mg, 0.17 mmol). *Spectral data for* ***26i****:* R_f = 0.24 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (s, 3H), 2.26 (s, 6H), 2.29 (s, 6H), 2.48-2.53 (m, 1H), 2.65-2.70 (m, 1H), 4.58 (dd, 1H, *J* = 7.0 Hz, 4.5 Hz), 4.93-5.00 (m, 2H), 5.67-5.73 (m, 1H), 6.52 (s, 2H), 6.99-7.04 (m, 3H), 7.09 (td, 1H, *J* = 1.5 Hz, 6.0 Hz, 12.0 Hz), 7.18 (t, 1H, *J* = 6.5 Hz), 7.28 (s, 2H), 7.68 (d, 1H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.87, 21.27, 21.31, 43.57, 62.26, 116.13, 125.29, 126.02, 126.10, 126.33, 127.66, 129.49, 129.80, 131.44, 134.13, 136.25, 137.36, 137.62, 137.78, 140.31, 143.86, 167.76; IR (thin film) 3070m, 2917m, 1619m, 1598m, 1198m cm^{-1};

HRMS (ES+) calcd for $C_{28}H_{32}N$ *m/z* 382.2535 (M^++1), meas 382.2540. The optical purity was determined to be 80% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.8:0.2, 222 nm, flow rate 0.1 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26i** with 80% ee. Retention times were 24.2 min (major enantiomer, (*S*)-**26i**) and 27.4 min (minor enantiomer, (*R*)-**26i**). $[\alpha]^{23}_D$ = -94.5 (*c* = 1.0, CH_2Cl_2) on 80% ee *R*-**26i**.



*(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(4-bromo-2-fluorophenyl)but-3-en-1-amine **26j***. 2-Fluoro-4-bromobenzaldehyde **25j** (45 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:50 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26j** as a viscous oil in 87% yield (81 mg, 0.17 mmol). *Spectral data for **26j**:* R_f = 0.18 (1:50 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 12H), 2.35-2.60 (m, 2H), 4.70 (t, 1H, *J* = 5.5 Hz), 4.92-4.96 (m, 2H), 5.62-5.67 (m, 1H), 6.57 (s, 2H), 7.01 (s, 2H), 7.12 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz), 7.24-7.26 (m, 3H), 7.55-7.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.31, 21.32, 42.68, 58.43, 116.99, 118.50 (d, *J* = 21.5 Hz), 119.97 (d, *J* = 8 Hz), 125.177, 126.40, 127.43 (d, *J* = 3.3 Hz), 129.88, 130.51, 130.54, 131.12 (d, *J* = 11 Hz), 131.77, 135.01, 136.89, 137.68 (d, *J* = 38 Hz),

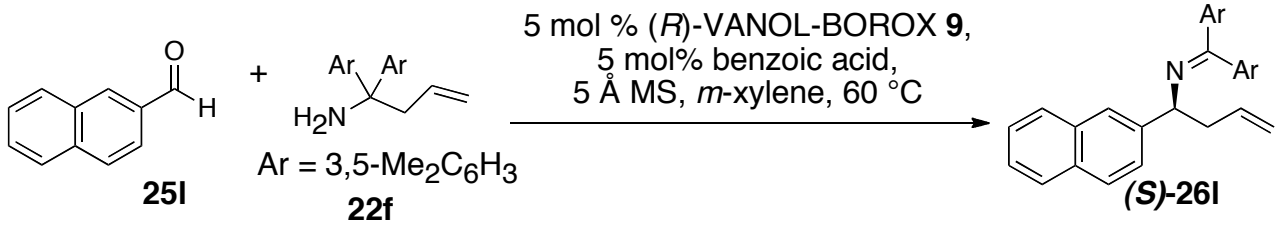
140.04, 159.32 (d, *J* = 207.5 Hz), 168.99; IR (thin film) 3074m, 2917m, 1600m, 1480, 1199m cm^{-1}; HRMS (ES+) calcd for $C_{27}H_{28}NFBr$ *m/z* 464.1389 (M^++1), meas 464.1402. The optical purity was determined to be 96% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.9:0.1, 222 nm, flow rate 0.1 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26j** with 94% ee. Retention times were 27 min (major enantiomer, (*S*)-**26j**) and 31 min (minor enantiomer, (*R*)-**26j**). $[\alpha]^{23}_D$ = +16.8 (*c* = 1.0, CH_2Cl_2) on 94% ee *R*-**26j**.



25k **22f** ***(S)*-26k**

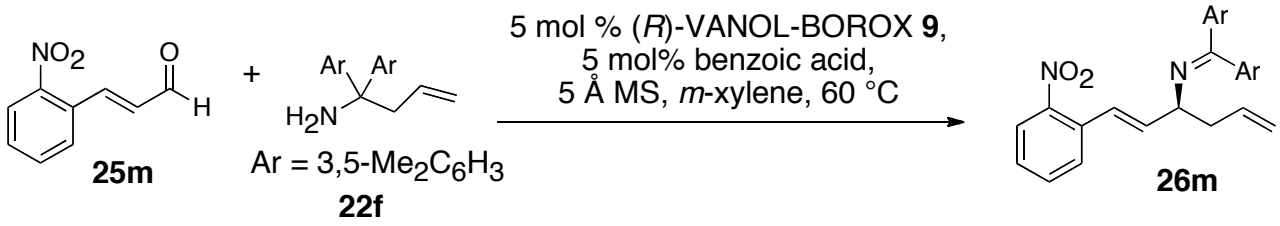
(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(naphthalen-1-yl)but-3-en-1-amine ***26k***. 1-Naphthaldehyde **25k** (34 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26k** as a viscous oil in 90% yield (75 mg, 0.18 mmol). *Spectral data for* ***26k****:* R_f = 0.40 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.14 (s, 6H), 2.30 (s, 6H), 2.70-2.73 (m, 1H), 2.81-2.85 (m, 1H), 4.92-5.00 (m, 2H), 5.18 (dd, 1H, *J* = 7.0 Hz, 4.0 Hz), 5.72-5.75 (m, 1H), 6.49 (s, 2H), 6.96 (s, 1H), 7.01 (s, 1H), 7.31 (s, 2H), 7.34-7.46 (m, 3H), 7.71 (d, 1H, *J* =7.0 Hz), 7.79-7.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.18, 21.33, 43.83, 62.32, 116.18, 123.43, 125.03, 125.26, 125.34, 125.61, 125.70, 126.45, 126.85, 127.72,

128.66, 129.64, 130.42, 131.49, 133.84, 136.29, 137.21, 137.39, 137.58, 140.39, 141.44, 167.91; IR (thin film) 3006m, 2918m, 1601m, 1325m cm^{-1}; HRMS (ES+) calcd for $C_{31}H_{32}N$ *m/z* 418.2535 (M^++1), meas 418.2519. The optical purity was determined to be 90% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.8:0.2, 222 nm, flow rate 0.2 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26k** with 88% ee. Retention times were 15.0 min (major enantiomer, (*S*)-**26k**) and 17.0 min (minor enantiomer, (*R*)-**26k**). $[\alpha]^{23}_D$ = -197.7 (*c* = 1.0, CH_2Cl_2) on 88% ee *R*-**26k**.



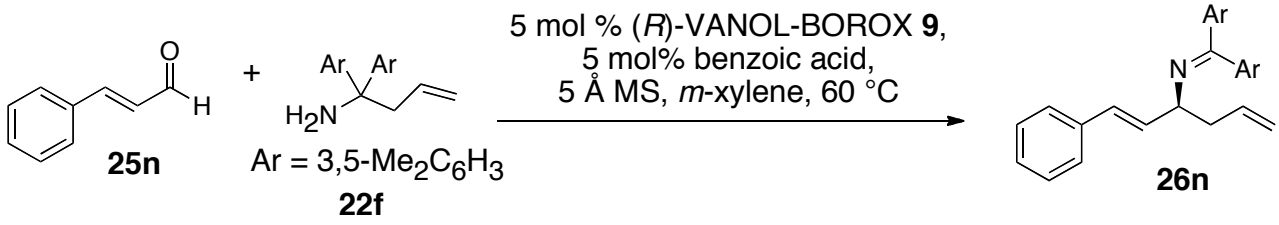
(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-(naphthalen-2-yl)but-3-en-1-amine ***26l***. 2-Naphthaldehyde **25l** (19 mg, 0.11 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26l** as a viscous oil in 83% yield (35 mg, 0.083 mmol). *Spectral data for* ***26l****:* R_f = 0.20 (1:15 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.31 (s, 12H), 2.70-2.73 (m, 1H), 2.78-2.80 (m, 1H), 4.57 (t, 1H, *J* = 7.0 Hz), 4.96-5.04 (m, 2H), 5.69-5.75 (m, 1H), 6.67 (s, 2H), 7.02 (s, 1H), 7.05 (s, 1H), 7.31 (s, 2H), 7.43-7.45 (m, 2H), 7.55-7.57 (m, 1H), 7.67 (s, 1H), 7.78-7.82 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.31, 21.32, 43.82, 66.65, 116.50, 125.29, 125.51, 125.63, 125.69, 125.84, 126.41, 127.58, 127.77, 127.83,

129.73, 131.54, 132.59, 133.49, 135.91, 137.39, 137.41, 137.65, 140.36, 142.30, 167.96; IR (thin film) 3052m, 2915m, 1618m, 1598, 1198m cm^{-1}; HRMS (ES+) calcd for $C_{31}H_{32}N$ *m/z* 418.2535 (M^++1), meas 418.2515. The optical purity was determined to be 80% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.6:0.4, 222 nm, flow rate 0.4 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26l** with 80% ee. Retention times were 6.9 min (major enantiomer, (*S*)-**26l**) and 8.0 min (minor enantiomer, (*R*)-**26l**). $[\alpha]^{23}_{D}$ = +22.4 (*c* = 1.0, CH_2Cl_2) on 80% ee *R*-**26l**.



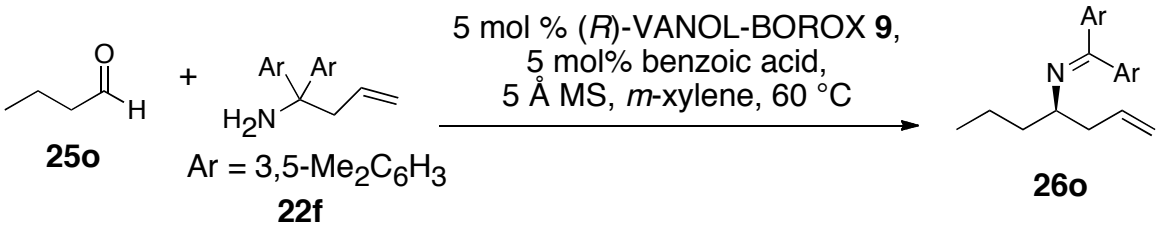
(S,E)-N-(bis(3,5-dimethylphenyl)methylene)-1-(2-nitrophenyl)hexa-1,5-dien-3-amine ***26m****.* *(E)*-3-(2-nitrophenyl)acrylaldehyde **25m** (39 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:15 acetone/hexanes) was complete in 5 min to afford the rearrangement product **26m** as a yellow solid (mp 87-88 °C) in 90% yield (80 mg, 0.18 mmol). *Spectral data for* ***26m****:* R_f = 0.22 (1:15 acetone/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 6H), 2.35 (s, 6H), 2.46-2.54 (m, 2H), 4.13 (dd, 1H, *J* = 12.5 Hz, 6.0 Hz), 5.01-5.08 (m, 2H), 5.71-5.76 (m, 1H), 6.37 (dd, 1H, *J* = 16 Hz, 6.5 Hz), 6.76 (d, 1H, *J* = 15.5 Hz), 6.80 (s, 2H), 7.02 (d, 2H, *J* = 18.0 Hz), 7.22 (s, 2H), 7.34 (td, 1H, *J* = 9.5 Hz, 8.5 Hz, 1.5 Hz), 7.50-7.53 (m, 1H), 7.59-7.61 (m, 1H), 7.87 (dd, 1H, *J* = 8.0 Hz, 1.0 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 21.27, 21.32, 41.49, 64.58, 116.95, 124.37, 124.83, 125.33, 126.37, 127.67, 128.70, 129.94, 131.69, 132.83, 133.14, 135.25, 137.17, 137.49, 137.73, 137.94, 140.26, 147.86, 169.24; IR (thin film) 3017m, 2916m, 1595m, 1345m cm^{-1}; HRMS (ES+) calcd for $C_{29}H_{31}N_2O_2$ *m/z* 439.2386 (M^++1), meas 439.2381. The optical purity was determined to be 95% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.8:0.2, 222 nm, flow rate 0.5 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26m** with 93% ee. Retention times were 8.5 min (major enantiomer, (*S*)-**26m**) and 9.9 min (minor enantiomer, (*R*)-**26m**). $[\alpha]^{23}_D$ = +91.7 (*c* = 1.0, CH_2Cl_2) on 93% ee *R*-**26m**.



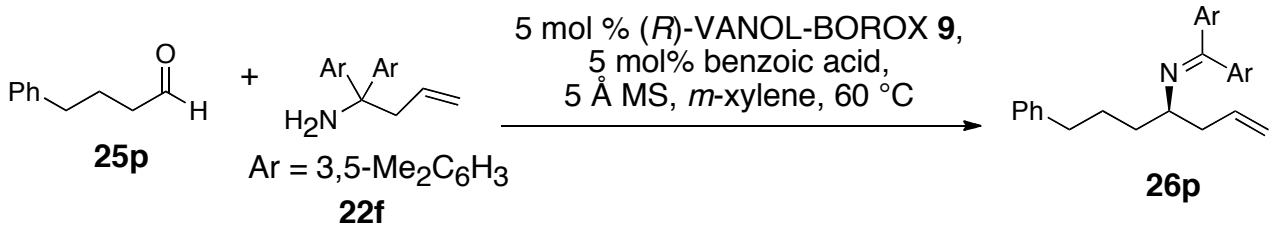
(S,E)-N-(bis(3,5-dimethylphenyl)methylene)-1-phenylhexa-1,5-dien-3-amine ***26n****.* Trans-cinnamaldehyde **25n** (29 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26n** as a viscous oil in 89% yield (73 mg, 0.18 mmol). *Spectral data for* ***26n****:* R_f = 0.17 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.32 (s, 6H), 2.37 (s, 6H), 2.48-2.57 (m, 2H), 4.09 (dd, 1H, *J* = 13.0 Hz, 6.0 Hz), 5.02-5.10 (m, 2H), 5.73-5.80 (m, 1H), 6.31 (d, 1H, *J* = 16 Hz), 6.43 (dd, 1H, *J* = 16.0 Hz, 6.0 Hz), 6.80 (s, 2H), 7.07 (dd, 2H, *J* = 14.0

Hz, 2.0 Hz), 7.21-7.27 (m, 3H), 7.07-7.10 (m, 2H), 7.17-7.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.27, 21.35, 41.76, 64.80, 116.60, 125.46, 126.27, 126.34, 127.13, 128.44, 129.40, 129.77, 131.58, 132.32, 135.66, 137.40, 137.48, 137.68, 140.39, 168.50; IR (thin film) 3025m, 2918m, 1619m, 1592m, 1198m cm^{-1}; HRMS (ES+) calcd for $C_{29}H_{32}N$ *m/z* 394.2535 (M^++1), meas 394.2541. The optical purity was determined to be 92% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.9:0.1, 222 nm, flow rate 0.25 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26n** with 88% ee. Retention times were 13.6 min (major enantiomer, (*S*)-**26n**) and 16.2 min (minor enantiomer, (*R*)-**26n**). $[\alpha]^{23}_D$ = +109.7 (*c* = 1.0, CH_2Cl_2) on 88% ee *R*-**26n**.



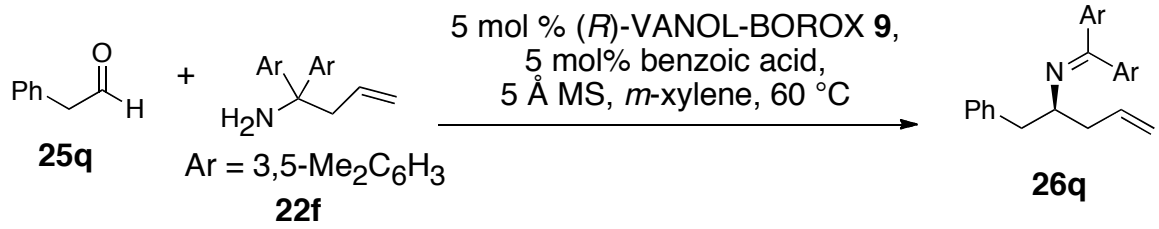
(R)-N-(bis(3,5-dimethylphenyl)methylene)hept-1-en-4-amine ***26o***. Butyraldehyde **25o** (16 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26o** as a viscous oil in 90% yield (60 mg, 0.18 mmol). *Spectral data for* ***26o****:* R_f = 0.25 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, 3H, *J* = 7.0 Hz), 1.10-1.17 (m, 1H), 1.25-1.34 (m, 1H), 1.47-1.54 (m, 1H), 1.57-1.65 (m, 1H), 2.69-2.41 (m, 14H), 3.31-3.36 (m, 1H), 4.97-5.02 (m,

2H), 5.68-5.77 (m, 1H), 6.74 (s, 2H), 6.99 (d, 2H, *J* = 6.5 Hz), 7.20 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.17, 19.96, 21.26, 21.32, 38.47, 41.45, 61.56, 116.04, 125.61, 126.16, 129.36, 131.27, 136.51, 137.39, 137.52, 137.84, 140.62, 167.44; HRMS (ES+) calcd for $C_{24}H_{32}N$ *m/z* 334.2535 (M^++1), meas 334.2527. To determine the optical purity, the product **26o** was hydrolyzed with NH_2OH•HCl (62 mg, 0.9 mmol) in THF (4 mL) and water (2 mL) to afford the homoallylic amine. Then the amine was reacted with benzoyl chloride (25 μL) and triethylamine (35 μL) in DCM (2.0 mL). Purification with column chromatography (1:6 EtOAc/hexanes) afforded (*R*)-*N*-(hept-1-en-4-yl)benzamide as a white solid in 60% yield. The optical purity was determined to be 96% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 94:6, 222 nm, flow rate 1.0 mL min^{-1}). A second run with (*S*)-VANOL gave (*S*)-**26o** with 94% ee. Retention times were 21.8 min (major enantiomer) and 14.3 min (minor enantiomer). $[\alpha]^{23}_D$ = -11.8 (*c* = 1.0, CH_2Cl_2) on 94% ee *S*-**26o.**



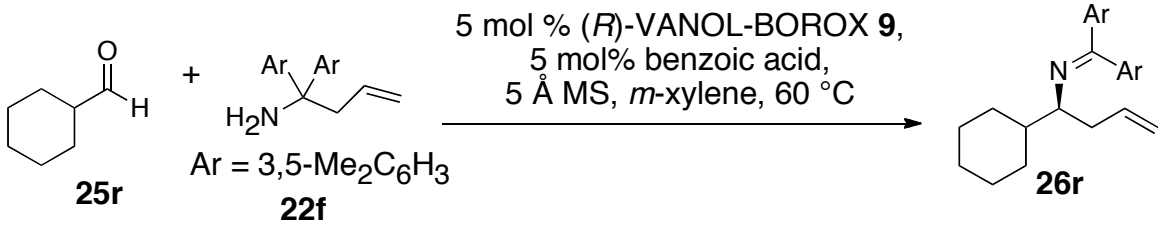
(R)-N-(bis(3,5-dimethylphenyl)methylene)-7-phenylhept-1-en-4-amine ***26p***. 4-Phenylbutanal **25p** (33 mg, 0.22 mmol)[59] was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26p** as a

viscous oil in 89% yield (73 mg, 0.18 mmol). *Spectral data for **26p**:* R_f = 0.20 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46-1.49 (m, 1H), 1.60-1.70 (m, 3H), 2.30 (s, 6H), 2.32 (s, 6H), 2.30-2.34 (m, 2H), 2.53 (t, 2H, *J* = 5.5 Hz), 3.37-3.38 (m, 1H), 4.98-5.03 (m, 2H), 5.71-5.75 (m, 1H), 6.73 (s, 2H), 7.01-7.02 (m, 2H), 7.13-7.18 (m, 3H), 7.20 (s, 2H), 7.25-7.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.28, 21.32, 28.18, 35.81, 35.85, 41.42, 61.61, 116.19, 125.54, 125.61, 126.18, 128.17, 128.30, 129.45, 131.35, 136.37, 137.43, 137.58, 137.73, 140.53, 142.65, 167.62; IR (thin film) 3026m, 2901m, 1598m, 1324m cm^{-1}. To determine the optical purity, the product **26p** was hydrolyzed with NH_2OH•HCl (62 mg, 0.9 mmol) in THF (4 mL) and water (2 mL) to afford the homoallylic amine. Then the amine was reacted with benzoyl chloride (25 μL) and triethylamine (35 μL) in DCM (2.0 mL). Purification with column chromatography (1:6 EtOAc/hexanes) afforded (*R*)-*N*-(7-phenylhept-1-en-4-yl)benzamide as a white solid in 67% yield. HRMS (ES+) calcd for $C_{20}H_{24}NO$ *m/z* 294.1858 (M^++1), meas 294.1869. The optical purity was determined to be 93% ee by HPLC analysis (ChiralPAK AS column, hexanes:2-propanol 90:10, 222 nm, flow rate 1.0 mL min^{-1}). A second run with (*S*)-VANOL gave (*S*)-**26p** with 95% ee. Retention times were 15.8 min (major enantiomer) and 12.4 min (minor enantiomer). $[\alpha]^{23}_D$ = +8.2 (*c* = 1.0, CH_2Cl_2) on 95% ee *S*-**26p**.



(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-phenylpent-4-en-2-amine ***26q***. 2-Phenylacetaldehyde **25q** (26 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26q** as a viscous oil in 72% yield (55 mg, 0.14 mmol). *Spectral data for* ***26q****:* R_f = 0.20 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 6H), 2.28 (s, 6H), 2.32-2.47 (m, 2H), 2.82-2.93 (m, 2H), 3.45-3.50 (m, 1H), 5.00-5.06 (m, 2H), 5.70-5.78 (m, 1H), 6.05 (s, 2H), 6.89 (s, 1H), 6.98 (s, 1H), 7.02 (d, 2H, *J* = 6.5 Hz), 7.15-7.22 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.26, 21.30, 41.32, 42.88, 64.10, 116.48, 125.16, 125.73, 126.13, 127.98, 129.15, 129.92, 131.31, 136.28, 137.16, 137.34, 137.46, 139.89, 140.35, 168.09; IR (thin film) 3023m, 2921m, 1595m, 1324m cm^{-1}. HRMS (ES+) calcd for $C_{28}H_{32}N$ *m/z* 382.2535 (M^++1), meas 382.2516. To determine the optical purity, the product **26q** was hydrolyzed with NH_2OH•HCl (62 mg, 0.9 mmol) in THF (4 mL) and water (2 mL) to afford the homoallylic amine. Then the amine was reacted with benzoyl chloride (25 μL) and triethylamine (35 μL) in DCM (2.0 mL). Purification with column chromatography (1:6 EtOAc/hexanes) afforded (*S*)-*N*-(1-phenylpent-4-en-2-yl)benzamide as a white solid in 50% yield. The optical purity was determined to be

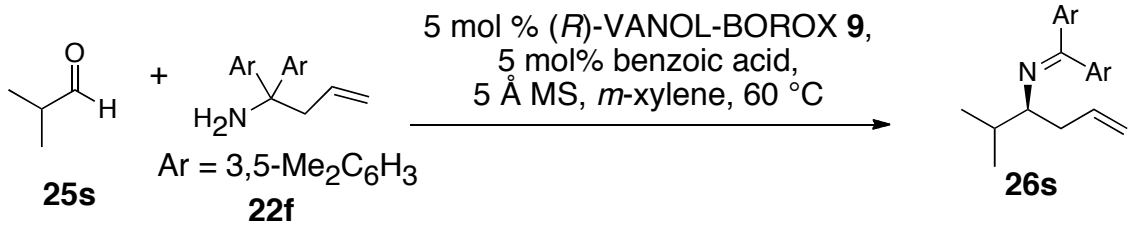
90% ee by HPLC analysis (ChiralPAK AS column, hexanes:2-propanol 90:10, 222 nm, flow rate 1.0 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26q** with 90% ee. Retention times were 14.5 min (major enantiomer) and 17.8 min (minor enantiomer). $[\alpha]^{23}_{D}$ = -18.3 (*c* = 1.0, CH_2Cl_2) on 90% ee *R*-**26q**.



25r **22f** **26r**

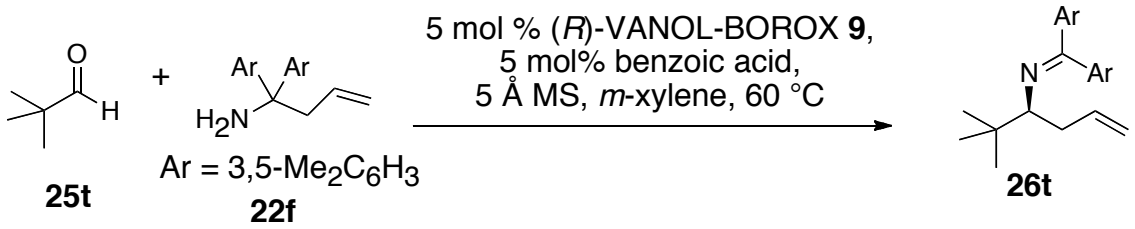
(S)-N-(bis(3,5-dimethylphenyl)methylene)-1-cyclohexylbut-3-en-1-amine ***26r***. Cyclohexanecarbaldehyde **25r** (25 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26r** as a viscous oil in 84% yield (63 mg, 0.17 mmol). *Spectral data for **26r**:* R_f = 0.20 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88-0.91 (m, 1H), 1.01-1.22 (m, 4H), 1.49-1.79 (m, 6H), 2.28 (s, 6H), 2.32 (s, 6H), 2.31-2.37 (m, 2H), 3.09-3.13 (m, 1H), 4.96-5.01 (m, 2H), 5.70-5.76 (m, 1H), 6.72 (s, 2H), 6.98 (s, 2H), 7.19 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.32, 21.37, 26.56, 26.58, 26.68, 29.28, 30.16, 38.40, 42.87, 66.35, 115.90, 125.85, 126.16, 129.24, 131.20, 136.98, 137.36, 137.82, 140.77, 167.01; IR (thin film) 2923m, 1606m, 1323m cm^{-1}. HRMS (ES+) calcd for $C_{27}H_{36}N$ *m/z* 374.2848 (M^++1), meas 374.2849. To determine the optical purity, the product **26r** was

hydrolyzed with $NH_2OH•HCl$ (62 mg, 0.9 mmol) in THF (4 mL) and water (2 mL) to afford the homoallylic amine. Then the amine was reacted with benzoyl chloride (25 µL) and triethylamine (35 µL) in DCM (2.0 mL). Purification with column chromatography (1:6 EtOAc/hexanes) afforded (*S*)-*N*-(1-cyclohexylbut-3-en-1-yl)benzamide as a white solid in 60% yield. The optical purity was determined to be 90% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol:diethylamine 95:5:0.05, 222 nm, flow rate 0.2 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26r** with 92% ee. Retention times were 28.0 min (major enantiomer) and 25.9 min (minor enantiomer). $[\alpha]^{23}_{D}$ = -31.8 (*c* = 1.0, CH_2Cl_2) on 92% ee *R*-**26r**.



(S)-N-(bis(3,5-dimethylphenyl)methylene)-2-methylhex-5-en-3-amine ***26s****.* Isobutyraldehyde **25s** (16 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26s** as a viscous oil in 93% yield (62 mg, 0.19 mmol). *Spectral data for* ***26s****:* R_f = 0.20 (1:30 EtOAc/hexanes). ^1H NMR ($CDCl_3$, 600 MHz) δ 0.84 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 1.81-1.84 (m, 1H), 2.28 (s, 6H), 2.32 (s, 6H), 2.29-2.37 (m, 2H), 3.12 (dd, 1H, *J* = 13.2 Hz, 6.0 Hz), 4.96-5.02 (m, 2H), 5.70-5.75 (m, 1H), 6.73 (s, 2H), 6.98 (s, 2H), 7.19

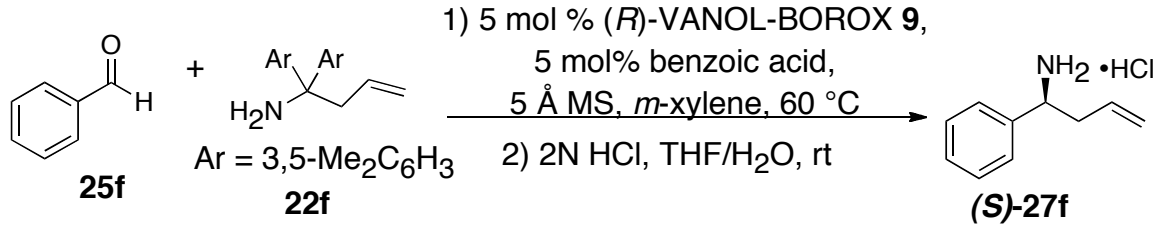
(d, 2H, *J*= 0.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.72, 19.77, 21.31, 21.36, 32.95, 38.65, 66.94, 115.91, 125.83, 126.19, 129.27, 131,23, 136.96, 137.37, 137.40, 137.79, 140.78, 167.21; IR (thin film) 2935m, 1595m, 1199m cm^{-1}. HRMS (ES+) calcd for $C_{24}H_{32}N$ *m/z* 334.2535 (M^++1), meas 334.2539. To determine the optical purity, the product **26s** was hydrolyzed with NH_2OH•HCl (62 mg, 0.90 mmol) in THF (4 mL) and water (2 mL) to afford the homoallylic amine. Then the amine was reacted with benzoyl chloride (25 µL) and triethylamine (35 µL) in DCM (2.0 mL). Purification with column chromatography (1:6 EtOAc/hexanes) afforded (*S*)-*N*-(2-methylhex-5-en-3-yl)benzamide as a white solid in 67% yield. The optical purity was determined to be 92% ee by HPLC analysis (ChiralPAK AS column, hexanes:2-propanol 90:10, 222 nm, flow rate 0.5 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26s** with 93% ee. Retention times were 21.6 min (major enantiomer) and 17.2 min (minor enantiomer). $[\alpha]^{23}_D$ = -41.4 (*c* = 1.0, CH_2Cl_2) on 93% ee *R*-**26s**.



(S)-N-(bis(3,5-dimethylphenyl)methylene)-2,2-dimethylhex-5-en-3-amine ***26t***. Pivalaldehyde **25t** (19 mg, 0.22 mmol) was reacted according to the general procedure described above and purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min to afford the rearrangement product **26t** as a

viscous oil in 87% yield (60 mg, 0.18 mmol). *Spectral data for **26t**:* R_f = 0.34 (1:30 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (s, 9H), 2.29 (s, 6H), 2.32 (s, 6H), 2.38-2.40 (m, 2H), 3.05 (dd, 1H, *J* = 7.2 Hz, 4.8 Hz), 4.95-5.00 (m, 2H), 5.64-5.69 (m, 1H), 6.76 (s, 2H), 6.98 (s, 2H), 7.21 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.34, 26.99, 35.55, 36.01, 69.85, 115.59, 126.25, 126.37, 129.17, 131.15, 137.08, 137.31, 137.57, 138.45, 141.00, 166.58; IR (thin film) 2945m, 1581m, 1321m cm^{-1}. HRMS (ES+) calcd for $C_{25}H_{34}N$ *m/z* 348.2691 (M^++1), meas 348.2706. To determine the optical purity, the product **26t** was hydrolyzed with NH_2OH•HCl (62 mg, 0.9 mmol) in THF (4 mL) and water (2 mL) to afford the homoallylic amine. Then the amine was reacted with benzoyl chloride (25 µL) and triethylamine (35 µL) in DCM (2.0 mL). Purification with column chromatography (1:6 EtOAc/hexanes) afforded (*S*)-*N*-(2,2-dimethylhex-5-en-3-yl)benzamide as a white solid in 46% yield. The optical purity was determined to be 73% ee by HPLC analysis (ChiralPAK AS column, hexanes:2-propanol 90:10, 222 nm, flow rate 0.5 mL min^{-1}). A second run with (*S*)-VANOL gave (*R*)-**26t** with 71% ee. Retention times were 12.4 min (major enantiomer) and 10.8 min (minor enantiomer). $[\alpha]^{23}_D$ = -46.7 (*c* = 1.0, CH_2Cl_2) on 71% ee *R*-**26t**.

6.1.7 General procedure for direct catalytic asymmetric synthesis of homoallylic amines from aldehydes – Illustrated for the synthesis of (*S*)-1-phenylbut-3-en-1-amine Hydrochloride 27f

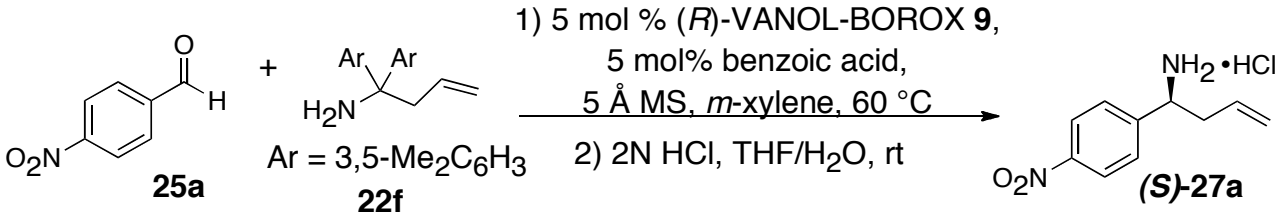


25f **22f** ***(S)*-27f**

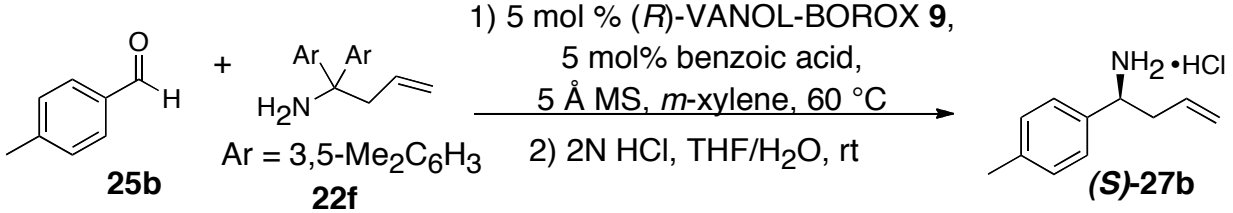
Preparation of catalyst stock solution. A 50 mL Schlenk flask was flame dried under high vacuum and cooled under a low flow of Argon. To the flask was added sequentially (*R*)-VANOL (0.35 g, 0.80 mmol), 2,4,6-trimethylphenol (0.21 g, 1.6 mmol), dry toluene (16.0 mL), BH_3•SMe_2 (2 *M* solution in toluene, 1.2 mL, 2.4 mmol) and water (43.0 μL, 2.4 mmol) under a low flow of Argon. The threaded Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. The valve was carefully opened to gradually apply high vacuum (0.1 mm Hg) and the solvent was removed. The vacuum was maintained for a period of 30 min at 100 °C. The flask was then removed from the oil bath and allowed to cool to room temperature under a low flow of Argon. This was then completely dissolved in 8.0 mL of dry *m*-xylene to afford the stock solution of the catalyst.

The aminoallylation of aldehydes. A 100 mL Schlenk flask charged with 5Å powdered molecular sieves (2.0 g) and fitted with a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Argon. To the test tube was then added amine **22f** (1.1 g, 4.0 mmol, 1.0 equiv), 2.0 mL of the catalyst stock solution (5 mol% catalyst) and *m*-xylene (17.0 mL) via a plastic syringe fitted with a metallic needle. The mixture was stirred for 30 min at 60 °C. At the same time, to an oven-dried 5 mL vial was added benzoic acid (1.0 g, 0.8 mmol) and *m*-xylene (4.0 mL). Then benzaldehyde **25f** (0.47 g, 0.44 mL) and 1.0 mL of the benzoic acid stock solution (5

mol%) were transferred to the above catalyst-amine complex under a high flow of Argon via a plastic syringe fitted with a metallic needle. The test tube was closed and the reaction was stirred at 60 °C for 18 h. Thereafter, 5Å MS was filtered off through a Celite pad, and the pad was washed with EtOAc (10 mL). The filtrate was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) for 1 h to further remove *m*-xylene. The residual was then dissolved in THF (16 mL), followed by the addition of 2N aqueous HCl solution (8.0 mL). The mixture was stirred at room temperature for 4 h and monitored by TLC. Upon completion, THF was removed by rotary evaporation and another 8.0 mL of H_2O was added. The mixture was washed with EtOAc (4 x 4 mL) and the combined organic phase was extracted with H_2O (5 mL) which was then washed with EtOAc (1.0 mL). The combined aqueous phase was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) to further remove H_2O until no weight loss was observed. Compound **27f** was obtained as a white solid (mp 231-233 °C) in 91% yield (0.67 g, 3.6 mmol). *Spectral data for **27f:*** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.66-2.71 (m, 1H), 2.77-2.82 (m, 1H), 4.19 (s, 1H), 4.99-5.07 (m, 2H), 5.49-5.56 (m, 1H), 7.30-7.33 (m, 3H), 7.40-7.42 (m, 2H), 8.76 (bs, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.79, 55.84, 120.13, 127.42, 128.96, 128.98, 131.43, 135.67; Anal calcd for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68; N, 7.63. Found: C, 64.82; H, 7.35; N, 7.49; $[\alpha]^{23}_D$ = -8.8 (*c* = 1.0, H_2O) on 80% ee *S*-**27f** (*R* configuration, $[\alpha]^{23}_D$ = + 36.2, c = 1.4, $CHCl_3$[60]).

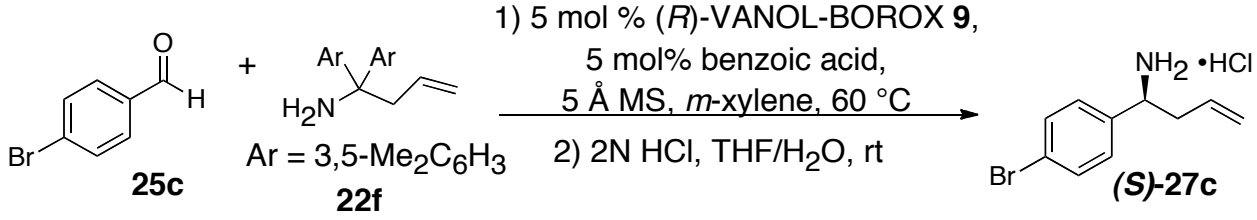


(S)-1-(4-nitrophenyl)but-3-en-1-amine hydrochloride ***27a****. p*-Nitrobenzaldehyde **25a** (0.66 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27a** as a white solid (mp 205-206 °C) in 80% yield (0.74 g, 3.2 mmol). *Spectral data for* ***27a:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.62-2.67 (m, 1H), 2.81-2.85 (m, 1H), 4.53 (dd, 1H, *J* = 9.0 Hz, 5.4 Hz), 4.99-5.03 (m, 2H), 5.58-5.65 (m, 1H), 7.82-7.84 (m, 2H), 8.25-8.27 (m, 2H), 8.96 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 38.32, 53.05, 119.33, 123.55, 129.19, 132.23, 144.81, 147.40; Anal calcd for $C_{10}H_{13}ClN_2O_2$: C, 52.52; H, 5.73; N, 12.25. Found: C, 53.30; H, 5.39; N, 12.12; $[\alpha]^{23}_{D}$ = -11.0 (*c* = 1.0, H_2O) on 97% ee *S*-**27a.**

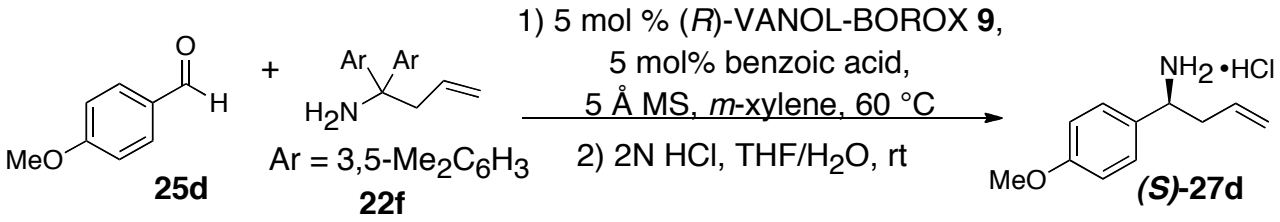


(S)-1-(p-tolyl)but-3-en-1-amine hydrochloride ***27b.*** *p*-Tolualdehyde **25b** (0.53 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27b** as a white solid (mp 222-224 °C) in 94% yield (0.74 g, 3.8 mmol). *Spectral data for* ***27b:*** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.32 (s, 3H), 2.67-2.71 (m, 1H),

2.76-2.80 (m, 1H), 4.15 (bs, 1H), 5.00-5.07 (m, 2H), 5.51-5.55 (m, 1H), 7.12 (d, 2H, *J* = 7.8 Hz), 7.30-7.31 (m, 2H, *J* = 7.8 Hz), 8.71 (bs, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.18, 38.73, 55.62, 119.87, 127.38, 129.64, 131.67, 132.73, 138.67; $[\alpha]^{23}_D$ = -13.5 (*c* = 1.0, H_2O) on 87% ee *S*-**27b**.

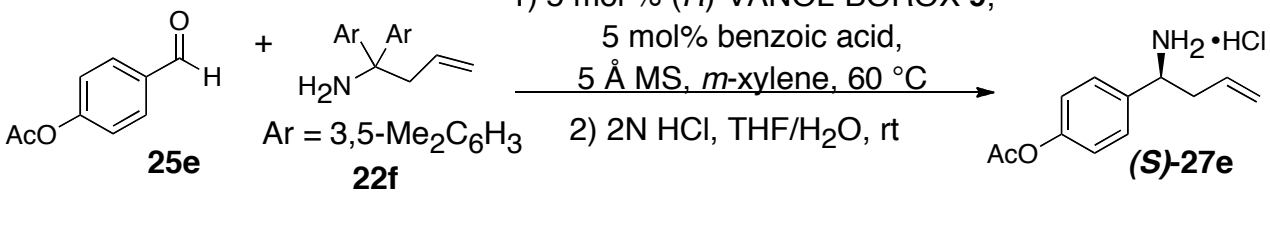


(S)-1-(4-bromophenyl)but-3-en-1-amine hydrochloride ***27c****.* *p*-Bromobenzaldehyde **25c** (0.81 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27c** as a white solid (mp 265-266 °C) in 81% yield (0.85 g, 3.2 mmol). *Spectral data for* ***27c:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.56-2.61 (m, 1H), 2.75-2.79 (m, 1H), 4.31 (dd, 1H, *J* = 9.0 Hz, 5.4 Hz), 4.99-5.03 (m, 2H), 5.55-5.62 (m, 1H), 7.47-7.49 (m, 2H), 7.59-7.61 (m, 2H), 8.75 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 38.72, 53.17, 119.00, 121.69, 129.95, 131.43, 132.56, 136.79; Anal calcd for $C_{10}H_{13}BrClN$: C, 45.74; H, 4.99; N, 5.33. Found: C, 46.61; H, 4.55; N, 5.37; $[\alpha]^{23}_D$ = -8.4 (*c* = 1.0, H_2O) on 95% ee *S*-**27c** (*R* configuration, $[\alpha]^{23}_D$ = + 29.8, c = 1.3, $CHCl_3$[60]).



25d **22f** ***(S)*-27d**

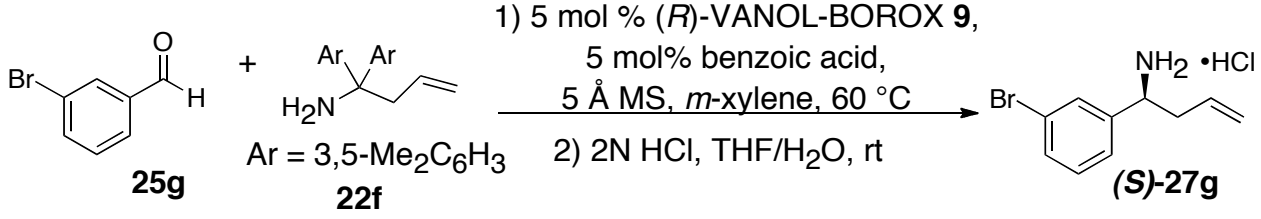
(S)-1-(4-methoxyphenyl)but-3-en-1-amine hydrochloride ***27d****.* *p*-Methoxybenzaldehyde **25d** (0.60 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27d** as a white solid (mp 158-160 °C) in 94% yield (0.81 g, 3.8 mmol). *Spectral data for* ***27d:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.59-2.62 (m, 1H), 2.77-2.80 (m, 1H), 3.74 (s, 3H), 4.20 (t, 1H, *J* = 4.8 Hz), 4.97-5.02 (m, 2H), 5.54-5.59 (m, 1H), 6.93 (d, 2H, *J* = 8.4 Hz), 7.43-7.45 (m, 2H), 8.69 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 38.41, 53.45, 55.14, 113.85, 118.57, 129.03, 129.28, 133.03, 159.21; Anal calcd for $C_{11}H_{16}ClNO$: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.16; H, 7.06; N, 6.44; $[\alpha]^{23}_{D}$ = -9.2 (*c* = 1.0, H_2O) on 86% ee *S*-**27d**.



25e **22f** ***(S)*-27e**

(*S*)-4-(1-aminobut-3-en-1-yl)phenol *hydrochloride* ***27e****. p*-acetoxybenzaldehyde **25e** (0.72 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27e** as a white solid (mp 178-180 °C) in 84% yield (0.67 g, 3.4 mmol). *Spectral data for* ***27e:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.55-2.59 (m, 1H), 2.70-

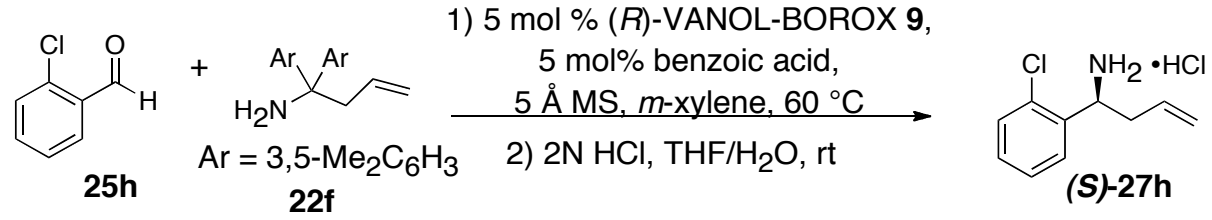
2.74 (m, 1H), 4.13 (bs, 1H), 4.98-5.04 (m, 2H), 5.53-5.58 (m, 1H), 6.77-6.79 (m, 2H), 7.27-7.29 (m, 2H), 8.49 (bs, 3H), 9.66 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 38.40, 53.56, 115.25, 118.56, 127.37, 128.84, 133.07, 157.61; $[\alpha]^{23}_{D}$ = -13.3 (*c* = 1.0, H_2O) on 94% ee *S*-**27e**.



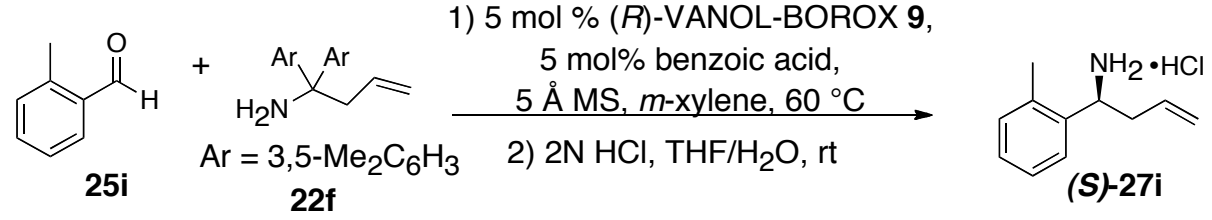
25g **22f** ***(S)*-27g**

Ar = 3,5-$Me_2C_6H_3$

(S)-1-(3-bromophenyl)but-3-en-1-amine hydrochloride ***27g****.* 3-Bromobenzaldehyde **25g** (0.74 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27g** as a white solid (mp 233-235 °C) in 83% yield (0.87 g, 3.3 mmol). *Spectral data for* ***27g:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.58-2.63 (m, 1H), 2.77-2.81 (m, 1H), 4.32 (dd, 1H, *J* = 8.0 Hz, 5.4 Hz), 4.99-5.04 (m, 2H), 5.56-5.63 (m, 1H), 7.36 (t, 1H, *J* = 7.8 Hz), 7.53-7.55 (m, 2H), 7.85 (t, 1H, *J* = 1.8 Hz), 8.83 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 38.32, 53.18, 119.03, 121.71, 126.83, 130.50, 130.69, 131.27, 132.52, 140.11; Anal calcd for $C_{10}H_{13}BrClN$: C, 45.74; H, 4.99; N, 5.33. Found: C, 45.12; H, 4.46; N, 5.52; $[\alpha]^{23}_{D}$ = -20.2 (*c* = 1.0, H_2O/CH_3CN 4:1) on 90% ee *S*-**27g**.

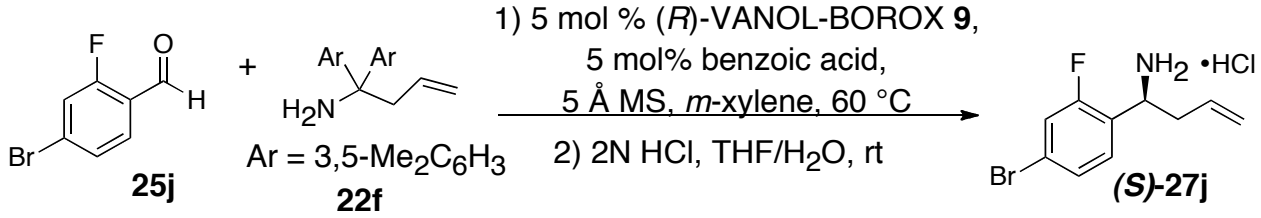


(S)-1-(2-chlorophenyl)but-3-en-1-amine hydrochloride ***27h****.* 2-Chlorobenzaldehyde **25h** (0.62 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27h** as a white solid (mp 173-175 °C) in 99% yield (0.86 g, 4.0 mmol). *Spectral data for* ***27h:*** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.74-2.79 (m, 1H), 2.82-2.86 (m, 1H), 4.88 (d, 1H, *J* = 5.4 Hz), 5.09-5.15 (m, 2H), 5.63-5.70 (m, 1H), 7.26-7.29 (m, 2H), 7.40 (d, 1H, *J* = 7.8 Hz), 7.68 (d, 1H, *J* = 7.2 Hz), 8.95 (bs, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 38.22, 51.64, 120.84, 127.60, 127.85, 129.99, 130.05, 130.81, 133.24, 133.54; Anal calcd for $C_{10}H_{13}Cl_2N$: C, 55.06; H, 6.01; N, 6.42. Found: C, 54.60; H, 6.24; N, 6.44; $[\alpha]^{23}_{D}$ = -16.0 (*c* = 1.0, H_2O) on 92% ee *S*-**27h**.

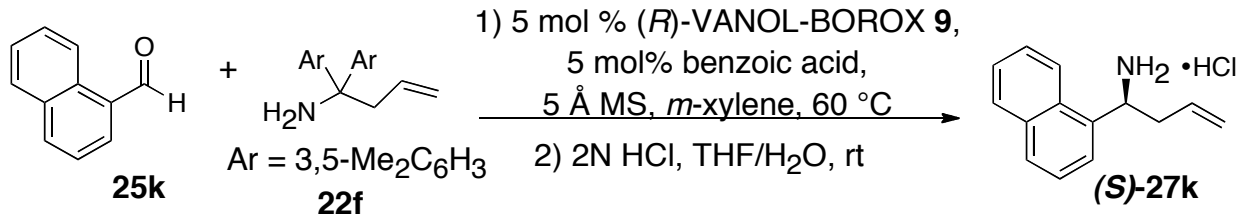


(*S*)-1-(*o*-tolyl)but-3-en-1-amine *hydrochloride* ***27i****.* 2-Tolualdehyde **25i** (0.53 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27i** as a white solid (mp 174-176 °C) in 90% yield (0.71 g, 3.6 mmol). *Spectral data for* ***27i:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.31 (s, 3H), 2.60-2.64 (m, 1H),

2.78-2.80 (m, 1H), 4.44 (t, 1H, *J* = 6.0 Hz), 4.99-5.06 (m, 2H), 5.58-5.62 (m, 1H), 7.20-7.28 (m, 3H), 7.65 (t, 1H, J = 1.2 Hz), 8.68 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 19.15, 38.35, 49.57, 118.95, 126.25, 126.41, 128.13, 130.38, 132.63, 135.80, 135.85; Anal calcd for $C_{11}H_{16}ClN$: C, 66.83; H, 8.16; N, 7.08. Found: C, 67.05; H, 8.06; N, 7.02; $[\alpha]^{23}_{D}$ = -17.4 (*c* = 1.0, H_2O) on 80% ee *S*-**27i.**

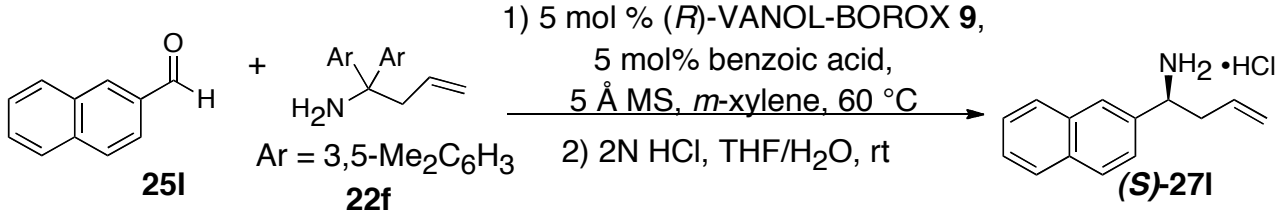


(S)-1-(4-bromo-2-fluorophenyl)but-3-en-1-amine hydrochloride ***27j.*** 4-Bromo-2-fluorobenzaldehyde **25j** (0.89 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27j** as a white solid (mp 158-160 °C) in 81% yield (0.89 g, 3.2 mmol). *Spectral data for* ***27j:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.59-2.64 (m, 1H), 2.80-2.84 (m, 1H), 4.49 (dd, 1H, *J* = 9.6 Hz, 5.4 Hz), 4.99-5.02 (m, 2H), 5.56-5.63 (m, 1H), 7.51 (dd, 1H, *J* = 9.0 Hz, 2.4 Hz), 7.59 (dd, 1H, *J* = 11.2 Hz, 1.8 Hz), 7.73-7.76 (m, 1H), 8.93 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 37.55, 46.58, 118.84 (d, *J* = 25.8 Hz), 119.31, 122.05 (d, *J* = 9.8 Hz), 123.95 (d, *J* = 13.5 Hz), 127.99, 130.49 (d, *J* = 3.5 Hz), 132.08, 159.52 (d, *J* = 250 Hz); Anal calcd for $C_{10}H_{12}BrClFN$: C, 42.81; H, 4.31; N, 4.99. Found: C, 42.29; H, 4.12; N, 5.09; $[\alpha]^{23}_{D}$ = -10.3 (*c* = 1.0, H_2O) on 96% ee *S*-**27j**.



25k **22f** ***(S)*-27k**

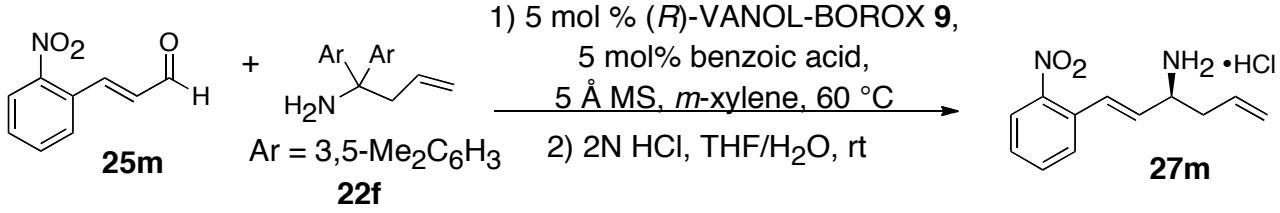
(*S)-1-(naphthalen-1-yl)but-3-en-1-amine hydrochloride* ***27k****.* 1-Naphthaldehyde **25k** (0.68 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27k** as a white solid (mp 227-229 °C) in 86% yield (0.80 g, 3.4 mmol). *Spectral data for* ***27k:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.77-2.81 (m, 1H), 2.88-2.91 (m, 1H), 4.94-5.06 (m, 2H), 5.22 (t, 1H, *J* = 6.6 Hz), 5.65-5.70 (m, 1H), 7.55-7.62 (m, 3H), 7.90-7.99 (m, 3H), 8.19 (d, 1H, *J* = 8.4 Hz), 8.85 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 38.59, 48.69, 119.03, 122.84, 124.33, 125.36, 126.02, 126.72, 128.72, 128.79, 130.38, 132.60, 133.21, 133.73; Anal calcd for $C_{14}H_{16}ClN$: C, 71.94; H, 6.90; N, 5.99. Found: C, 71.88; H, 6.93; N, 5.93; $[\alpha]^{23}_{D}$ = -32.5 (*c* = 1.0, H_2O) on 90% ee *S*-**27k** (*R* configuration, $[\alpha]^{23}_{D}$ = + 82.3, c = 1.3, $CHCl_3$[60]).



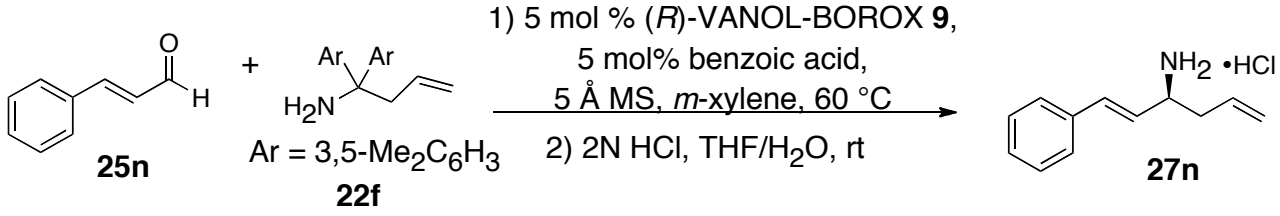
25l **22f** ***(S)*-27l**

(S)-1-(naphthalen-2-yl)but-3-en-1-amine Hydrochloride ***27l.*** 2-Naphthaldehyde **25l** (0.68 g, 4.4 mmol, 1.1 equiv) was reacted according to the general procedure described above to afford product **27l** as a white solid (mp 204-205 °C) in 77% yield (0.73 g, 3.1

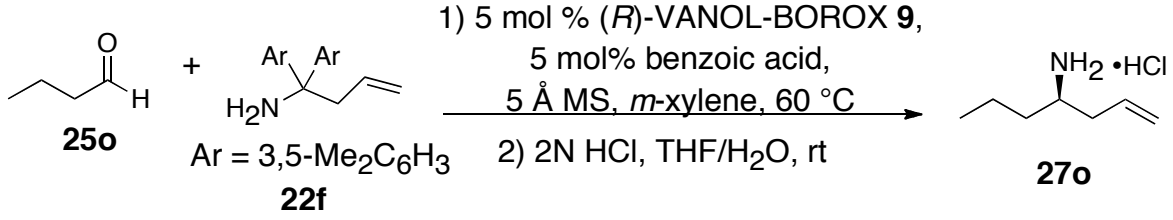
mmol). *Spectral data for **27l:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.72-2.76 (m, 1H), 2.85-2.88 (m, 1H), 4.46 (dd, 1H, *J* = 8.0 Hz, 6.0 Hz), 4.97-5.06 (m, 2H), 5.60-5.65 (m, 1H), 7.53-7.55 (m, 2H), 7.69 (dd, 1H, *J* = 7.8 Hz, 2.4 Hz), 7.89-8.00 (m, 4H), 8.80 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 38.34, 54.05, 118.87, 124.91, 126.52, 126.55, 126.96, 127.60, 127.80, 128.30, 132.50, 132.69, 132.78, 134.82; Anal calcd for $C_{14}H_{16}ClN$: C, 71.94; H, 6.90; N, 5.99. Found: C, 71.48; H, 6.55; N, 5.99; $[\alpha]^{23}_{D}$ = -8.0 (*c* = 1.0, H_2O) on 80% ee *S*-**27l**.



*(S,E)-1-(2-nitrophenyl)hexa-1,5-dien-3-amine hydrochloride **27m**.* (*E*)-3-(2-nitrophenyl)acrylaldehyde **25m** (0.78 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27m** as a white solid (mp 147-148 °C) in 84% yield (0.86 g, 3.4 mmol). *Spectral data for **27m:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.48-2.51 (m, 1H), 2.61 (s, 1H), 3.97 (bs, 1H), 5.12-5.19 (m, 2H), 5.74-5.81 (m, 1H), 6.25-6.30 (m, 1H), 7.00 (d, 1H, *J* = 15.6 Hz), 7.56-7.58 (m, 2H), 7.69-7.76 (m, 1H), 7.97 (d, 1H, *J* = 8.4 Hz), 8.54 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 36.89, 51.70, 118.95, 124.32, 128.40, 128.45, 129.33, 130.42, 131.05, 132.69, 133.63, 147.71. Anal calcd for $C_{12}H_{15}ClN_2O_2$: C, 56.58; H, 5.94; N, 11.00. Found: C, 55.69; H, 5.79; N, 10.80; $[\alpha]^{23}_{D}$ = -18.8 (*c* = 1.0, H_2O) on 95% ee *S*-**27m.**

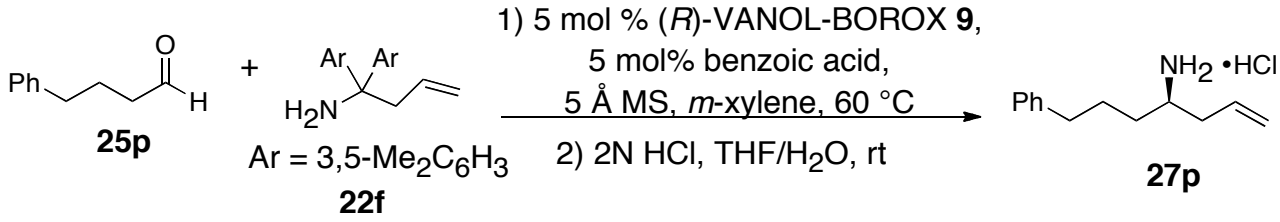


*(S,E)-1-phenylhexa-1,5-dien-3-amine hydrochloride **27n**.* Cinnamaldehyde **25n** (0.58 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27n** as a white solid (mp 197-198 °C) in 85% yield (0.71 g, 3.4 mmol). *Spectral data for **27n:*** ^{1}H NMR (DMSO, 600 MHz) δ 2.47-2.50 (m, 1H), 2.60-2.64 (m, 1H), 3.88 (dd, 1H, *J* = 13.2 Hz, 8.4 Hz), 5.09-5.17 (m, 2H), 5.74-5.78 (m, 1H), 6.22 (q, 1H, *J* = 16.2 Hz, 7.8 Hz), 6.70 (d, 1H, J = 16.2 Hz), 7.27-7.41 (m, 5H), 8.53 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 37.08, 52.07, 118.81, 125.54, 126.42, 128.23, 128.75, 132.94, 133.71, 135.59. $[\alpha]^{23}_{D}$ = -1.3 (*c* = 1.0, H_2O/CH_3CN 2:1) on 92% ee *S*-**27n.**



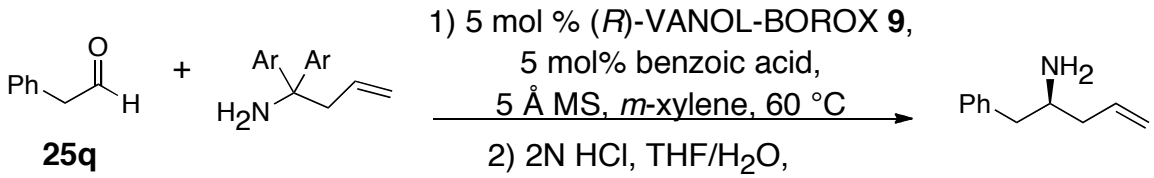
*(R)-hept-1-en-4-amine hydrochloride **27o.*** Butyraldehyde **25o** (0.32 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27o** as a white solid (mp 195-197 °C) in 81% yield (0.49 g, 3.2 mmol). The difference was that upon completion, THF was removed by rotary evaporation and another 8.0 mL of H_2O was added. The mixture was washed with EtOAc (4 x 4 mL) and the combined

organic phase was extracted with H_2O/CH_3CN (10:1 5.5 mL). After removal of CH_3CN, H_2O phase was then washed with EtOAc (1.0 mL). The combined aqueous phase was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) to further remove H_2O until no weight loss was observed. *Spectral data for* ***27o:*** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.43- 1.50 (m, 2H), 1.62-1.70 (m, 2H), 2.43-2.50 (m, 2H), 3.21 (bs, 1H), 5.12-5.23 (m, 2H), 5.77-5.82 (m, 1H), 8.31 (bs, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.65, 18.64, 34.28, 36.93, 51.88, 120.33, 131.67; Anal calcd for $C_7H_{16}ClN$: C, 56.18; H, 10.78; N, 9.36. Found: C, 55.76; H, 10.31; N, 9.19; $[\alpha]^{23}_D$ = -3.2 (*c* = 1.0, H_2O/CH_3CN 2:3) on 96% ee *R*-**27o.**



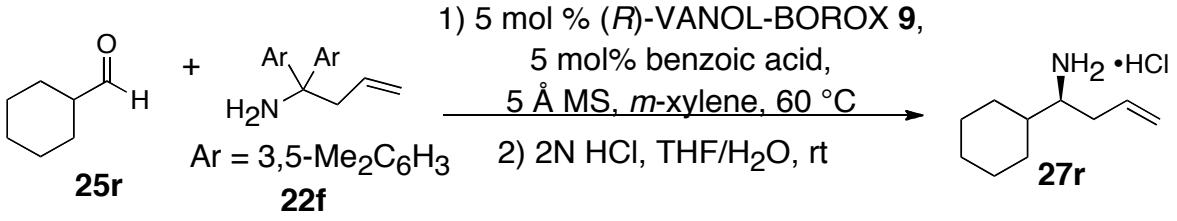
(R)-7-phenylhept-1-en-4-amine hydrochloride ***27p.*** 4-Phenylbutanal **25p** (0.66 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27p** as a white solid (mp 83-85 °C) in 71% yield (0.64 g, 2.8 mmol). The difference was that upon completion, THF was removed by rotary evaporation and another 8.0 mL of H_2O was added. The mixture was washed with EtOAc (4 x 4 mL) and the combined organic phase was extracted with H_2O/CH_3CN (10:1 5.5 mL). After removal of CH_3CN, H_2O phase was then washed with EtOAc (1.0 mL). The combined

aqueous phase was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) to further remove H_2O until no weight loss was observed. *Spectral data for* ***27p:*** ^{1}H NMR (DMSO, 600 MHz) δ 1.52- 1.56 (m, 2H), 1.62-1.68 (m, 2H), 2.30-2.39 (m, 2H), 2.48-2.57 (m, 2H), 3.13 (bs, 1H), 5.09-5.15 (m, 2H), 5.74-5.80 (m, 1H), 7.15-7.20 (m, 3H), 7.27 (t, 2H, *J* = 7.2 Hz), 8.17 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 26.27, 31.16, 34.81, 36.25, 49.89, 118.85, 125.75, 128.22, 128.27, 133.01, 141.61; $[\alpha]^{23}_D$ = -9.8 (*c* = 1.0, H_2O/CH_3CN 2:1) on 93% ee *R*-**27p.**



(S)-1-phenylpent-4-en-2-amine hydrochloride ***27q****.* 2-Phenylacetaldehyde **25q** (0.53 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27q** as a light yellow solid (mp 122-123 °C) in 57% yield (0.45 g, 2.3 mmol). The difference was that upon completion, THF was removed by rotary evaporation and another 8.0 mL of H_2O was added. The mixture was washed with EtOAc (4 x 4 mL) and the combined organic phase was extracted with H_2O/CH_3CN (10:1 5.5 mL). After removal of CH_3CN, H_2O phase was then washed with EtOAc (1.0 mL). The combined aqueous phase was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) to further remove H_2O until no weight loss was observed. *Spectral data for*

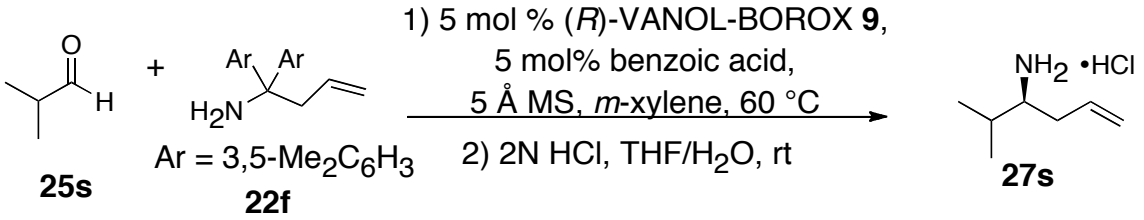
27q: ^{1}H NMR (DMSO, 600 MHz) δ 2.29 (t, 2H, *J* = 1.2 Hz), 2.76-2.79 (m, 1H), 2.99-3.04 (m, 1H), 3.39 (bs, 1H), 5.09-5.13 (m, 2H), 5.80-5.85 (m, 1H), 7.23-7.26 (m, 3H), 7.30-7.33 (m, 2H), 8.28-8.34 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 35.50, 37.53, 51.35, 119.17, 126.76, 128.55, 129.34, 132.78, 136.56; $[\alpha]^{23}_{D}$ = +12.0 (*c* = 1.0, H_2O) on 90% ee *S*-**27q.**



25r **22f** **27r**

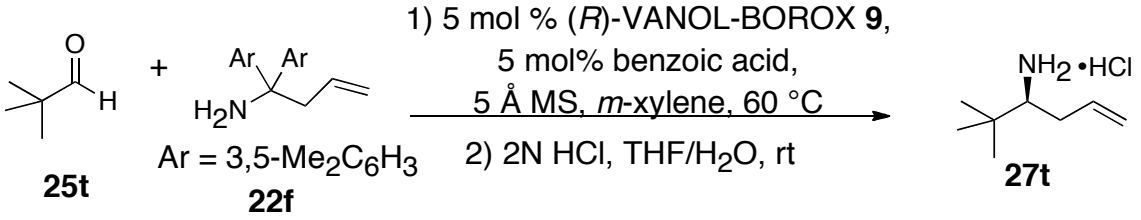
*(S)-1-cyclohexylbut-3-en-1-amine hydrochloride **27r**.* Cyclohexanecarbaldehyde **25r** (0.50 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27r** as a white solid (mp 234-235 °C) in 85% yield (0.64 g, 3.4 mmol). The difference was that upon completion, THF was removed by rotary evaporation and another 8.0 mL of H_2O was added. The mixture was washed with EtOAc (4 x 4 mL) and the combined organic phase was extracted with H_2O/CH_3CN (10:1 5.5 mL). After removal of CH_3CN, H_2O phase was then washed with EtOAc (1.0 mL). The combined aqueous phase was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) to further remove H_2O until no weight loss was observed. *Spectral data for **27r:*** ^{1}H NMR (DMSO, 600 MHz) δ 0.98-1.18 (m, 5H), 1.52-1.71 (m, 6H), 2.30-2.39 (m, 2H), 2.93 (bs, 1H), 5.10-5.19 (m, 2H), 5.78-5.85 (m, 1H), 8.11 (bs, 3H); ^{13}C NMR (150

MHz, DMSO) δ 25.54, 25.62, 27.65, 27.78, 33.71, 38.71, 54.62, 118.66, 133.39; Anal calcd for $C_{10}H_{20}ClN$: C, 63.31; H, 10.63; N, 7.38. Found: C, 62.58; H, 10.02; N, 7.26; $[\alpha]^{23}_{D}$ = -5.8 (*c* = 1.0, H_2O) on 90% ee *S*-**27r.**



25s **22f** **27s**

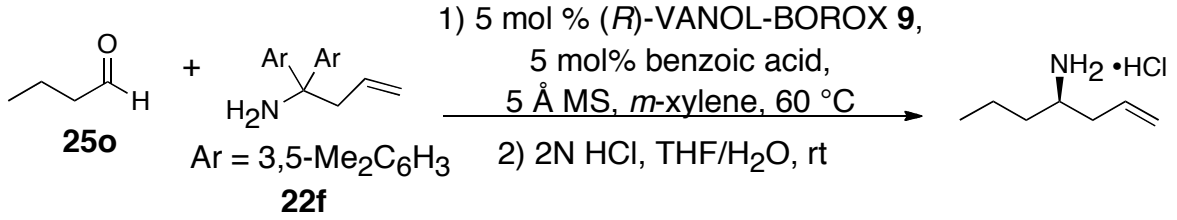
*(S)-2-methylhex-5-en-3-amine hydrochloride **27s**.* Isobutyraldehyde **25s** (0.32 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27s** as a white solid (mp 189-191 °C) in 75% yield (0.45 g, 3.0 mmol). The difference was that upon completion, THF was removed by rotary evaporation and another 8.0 mL of H_2O was added. The mixture was washed with EtOAc (4 x 4 mL) and the combined organic phase was extracted with H_2O/CH_3CN (10:1 5.5 mL). After removal of CH_3CN, H_2O phase was then washed with EtOAc (1.0 mL). The combined aqueous phase was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) to further remove H_2O until no weight loss was observed. *Spectral data for **27s:*** ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.04 (q, 6H, *J* = 13.2 Hz, 7.2 Hz), 2.03-2.08 (m, 1H), 2.42-2.49 (m, 2H), 3.01 (bs, 1H), 5.16-5.24 (m, 2H), 5.80-5.84 (m, 1H), 8.34 (bs, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.71, 18.51, 29.47, 34.22, 57.35, 119.88, 132.17. $[\alpha]^{23}_{D}$ = +6.2 (*c* = 1.0, H_2O/CH_3CN 2:3) on 92% ee *S*-**27s.**



25t **22f** **27t**

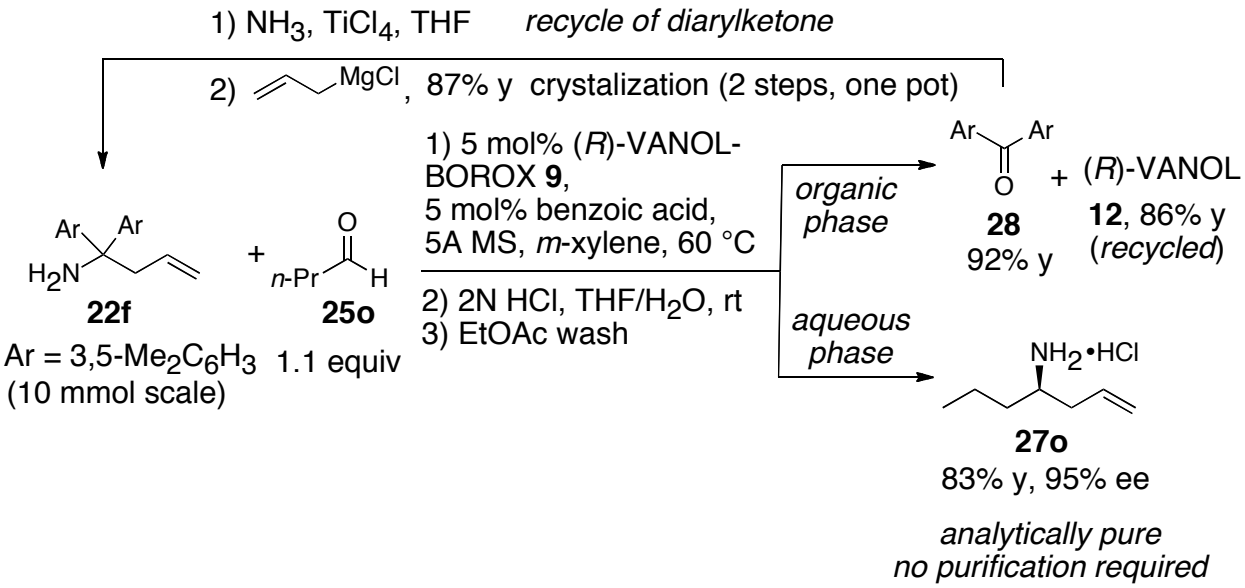
*(S)-2,2-dimethylhex-5-en-3-amine hydrochloride **27t**.* Pivalaldehyde **25t** (0.38 g, 4.4 mmol) was reacted according to the general procedure described above to afford product **27t** as a white solid (mp 178-180 °C) in 94% yield (0.61 g, 3.8 mmol). The difference was that upon completion, THF was removed by rotary evaporation and another 8.0 mL of H_2O was added. The mixture was washed with EtOAc (4 x 4 mL) and the combined organic phase was extracted with H_2O/CH_3CN (10:1 5.5 mL). After removal of CH_3CN, H_2O phase was then washed with EtOAc (1.0 mL). The combined aqueous phase was concentrated by rotary evaporation and placed under high vacuum (0.5 mm Hg) to further remove H_2O until no weight loss was observed. *Spectral data for **27t:*** ^{1}H NMR (DMSO, 600 MHz) δ 0.94 (s, 9H), 2.21-2.27 (m, 1H), 2.37-2.49 (m, 1H), 2.80 (d, 1H, *J* = 4.8 Hz), 5.05-5.19 (m, 2H), 5.88-5.95 (m, 1H), 8.07 (bs, 3H); ^{13}C NMR (150 MHz, DMSO) δ 26.15, 33.21, 33.34, 59.39, 118.06, 134.82. $[\alpha]^{23}_D$ = +8.9 (*c* = 1.0, H_2O) on 73% ee *S*-**27t.**

6.1.8 Recrystalization of salt 27o



Butyraldehyde 25o (0.80 g, 11 mmol) was reacted according to the general procedure described above for the preparation of **27o** to afford the product as a white solid in 83% yield (1.26 g, 8.40 mmol). The optical purity of the unpurified **27o** was determined to be 93% ee, and [α]23D = -3.5 (c = 1.0, H2O/CH3CN). Compound **27o** (0.9 g, 6 mmol) was then purified with crystalization (EtOAc/CH2Cl2 12:1); the mixture was brought to reflux and then cooled down to room temperature to afford a white crystal in 92% yield (0.83 g, 0.55 mmol). The optical purity of the crystalized **27o** was determined to be 93% ee, and [α]23D = -3.8 (c = 1.0, H2O/CH3CN) on 93% ee R-**27o**.

6.1.9 Recycle of amine 22f and VANOL ligand 12

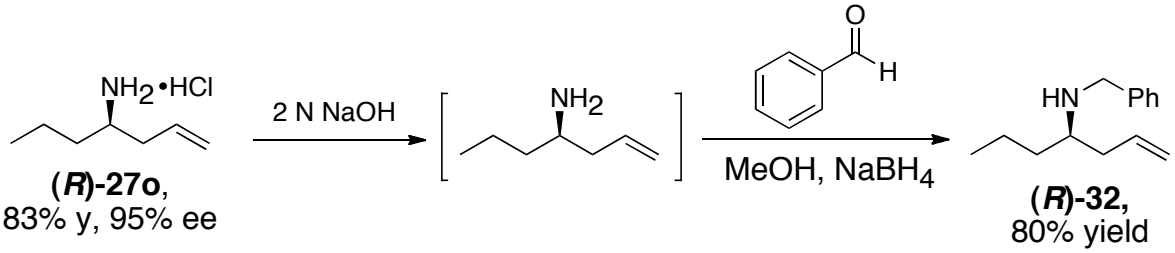


Butyraldehyde **25o** (0.80 g, 11 mmol) was reacted according to the general procedure described above for the preparation of **27o** to afford the product as a white solid in 83% yield (1.25 g, 8.3 mmol). The organic phase was dried over Na_2SO_4, filtered, and concentrated to afford a mixture containing **28**. The mixture was then purified by crystallization with hexanes to afford compound **28** in 80% yield from the first crop (1.9 g, 8.0 mmol).

The same reaction described above was repeated. The difference was that the mixture containing compound **28** and VANOL **12** was subjected to column chromatography (EtOAc/Hexanes 1:20) to afford ketone **28** in 92% yield (2.2 g, 9.2 mmol) and VANOL **12** in 86% yield (0.19 g, 0.53 mmol).

Ketone **28** could be recycled back to amine **22f** in 86% yield according to the procedure described for large scale preparation of amine **22f** in section C.

6.1.10 Asymmetric synthesis of (R)-Coniine 35

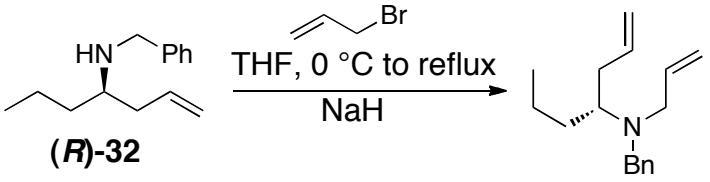


(***R***)**-27o**,
83% y, 95% ee

(***R***)**-32,**
80% yield

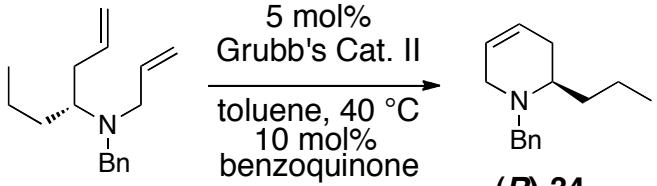
Compound ***R*-27o** (0.9 g, 6.0 mmol) was treated with 2N NaOH until the pH reached 13. Then the mixture was extracted with DCM (3 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to afford crude amine, which was used in the next step without further purification.

A solution of the crude amine and benzaldehyde (0.66 g, 6.3 mmol) in MeOH was stirred at room temperature for 16 h.[59] Then $NaBH_4$ (0.34 g, 9.0 mmol) was added and the mixture was stirred for 12 h. The resulting mixture was treated with H_2O (5 mL) and 1N NaOH and then extracted with DCM (5 mL x 3). The combined organic phase was dried over Na_2SO_4 and concentrated. The mixture was purified by column chromatography (EtOAc/Hexanes/TEA 1:6:0.1) to afford compound **32** as a clear viscous oil in 80% yield (0.96 g, 5.0 mmol). *Spectral data for **32:*** R_f = 0.20 (EtOAc/Hexanes/TEA 1:6:0.1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93-0.98 (m, 3H), 1.37-1.51 (m, 5H), 2.19-2.23 (m, 1H), 2.29-2.65 (m, 1H), 2.66-2.67 (m, 1H), 3.81 (s, 1H), 5.09-5.14 (m, 2H), 5.80-5.85 (m, 1H), 7.25-7.28 (m, 1H), 7.32-7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.26, 18.92, 36.24, 38.34, 51.14, 55.96, 117.02, 126.73, 128.08, 128.28, 135.79, 140.87. IR (thin film) 3065m, 2957m, 1454, 912m cm^{-1}; HRMS (ES+) calcd for $C_{14}H_{22}N$ *m/z* 204.1752 (M^++1), meas 204.1745. $[\alpha]^{23}_D$ = +19.7 (*c* = 1.0, CH_2Cl_2) on 96% ee *R*-**32.**



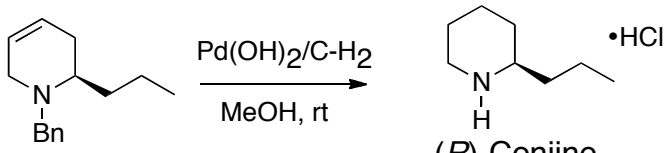
(***R***)-**32** (***R***)-**33**, 83% yield

To a solution of ***R*-32** (0.12 g, 0.50 mmol) in THF (5 mL) at 0 °C was added NaH (0.48 mg, 2.0 mmol) and stirred for 30 min. To this mixture was added allyl bromide (73 mg, 0.60 mmol) and nBu_4NI (37 mg, 0.10 mmol).[61] The resulting mixture was refluxed for 12 h and then cooled down to room temperature. The reaction was quenched with satd. NH_4Cl solution and extracted with ether, washed with H_2O and brine. The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The mixture was purified by column chromatography (acetone/Hexanes/TEA 1:30:0.1) to afford compound **33** as a light yellow oil in 83% yield (0.10 g, 0.42 mmol). *Spectral data for **33:*** R_f = 0.20 (acetone/Hexanes/TEA 1:30:0.1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84 (t, 3H, *J* = 8.4 Hz), 1.26-1.32 (m, 2H), 1.42-1.52 (m, 2H), 1.93-1.99 (m, 1H), 2.34-2.40 (m, 1H), 2.65-2.68 (m, 1H), 2.99-3.04 (m, 1H), 3.11-3.15 (m, 1H), 3.52 (d, 1H, *J* = 14.0 Hz), 3.69 (d, 1H, *J* = 14.5 Hz), 4.97-5.05 (m, 3H), 5.13-5.17 (m, 1H), 5.75-5.83 (m, 2H), 7.19-7.22 (m, 1H), 7.27-7.30 (m, 2H), 7.34 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.17, 20.09, 32.76, 34.31, 52.51, 53.28, 57.85, 115.45, 116.09, 126.53, 128.02, 128.64, 137.76, 137.90, 140.93. IR (thin film) 3076m, 2930m, 1641m, 1454, 912m cm^{-1}; HRMS (ES+) calcd for $C_{17}H_{26}N$ *m/z* 244.2065 (M^++1), meas 244.2076. $[\alpha]^{23}_D$ = +27.3 (*c* = 1.0, CH_2Cl_2) on 96% ee *R*-**33.**



(***R***)-**33**, (***R***)-**34**, 89% yield

To a flame-dried 250 mL round bottom flask was added diene ***R*-33** (0.2 g, 0.8 mmol), toluene (80 mL) and benzoquinone (7 mg, 0.08 mmol). Grubb's second generation catalyst (34 mg, 0.040 mmol) was then added under nitrogen flow and the resulting mixture was stirred at 40 °C for 12 h. Upon completion, the reaction mixture was filtered through a Celite bed and the bed was washed with EtOAc. The resulting crude was concentrated and subjected to purification by column chromatography (acetone/Hexanes/TEA 1:30:0.1) to afford compound **34** as a light yellow oil in 89% yield (0.16 g, 0.72 mmol). *Spectral data for **34:*** R_f = 0.20 (acetone/Hexanes/TEA 1:30:0.1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.84 (t, 3H, *J* = 7.5 Hz), 1.26-1.35 (m, 3H), 1.51-1.54 (m, 1H), 1.82-1.86 (m, 1H), 2.14-2.19 (m, 1H), 2.71-2.74 (m, 1H), 2.90-3.00 (m, 2H), 3.53 (d, 1H, *J* = 13.0 Hz), 3.62 (d, 1H, *J* = 13.0 Hz), 5.51-5.53 (m, 1H), 5.64-5.68 (m, 1H), 7.14-7.17 (m, 1H), 7.21-7.24 (m, 2H), 7.27-7.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.37, 19.76, 27.99, 31.32, 48.26, 55.52, 56.17, 124.48, 125.03, 126.68, 128.13, 128.82, 139.92. IR (thin film) 3026m, 2928m, 1495m, 1095m cm^{-1}; HRMS (ES+) calcd for $C_{15}H_{22}N$ *m/z* 216.1752 (M^++1), meas 216.1762. $[\alpha]^{23}_D$ = +21.7 (*c* = 1.0, CH_2Cl_2) on 96% ee *R*-**34.**



(***R*)-34**,

(*R*)-Coniine
35, 81% yield

To a 100 mL round bottom flask fitted with a magnetic stir bar was added (*R*)-**34** (0.16 g, 0.76 mmol), $Pd(OH)_2$ (0.47 g, 0.019 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, *ca*. 60% moisture) and methanol (30 mL). The flask was then equipped with a 3-way valve connected to vacuum and a hydrogen balloon. The flask was opened to vacuum for a few seconds, and then switched to the hydrogen balloon; this manipulation was repeated three times. The reaction mixture was allowed to stir at room temperature for 12 h. It was then filtered through a Celite pad and the pH of the filtrate was adjusted to 2 with 2N HCl. Then the resulting mixture was concentrated and the residual was dissolved in 10 mL of H_2O, washed with ether (3x3 mL) and concentrated to give (*R*)-Coniine as a white solid (mp 215-216 °C, lit.[23] 215-216°C) which was further dried at 40 °C under vacuum until no weight loss was observed in 76 % yield (91 mg, 0. 58 mmol). *Spectral data for **35:*** ^{1}H NMR (DMSO, 500 MHz) δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.29-1.49 (m, 5H), 1.59-1.82 (m, 5H), 2.79 (q, 1H, *J* = 22.5 Hz, 11 Hz), 2.93 (bs, 1H), 3.15 (d, 1H, *J* = 12.5 Hz), 8.44 (d, 2H, *J* =9.3 Hz); ^{13}C NMR (125 MHz, DMSO) δ 13.71, 17.78, 21.71, 21.78, 27.76, 34.91, 43.68, 55.37. $[\alpha]^{23}_D$ = -6.7 (*c* = 0.6, EtOH) on 96% ee *R*-**35**.

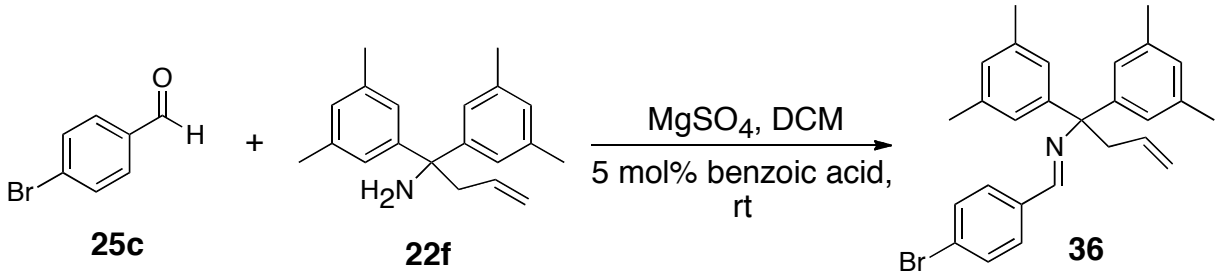
Supporting information for chapter 3

All experiments were performed under an argon atmosphere. Flasks were flame-dried and cooled under argon before use. All solvents were dried appropriately if used in the reaction. VANOL ligand is commercially available from Aldrich as well as Strem Chemicals. If desired, it could be purified using column chromatography on regular silica gel with 2:1 dichloromethane/hexanes. Phenol was sublimed and stored in a dry desiccator. Solid aldehydes were sublimed before use. Liquid aldehydes were distilled before use.

^{11}B NMR, ^{1}H NMR and ^{13}C NMR were recorded on a Varian 300 MHz, VXR-500 MHz or VXR-600 MHz instrument in $CDCl_3$ or toluene-d_8 unless otherwise noted. For toluene-d_8, toluene was used as the internal standard for both ^{1}H NMR (δ = 2.09) and ^{13}C NMR (δ = 20.4). For $CDCl_3$, $CHCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.24) and ^{13}C NMR (δ = 77.0). 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 m^2/g surface area and 0.4 g/mL bulk density. 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.

HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotation was 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.

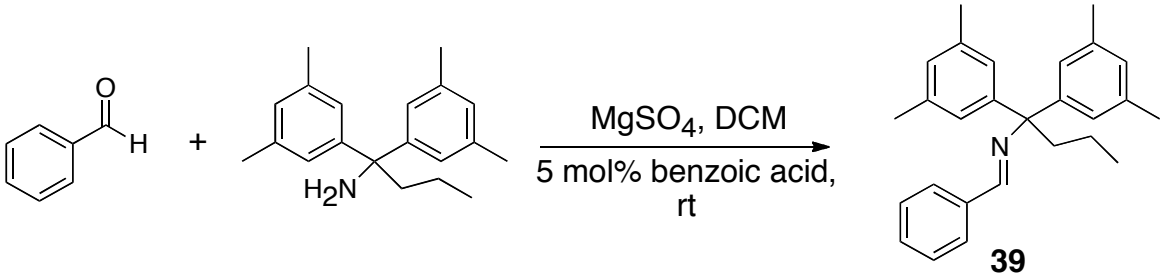
6.2.2 General procedure for the preparation of the imines – Illustrated for the synthesis of (*E*)-*N*-(4-bromobenzylidene)-1,1-bis(3,5-dimethylphenyl)but-3-en-1-amien 36



25c **22f** **36**

To a flame-dried 50 mL round bottomed flask filled with argon was added $MgSO_4$ (24 g, 0.20 mmol) and 240 mL dry CH_2Cl_2. This was followed by the addition of 1,1-bis(3,5-dimethylphenyl)but-3-en-1-amine **22f** (16.7 g, 60.0 mmol, 1 equiv). After stirring for 5 minutes, *p*-bromobenzaldehyde (13.3 g, 72.0 mmol, 1.1 equiv) was added, followed by the addition of 5 mol% benzoic acid (0.37 g, 3.0 mmol). The reaction mixture was stirred for 48 h at room temperature. Thereafter, the reaction mixture was filtered through a Celite bed and the Celite bed was washed with CH_2Cl_2. The filtrate was then concentrated by rotary evaporation and placed under high vacuum (0.05 mm Hg) for 1 h to give the crude imine **36** as a light yellow solid which was purified by crystallization with pure hexanes to give a white solid (mp. 147-148°C) in 95% yield (25.4 g, 57 mmol). *Spectral data for **36**:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 12H), 3.08-3.09 (d, 2H, *J* = 5.0 Hz, 4.92-4.96 (m, 2H), 5.72-5.76 (m, 1H), 6.86 (s, 2H), 6.93(s, 4H), 7.52-7.54(d, 2H, *J* = 8.5 Hz), 7.65-7.67 (d, 2H, J =8.0 Hz), 7.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.56, 46.76, 71.93, 117.20, 124.74, 126.16, 128.17, 129.75,

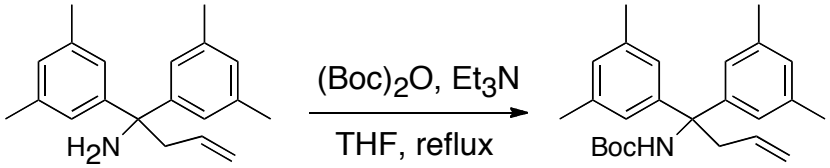
131.65, 134.79, 135.96, 137.13, 146.08, 158.35. IR (thin film) 2916, 1643, 1599, 1485 cm^{-1}; HRMS (ES+) calcd for $C_{27}H_{29}NBr$ *m/z* 446.1483 (M^++1), meas 446.1504.



39

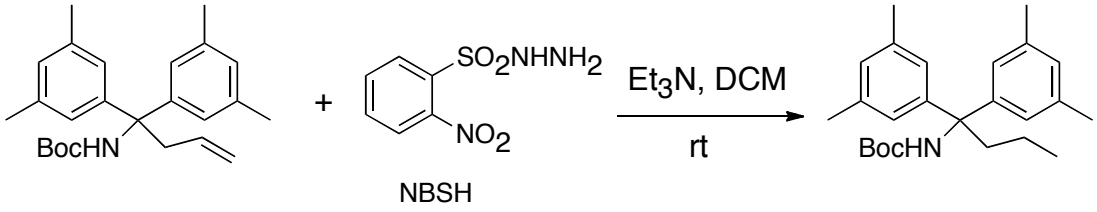
((E)-N-benzylidene-1,1-bis(3,5-dimethylphenyl)butan-1-amine ***39****.* 1,1-bis(3,5-dimethylphenyl)butan-1-amine (0.32 g, 1.1 mmol) was reacted according to the general procedure described above to afford the crude imine **39** as a light yellow solid. Crystallization with hexanes afforded **39** in 76% isolated yield (0.31 g, 0.84 mmol) as white solid (mp 124-125 °C). *Spectral data for **39**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81-0.88 (t, 3H, *J*=7.5 Hz), 1.22-1.30 (m, 2H), 2.19-2.27 (m, 2H), 2.27 (s, 12H), 6.84 (s, 2H), 6.95 (s, 4H), 7.37-7.42 (m, 3H), 7.77-7.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.78, 17.51, 21.60, 45.22, 71.92, 126.18, 127.85, 128.25, 128.43, 130.27, 136.95, 147.19, 159.01; IR (thin film) 3005, 2957, 1640, 1601, 1450 cm^{-1}.

6.2.3 Preparation of amine 1,1-bis(3,5-dimethylphenyl)butan-1-amine



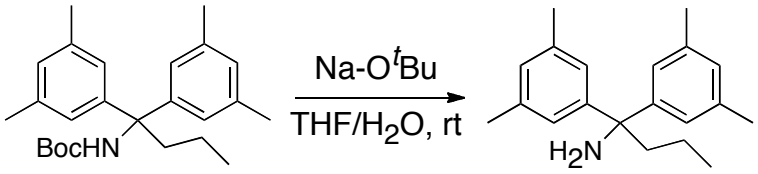
22f

To a flame-dried 100 mL round bottomed flask was added 1,1-bis(3,5-dimethylphenyl)but-3-en-1-amine (1.1 g, 4.0 mmol) and 40 mL of dry THF. This was followed by addition of $(Boc)_2O$ (1.6 g, 6.6 mmol) and triethylamine (1.2 g, 12 mmol). The mixture was heated to reflux for 48 h. Upon completion, THF was removed by rotary evaporation and the residue was dissolved in EtOAc (20 mL) , washed with H_2O (5 mLx3), dried over Na_2SO_4 , filtered and concentrated by rotary evaporation. The crude material was purified by column chromatography (hexanes/EtOAc 12:1) to give the product *tert*-butyl (1,1-bis(3,5-dimethylphenyl)but-3-en-1-yl)carbamate in 95% yield (1.4 g, 3.8 mmol) as a colorless viscous oil. *Spectral data for the product:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (bs, 9H), 2.27 (s, 12H), 3.28 (bs, 2H), 5.04-5.16 (m, 2H), 5.33 (bs, 1H), 6.83 (s, 2H), 6.93 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.55, 27.39, 28.19, 63.27, 79.21, 118.63, 124.30, 128.22, 134.15, 137.29, 145.24; IR (thin film) 3007, 2978, 1732, 1698, 1483 cm^{-1}; mass spectrum, *m/z* (% rel intensity) 379 M+ (0), 339 (1.91), 238 (100).



To a flame-dried 100 mL round bottomed flask was added *tert*-butyl (1,1-bis(3,5-dimethylphenyl)but-3-en-1-yl)carbamate (1.4 g, 3.8 mmol) and 20 mL of dry DCM. This was followed by addition of NBSH[62] (4.18 g, 19.0 mmol) and triethylamine (5.5 mL, 38

mmol) at room temperature. White suspension was formed in the flask, which then disappeared after 5 h to give a clear orange solution. Upon completion, silica gel (5 g) was added to the reaction mixture. DCM was removed by rotary evaporation. The residue was directly loaded to a column and eluted with EtOAc/hexanes (1:15) to afford the product tert-butyl (1,1-bis(3,5-dimethylphenyl)butyl)carbamate in 88% yield (1.2 g, 3.3 mmol) as an off-white solid (mp 135-136°C). *Spectral data for the product:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89-0.94 (t, 3H, *J* = 7.2 Hz), 1.15-1.28 (m, 2H), 1.32 (bs, 9H), 2.26 (s, 12H), 2.47 (bs, 2H), 5.35 (bs, 1H), 6.80 (s, 2H), 6.90 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.35, 17.43, 21.55, 28.20, 63.81, 124.13, 128.02, 137.19, 146.08, 162.20; IR (thin film) 3281, 3005, 2964, 1734, 1691cm^{-1}. mass spectrum, *m/z* (% rel intensity) 381 M+ (0), 339 (1.67), 238 (100).

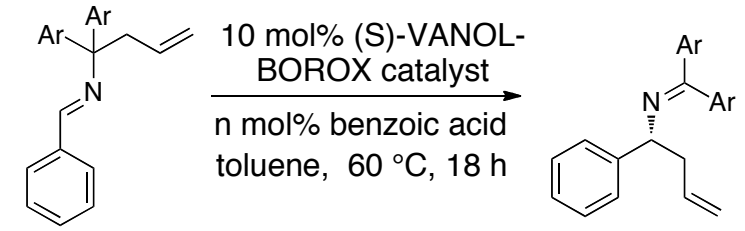


To a flame-dried 10 mL round bottomed flask was added tert-butyl (1,1-bis(3,5-dimethylphenyl)butyl)carbamate (74 mg, 0.2 mmol) and 1.0 mL of dry THF. This was followed by addition of H_2O (3.6 µL, 0.2 mmol) and Na-O^{t}Bu (58 mg, 0.6 mmol) at room temperature. The mixture turned purple after addition of Na-O^{t}Bu, then became brown upon heat at 70°C for 5 min. Thereafter, the mixture was refluxed for 6 h. Upon completion, solvent was removed by rotary evaporation. The residue was purified with column chromatography with EtOAc/hexanes (1:6) to afford the product in 66% yield (37

mg, 0.13 mmol) as a viscous oil. *Spectral data for the product:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90-0.93 (t, 3H, 7.5 Hz), 1.18-1.21 (m, 2H), 1.71 (bs, 2H), 2.11-2.14 (m, 2H), 2.28 (s, 12H), 6.83 (s, 2H), 6.96 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.59, 17.46, 21.51, 45.08, 60.67, 124.31, 127.72, 137.23, 148.98; IR (thin film) 3005, 2957, 1599, 1450 cm^{-1}. mass spectrum, *m/z* (% rel intensity) 281 M+ (0), 266 (7.89), 223 (100).

6.2.4 Probing the role of benzoic acid additive in the aza-Cope rearrangement

I. Benzoic acid equivalent study



Ar = 3,5-dimethylphenyl **23f** **24f**

Preparation of the catalyst stock solution.

A 50 mL Schlenk flask was flame dried under high vacuum and cooled under a low flow of Nitrogen. To the flask was added sequentially (*S*)-VANOL (44 mg, 0.1 mmol), phenol (19 mg, 0.2 mmol), dry toluene (2.0 mL), BH_3•SMe_2 (2 *M* solution in toluene, 150 μL, 0.3 mmol) and water (5.4 μL, 0.3 mmol) under a low flow of Nitrogen. The threaded Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. The valve was carefully and slowly opened to gradually apply high vacuum (0.1 mm Hg) and the solvent was removed. The vacuum was maintained for a period of 30 min at 100 °C. The flask was then removed from the oil bath and allowed to

cool to room temperature under a low flow of Nitrogen. This was then completely dissolved in 2 mL of dry toluene to afford the stock solution of the catalyst.

The Aza-cope rearrangement – Illustrated with 1 equivalent of benzoic acid with respect to (S)-VANOL-BOROX catalyst.

A 5 mL Schlenk test tube fitted with a threaded Teflon valve and a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Nitrogen. To the test tube was then added imine **23f** (37 mg, 0.10 mmol, 1 equiv), toluene (0.1 mL) and 0.20 mL of the catalyst stock solution (10 mol% catalyst) via a plastic syringe fitted with a metallic needle. At the same time, to an oven-dried 5 mL vial was added benzoic acid (24 mg, 0.2 mmol) and toluene (1 mL). Then 50 μL of the benzoic acid stock solution (10 mol%) was transferred to the above catalyst-imine complex via a plastic syringe fitted with a metallic needle. After addition of the rest of the toluene (0.15 mL), the Schlenk test tube was closed and the reaction was stirred at 60 °C for 18 h. Upon completion, the reaction mixture was directly loaded to a silica gel column (2 cm x 20 cm) with a pipette. Purification with flash column chromatography (1:30 EtOAc/hexanes) was complete in 5 min and gave the rearrangement product **24f** as a white solid in 81% yield (30 mg, 0.081 mmol). The optical purity of **24f** was determined to be 72% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.7:0.3, 222 nm, flow rate 0.3 mL min^{-1}).

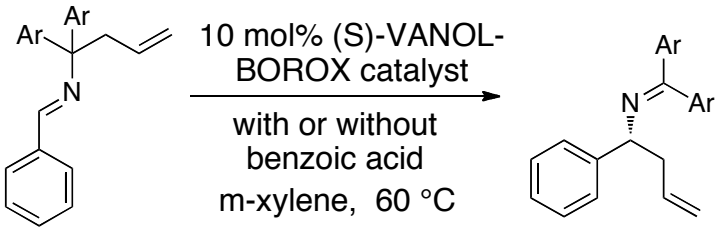
The above described reaction was then carried out with 0, 0.1, 0.5, 1.5, 2.0, 4.0, and 6.0 equivalent of benzoic acid with respect to (*S*)-VANOL-BOROX catalyst. The data was presented in table 1.

Table 1. Study of Equivalent of Benzoic Acid

Entry[a]	n	%Yield[b]	%ee[c]
1	0	77	25
2	1	80	40
3	5	85	69
4	10	81	72
5	15	81	72
6	20	83	70
7	40	84	68
8	60	84	66

[a.] Catalyst made from 1equiv ligand, 3 equiv $BH_3.SMe_2$, 2 equiv phenol and 3equiv H_2O at 100 °C for 1h, followed by full vacuum, 100 °C, 30 min. [b.] Isolated yield. [c.] Chiral HPLC analysis.

II. Reaction rate study with/without benzoic acid



Ar = 3,5-dimethylphenyl **23f** **24f**

Catalyst stock solution was prepared as described in 6.2.4, except that the catalyst was dissolved in *m*-xylene, which was used for the rate study thereafter.

A 5 mL Schlenk test tube fitted with a threaded Teflon valve and a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Nitrogen. To the test tube was then added imine **23f** (37 mg, 0.10 mmol, 1 equiv), *m*-xylene (0.1 mL) and 0.20 mL of the catalyst stock solution (10 mol% catalyst) via a plastic syringe fitted with a metallic needle. At the same time, to an oven-dried 5 mL vial was added benzoic acid (24 mg, 0.2 mmol) and *m*-xylene (1 mL). Then 50 μL of the benzoic acid stock solution (10 mol%) was transferred to the above catalyst-imine complex via a plastic

syringe fitted with a metallic needle. After addition of the rest of the *m*-xylene (0.15 mL), the Schlenk test tube was closed and the reaction was stirred at 60 °C. After 30 minutes, 50 μL of the reaction mixture was taken and quickly striped of solvent under full vacuum, and the residue was then dissolved in 0.7 mL of $CDCl_3$ for NMR analysis. ^1H NMR was taken on a VXR-500 MHz instrument. Conversion was calculated to be 35% based on the integrals of the allyl-CH_2 of the starting material and methine of the product. Thereafter, sample was prepared and subjected to ^1H NMR analysis after 1 h, 4 h, and 8 h.

The same study was also performed without benzoic acid. The data was listed in table 2.

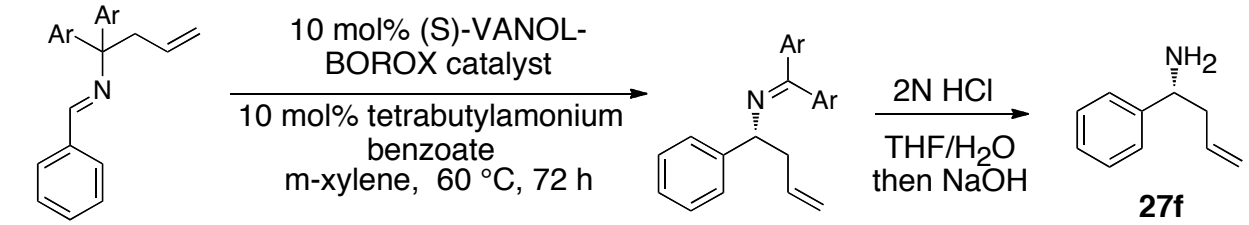
Table 2. Effects of benzoic acid on reaction rate

Entry[a]	Additive	time (h)	conver.(%)[b]
1	10 mol% benzoic acid	0.5	35
2	10 mol% benzoic acid	1	50
3	10 mol% benzoic acid	4	77
4	10 mol% benzoic acid	8	91
5	10 mol% benzoic acid	20	100
6	none	0.5	25
7	none	1	35
8	none	4	52
9	none	8	65
10	none	20	82

Pre-catalyst was prepared by heating 0.050 mmol VANOL ligand, 0.15 mmol $BH_3 \bullet SMe_2$, 0.10 mmol 2, 4, 6-trimethylphenol, and 0.15 mmol H_2O in 2 mL toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mm Hg.

III. Aza-Cope rearrangement with tetrabutylammonium benzoate and methyl benzoate

Catalyst stock solution was prepared as described in 6.2.4, except that the catalyst was dissolved in *m*-xylene, which was used for the aza-Cope rearrangement with tetrabutylammonium benzoate.

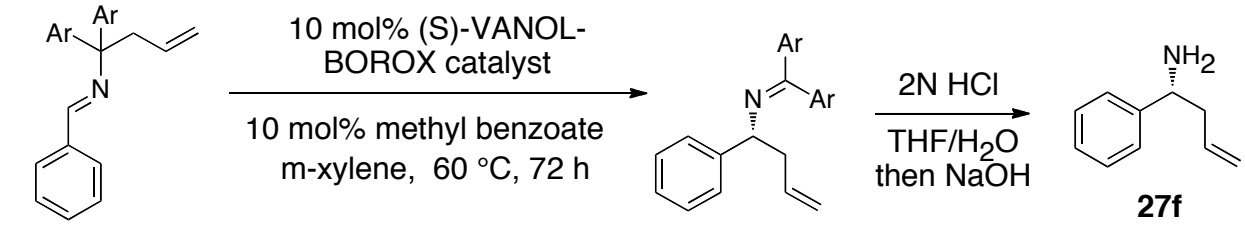


Ar = 3,5-dimethylphenyl

23f **24f** **27f**

A 5 mL Schlenk test tube fitted with a threaded Teflon valve and a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Nitrogen. To the test tube was then added imine **23f** (37 mg, 0.10 mmol, 1 equiv), *m*-xylene (0.1 mL) and 0.20 mL of the catalyst stock solution (10 mol% catalyst) via a plastic syringe fitted with a metallic needle. At the same time, to an oven-dried 5 mL vial was added tetrabutylammonium benzoate (73 mg, 0.2 mmol) and *m*-xylene (1 mL) and the mixture was heated with a heat gun until tetrabutylammonium benzoate dissolved. Then 50 μL of the warm tetrabutylammonium benzoate stock solution (10 mol%) was transferred to the above catalyst-imine complex via a plastic syringe fitted with a metallic needle. After addition of the rest of the *m*-xylene (0.15 mL), the Schlenk test tube was closed and the reaction was stirred at 60 °C. The reaction turned bright yellow after addition of tetrabutylammonium benzoate; white precipitates then quickly formed in the tube and the mixture turned off-white. The reaction mixture was stirred for 3 days at 60 °C. Upon completion, the reaction mixture was directly loaded to a silica gel column (2 cm x 20 cm) with a pipette. Purification with flash column chromatography (1:30 EtOAc/hexanes)

was complete in 5 min and gave the rearrangement product **24f** as a white solid in 82% yield (30 mg, 0.082 mmol). The product was then dissolved in 0.4 mL THF followed by the addition of 0.2 mL of 2N HCl. Hydrolysis was complete in 6 h and THF was then removed by rotary evaporation. Another 1 mL of H_2O was added to the residue and the aqueous phase was washed with EtOAc (0.2 mL X 3). The aqueous phase was then treated with 10% NaOH solution until pH reached 12. The mixture was extracted with DCM (0.5 mL X 3) and the combined organic phase was dried over Na_2SO_4 and filtered. The optical purity of **27f** was determined to be 72% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol:diethylamine 95:5:0.05, 222 nm, flow rate 1.0 mL min^{-1}). Retention times were 3.8 min (major enantiomer, (*R*)-**27f**) and 4.8 min (minor enantiomer, (*S*)-**27f**).



Ar = 3,5-dimethylphenyl

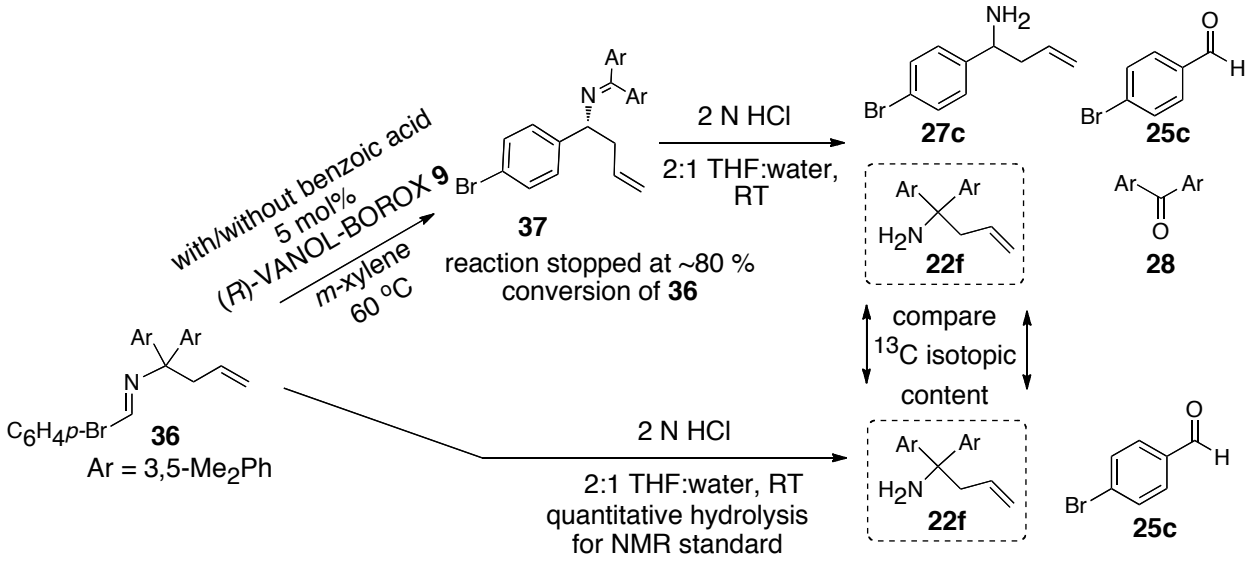
23f **24f** **27f**

Aza-Cope rearrangement was carried out with methyl benzoate according to the procedure described for tetrabutylammonium benzoate. However, color change after addition of methyl benzoate was not observed (Reaction mixture turned bright yellow after addition of benzoic acid or tetrabutylammonium benzoate). Purification with column afforded the ketimine product **24f** in 72% yield (27 mg, 0.72 mmol). The optical purity of **27f** was determined to be 28% ee by HPLC analysis (Chiralcel OD-H column,

hexanes:2-propanol:diethylamine 95:5:0.05, 222 nm, flow rate 1.0 mL min^{-1}). Retention times were 5.4 min (major enantiomer, (*S*)-**27f**) and 4.1 min (minor enantiomer, (*R*)-**27f**).

6.2.6 Experimental ^{13}C Kinetic Isotope Effects

I. KIEs from Starting Material Analysis



(*R*)-VANOL-BOROX Catalyst was prepared as described in 6.2.4, except that 2,4,6-trimethylphenol was used.

*Preparation of standard starting amine **22f**.* To a 25 mL round bottomed flask was added imine **36** (0.89 g, 2.0 mmol), THF (8.0 mL) and 2N HCl (4.0 mL). Hydrolysis was finished overnight and THF was then removed. To the residue was added another 10 mL of H_2O and the aqueous phase was washed with ether (4 mL x 4). The aqueous phase was then treated with NaOH to adjust pH to 13 and extracted with DCM (5 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated by

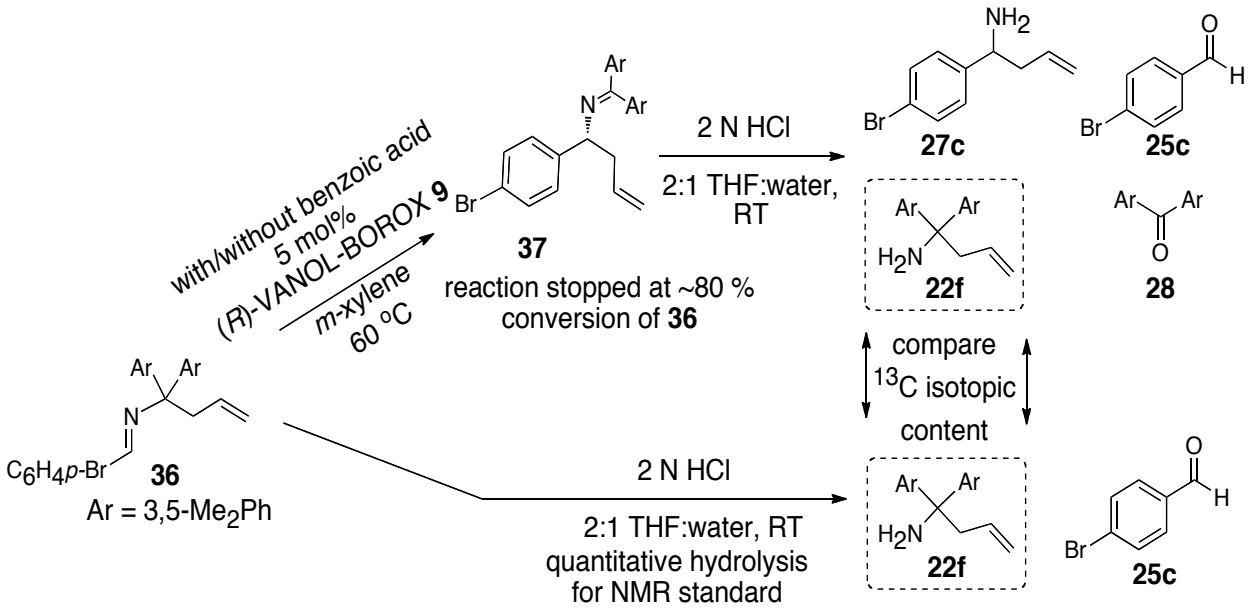
rotary evaporation to give the pure starting amine as a white solid in 75% yield (0.42 g, 1.5 mmol).

Recycle of sample starting amine with benzoic acid. Imine **36** (3.3 g, 7.5 mmol), from the same batch as the imine used to prepare the standard starting amine, was subjected to aza-Cope rearrangement according to the general procedure described in 6.2.4 except that 5 mol% catalyst and benzoic acid were used. When the reaction reached 72% conversion after 6 h, *m*-xylene was removed under full vacuum at 60°C. The residue was dissolved in 30 mL THF, and 0.1 mL of the mixture was taken for ^{1}H NMR analysis to determine the real conversion of the aza-Cope rearrangement after removal of m-xylene. The actual conversion was determined to be 74% by ^{1}H NMR analysis. Thereafter, 15 mL of 2N HCl was added, and hydrolysis was finished in 12 h, followed by the addition of 1N NaOH until the pH reached 13. The reaction mixture was then extracted with DCM (8 mL x 3), and the organic phase was combined and concentrated by rotary evaporation. The residue was purified by column chromatography (EtOAc/hexanes 1:40 then EtOAC/hexanes/triethylamine 1:6:0.07) to give pure starting amine in 72% yield (0.38 g, 1.4 mmol) as a white solid.

Recycle of sample starting amine without benzoic acid. Imine **36** (3.3 g, 7.5 mmol), from the same batch as the imine used to prepare the standard starting amine, was subjected to aza-Cope rearrangement according to the general procedure described above except that benzoic acid was not added to the reaction mixture. Reaction was stopped at 70% conversion and 0.41 g of pure starting amine (1.5 mmol) was obtained as a white solid.

NMR Sample preparation for experimental ^{13}C Kinetic Isotope Effect study. Starting amine (250 mg, 0.9 mmol) was dissolved in 0.3 mL of $CDCl_3$ in a small vial and the mixture was transferred to a clean NMR tube. The vial was washed with another 0.2 mL of $CDCl_3$ and the solution was transferred to the NMR tube as well. Thereafter, the NMR tube was filled up to exact 5.0 CM by adding $CDCl_3$ slowly with a 0.5 mL syringe. The sample was shaken carefully to get a homogeneous sample which will be used in the experimental ^{13}C Kinetic Isotope Effect study.

II. KIEs from Product Analysis



(*R*)-VANOL-BOROX Catalyst was prepared as described in 6.2.4, except that 2,4,6-trimethylphenol was used.

*Synthesis of standard product amine **27c** and diaryl ketone **28**.* Imine **36** (1.34 g, 3.00 mmol) was subjected to aza-Cope rearrangement according to the general procedure described in 6.2.4. Upon completion, *m*-xylene was removed under reduced

pressure. The residue was dissolved in 8 mL of THF and 4 mL of 2N HCl for hydrolysis. Hydrolysis was complete in 6 h, and THF was then removed by reduced pressure. Another 10 mL of H_2O was added, the aqueous phase was washed with EtOAc (4 mL x 4). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give a yellow solid which was purified by crystallization with pure hexanes to afford the pure product diaryl ketone in 59% yield (1^{st} crop, 0.42 g, 1.76 mmol). The aqueous phase was basified with 1N NaOH to pH = 12, and extracted with DCM (4 mL x 4). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give pure product amine ***27c*** in 72% yield (0.49 g, 2.2 mmol) as a viscous oil.

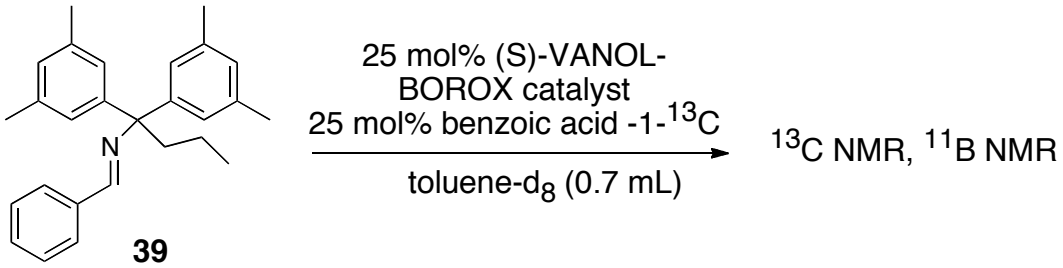
*Synthesis of standard product amine **27c** and diaryl ketone **28** with benzoic acid.* Imine **36** (5.3 g, 12 mmol), from the same batch as the imine used to prepare the standard product amine, was subjected to aza-Cope rearrangement according to the general procedure described in 6.2.4. *m*-Xylene was removed under full vacuum at 60°C after the reaction mixture was stirred for 1 h. The residue was dissolved in 32 mL THF, and 0.1 mL of the mixture was taken for ^1H NMR analysis to determine the real conversion of the aza-Cope rearrangement after removal of m-xylene. The actual conversion was determined to be 17% by ^1H NMR analysis. Thereafter, 16 mL of 2N HCl was added, and hydrolysis was finished in 12 h, followed by the addition of 1N NaOH until the pH reached 12. The reaction mixture was then extracted with DCM (8 mL x 3), and the organic phase was combined, dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The residue was purified by column

chromatography (EtOAc/hexanes 1:20 then 1:3). A mixture of product ketone, para-bromobenzaldehyde and a newly formed imine due to the condensation of product amine ***27c*** and para-bromobenzaldehyde was collected, which was subjected to hydrolysis with THF (32 mL) and 2N HCl (16 mL). Upon completion, THF was removed and the aqueous layer was washed with EtOAc (5 mL x 4). The aqueous phase was basified to pH = 12 with 1N NaOH, and extracted with DCM, dried over Na_2SO_4, filtered and concentrated to give the pure product amine **27c** as a viscous oil in 76% yield (0.330 g, 1.55 mmol). The combined EtOAc phase was then dried over Na_2SO_4, filtered and concentrated. para-Bromobenzaldehyde was removed under vacuum, and the residue was purified by crystallization with hexanes to give the product diaryl ketone as an off-white solid in 71% yield (0.340 g, 1.42 mmol).

*Synthesis of standard product amine **27c** and diaryl ketone **28** without benzoic acid.* Imine **36** (5.3 g, 12 mmol), from the same batch as the imine used to prepare the standard product amine and diaryl ketone, was subjected to aza-Cope rearrangement according to the general procedure described above except that benzoic acid was not added to the reaction mixture. Reaction was stopped at 20% conversion and 0.3 g of pure product amine ***27c*** (1.41 mmol) was obtained as a viscous oil. Diaryl ketone was obtained as an off-white solid in 63% yield (0.36 g, 1.51 mmol).

NMR Sample preparation for experimental ^{13}C Kinetic Isotope Effect study. Sample for NMR analysis was prepared following the procedure described in part I of 6.2.6.

6.2.7 NMR study



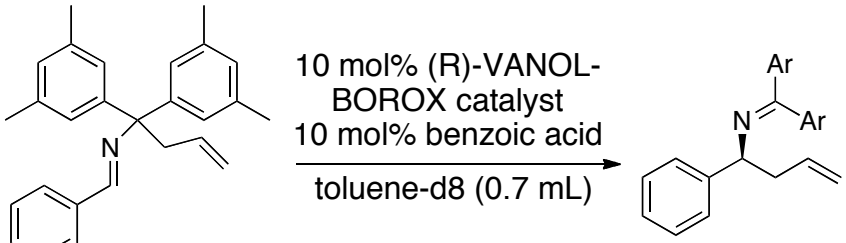
39

0.2 mmol

(*S*)-VANOL-BOROX Catalyst (0.25 mmol) was prepared as described in 6.2.4, and the catalyst was dissolved in 3.0 mL of toluene-d_8.

A flame-dried quartz NMR tube was charged with 0.6 mL of the catalyst stock solution (0.05 mmol), and imine **39** (73 mg, 0.02 mmol) was added as a solid. ^{1}H NMR, ^{13}C NMR, ^{11}B NMR were taken at room temperature and 60°C. Benzoic acid-α-^{13}C was added in toluene-d_8 solution (0.05 mmol, 0.1 mL). ^{1}H NMR, ^{13}C NMR, ^{11}B NMR were taken at room temperature and 60°C.

6.2.8 Kinetic experiment



23f **24f**

(*R*)-VANOL-BOROX Catalyst (0.1 mmol) was prepared as described in 6.2.4, and the catalyst was dissolved in 2 mL of toluene-d_8. Imine 3 (0.22 g, 0.6 mmol) was dissolved in 1.2 mL of toluene-d_8; benzoic acid (25 mg, 0.2 mmol) was dissolved in 1

mL of toluene-d_8; triphenylmethane (73 mg, 0.3 mmol), as an internal standard, was dissolved in 0.3 mL of toluene-d_8.

(*R*)-VANOL-BOROX Catalyst (0.01 mmol, 0.2 mL of catalyst stock solution) and benzoic acid (0.01 mmol, 0.05 mL of acid stock solution) and triphenylmethane (0.005 mmol, 0.05 mL of triphenylmethane stock solution) were transferred to a flame-dried NMR tube, followed by addition of imine **23f** (37 mg, 0.2 mL of imine stock solution). The NMR tube was then filled with toluene-d_8 till the total volume reached 0.7 mL. The reaction was warmed to 60 °C in the NMR probe, and the formation of product was monitored by ^{1}H NMR analysis.

Plot of K_{obs} vs. [benzoic acid] (*R*)-VANOL-BOROX Catalyst (0.01 mmol, 0.2 mL of catalyst stock solution), triphenylmethane (0.005 mmol, 0.05 mL of triphenylmethane stock solution) and imine **23f** (37 mg, 0.2 mL of imine stock solution) with varying benzoic acid in 0.7 mL of toluene-d_8 at 60 °C. Conversions were determined by ^{1}H NMR analysis.

Supporting information for chapter 4

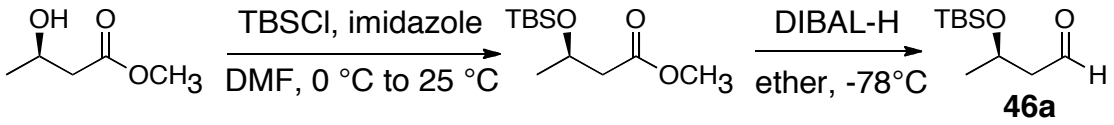
6.3.1 General information

All experiments were performed under a nitrogen atmosphere. Flasks were flame-dried and cooled under nitrogen before use. All solvents were dried appropriately if used in the reaction. VANOL ligand is commercially available from Aldrich as well as Strem Chemicals. If desired, it could be purified using column chromatography on regular silica gel with 2:1 dichloromethane/hexanes. Phenol was sublimed and stored in a dry desiccator. Liquid aldehydes were either used as purchased from Aldrich or distilled

before use. (*R*)-methyl 3-hydroxybutanoate was used as purchased from Aldrich with 98% optical purity. (*S*)-methyl 2-hydroxypropanoate was used as purchased from Aldrich with 96% optical purity.

6.3.2 Preparation of chiral aldehydes

Typical procedure for preparation of 46a and c-d – Illustrated for synthesis of (R)-3-((tert-butyldimethylsilyl)oxy)butanal 46a

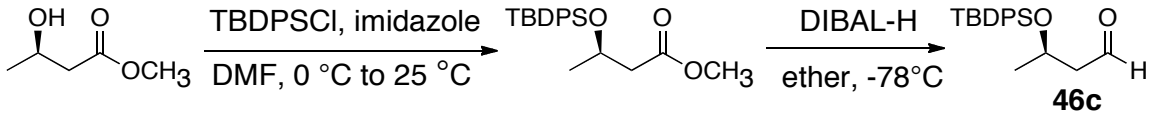


46a

To a flame-dried 100 mL round-bottomed flask, fitted with a magnetic stirrer and a nitrogen balloon was added (*R*)-methyl 3-hydroxybutanoate (98% *ee*, 0.96 g, 8.0 mmol) and DMF (20 mL). The mixture was cooled down to 0 °C, then TBSCl (1.44 g, 9.60 mmol) and imidazole (0.680 g, 9.60 mmol) were added. Stirring was continued at room temperature for 24 h. Upon completion, the mixture was charged with brine (60 mL) and stirred for 5 minutes at room temperature. The resulting solution was then extracted with hexanes (60 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product by column chromatography on silica gel (1:25 EtOAc/hexanes) gave the pure ester (*R*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)butanoate as a clear oil in 89% isolated yield (1.6 g, 7.1 mmol). R_f = 0.4 (1:25 ethyl acetate /hexanes). *Spectral data*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.013 (s, 3H), 0.035 (s, 3H), 0.84 (s, 9H), 1.16-1.17 (d, 3H, *J* = 6.0 Hz), 2.35 (dd, 1H, *J* = 14.5, 5.5 Hz), 2.46 (dd, 1H, *J* = 14.5, 7.5 Hz), 3.64 (s, 3H), 4.24-4.26 (m,

1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.08, -4.54, 17.93, 23.93, 25.70, 44.74, 51.37, 65.84, 172.04. The data matches that reported for this compound.[63]

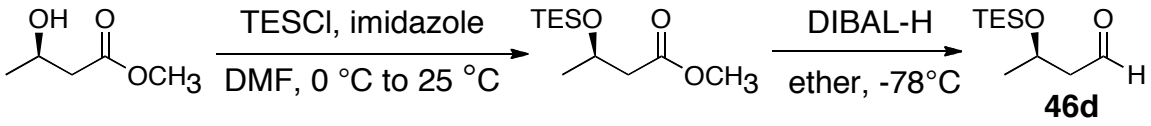
To a flame-dried 250 mL round-bottomed flask, fitted with a magnetic stirrer and a nitrogen balloon was added (*R*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)butanoate (2.0 g, 8.9 mmol) and ether (30 mL). The mixture was cooled to –78 °C and DIBAL-H (5.40 mL, 13.5 mmol) was added dropwise over a period of 4 minutes. The mixture was then stirred at –78 °C for 2 h. Upon completion, the mixture was quenched with a mixture of methanol and water (3.0 mL, 1:1 V/V), diluted with ether (40 mL) at –78 °C. The flask was then allowed to warm up to room temperature. The mixture was stirred with saturated potassium sodium tartrate solution until it became clear two layers. The organic layer was separated and the aqueous layer washed with ether (30 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product by column chromatography on silica gel (1:15 EtOAc/hexanes) gave the pure aldehyde (*R*)-**46a** as a clear oil in 71% isolated yield (1.2 g, 6.3 mmol). R_f = 0.2 (1:15 ethyl acetate /hexanes). *Spectral data for* (*R*)-***46a***[64]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 1.21 (d, 3H, *J* = 6.0 Hz), 2.41-2.55 (m, 2H), 4.31-4.35 (m, 1H), 9.78 (t, 1H, *J* = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.95, -4.39, 17.94, 24.17, 25.71, 52.99, 64.55, 202.16. The data matches that reported for this compound.[64]



46c

*(R)-3-((tert-butyldiphenylsilyl)oxy)butanal **46c**:* (*R*)-methyl 3-hydroxybutanoate (98% *ee*, 0.24 g, 2.0 mmol) was reacted according to the general procedure described above with the exception that TBDPSCl (0.66 g, 2.4 mmol) was added for the preparation of silyl protected ester. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 84% isolated yield (0.66 g, 1.8 mmol). R_f = 0.40 (1:15 ethyl acetate /hexanes). *Spectral data*[65]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.11 (d, 3H, *J* = 6.0 Hz), 2.38 (dd, 1H, *J* =15, 5.5 Hz), 2.55 (dd, 1H, *J* =15, 7.0 Hz), 3.58 (s, 3H), 4.28-4.32 (m, 1H), 7.34-7.43 (m, 6H), 7.65-7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.16, 23.60, 26.86, 44.42, 51.34, 66.86, 127.46, 127.53, 129.54, 129.60, 133.88, 134.30, 135.84, 171.76.

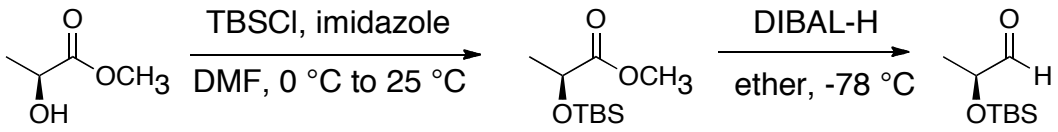
The ester (0.66 g, 1.8 mmol) was reduced according to the procedure described for the preparation of (*R*)-**46a**. Purification of (*R*)-**46c** by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure aldehyde (*R*)-**46c** as a clear oil in 84% isolated yield (0.54 g, 1.5 mmol). R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data for* (*R*)-***46c***[65]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.19 (d, 3H, *J* = 6.0 Hz), 2.42-2.48 (m, 2H), 4.28-4.32 (m, 1H), 7.35-7.43 (m, 6H), 7.62-7.69 (m, 4H), 9.78 (t, 1H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.14, 23.22, 26.92, 43.74, 66.71, 127.59, 127.68, 127.72, 129.75, 129.84, 133.56, 134.80, 135.80, 202.19.



46d

*(R)-3-((triethylsilyl)oxy)butanal **46d**:* (*R*)-methyl 3-hydroxybutanoate (98% *ee,* 3.50 g, 30.0 mmol) was reacted according to the general procedure described above with the exception that TESCl (5.4 g, 36 mmol) was added for the preparation of silyl protected ester. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 87% isolated yield (6.08 g, 26.1 mmol). R_f = 0.40 (1:15 ethyl acetate /hexanes). *Spectral data*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.57 (t, 6H, *J* = 8.0 Hz), 0.93 (t, 9H, *J* = 7.5 Hz), 1.19 (d, 3H, *J* = 6.5 Hz), 2.34-2.38 (m, 1H), 2.46-2.51 (m, 1H), 3.64 (s, 3H), 4.25-4.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.80, 6.72, 24.00, 44.74, 51.38, 65.06, 172.02.

The ester (6.08 g, 26.1 mmol) was reduced according to the procedure described for the preparation of (*R*)-**46a**. Purification of (*R*)-**46d** by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure aldehyde (*R*)-**46d** as a clear oil in 68% isolated yield (3.57 g, 17.7 mmol). R_f = 0.20 (1:15 ethyl acetate /hexanes). *Spectral data for* (*R*)-***46d***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.58 (t, 6H, *J* = 7.5 Hz), 0.93 (t, 9H, *J* = 7.5 Hz), 1.23 (d, 3H, *J* = 6.0 Hz), 2.43-2.57 (m, 2H), 4.32-4.36 (m, 1H), 9.79 (t, 1H, *J* = 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.82, 6.76, 24.25, 53.05, 64.29, 202.16; IR (thin film) 2957, 1730, 1458, 1016 cm^{-1}; HRMS (ES+) calcd for $C_{10}H_{22}O_2Si$ *m/z* 203.1463 (M+1), meas 203.1467. $[\alpha]^{23}_D$ = –11.3 (*c* = 1.0, CH_2Cl_2) on **(*R*)-46d**.

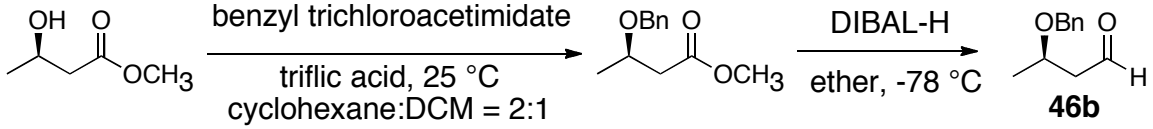


51

(S)-2-((tert-butyldimethylsilyl)oxy)propanal ***51***: (*S*)-methyl 2-hydroxypropanoate (96% *ee*, 0.21 g, 2.0 mmol) was reacted according to the general procedure described above. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 75% isolated yield (0.33 g, 1.5 mmol). R_f = 0.30 (1:15 ethyl acetate /hexanes). *Spectral data*[66]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.41 (d, 3H, *J* = 7.0 Hz), 3.70 (s, 3H), 4.31 (dd, 1H, *J* = 13.0, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.32, -5.12, 18.30, 21.35, 25.70, 51.85, 68.38, 174.56.

The ester (0.33 g, 1.5 mmol) was reduced according to the procedure described for the preparation of (*R*)-**46a**. Purification of (*S*)-**51** by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure aldehyde (*S*)-**51** as a clear oil in 45% isolated yield (0.13 g, 0.68 mmol). R_f = 0.20 (1:15 ethyl acetate /hexanes). *Spectral data for* (*S*)-***51***[67]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91(s, 9H), 1.25 (d, 3H, J = 6.5 Hz), 4.07 (dd, 1H, *J* = 6.5, 1.0 Hz), 9.59 (d, 1H, *J* = 1.0 Hz).

Procedure for preparation of (R)-3-(benzyloxy)butanal **46b**



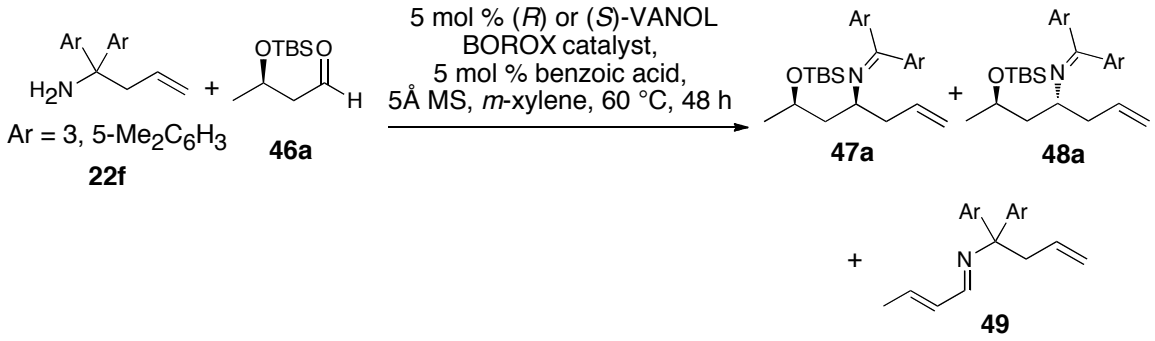
46b

To a stirred solution of (*R*)-methyl 3-hydroxybutanoate (98% *ee,* 0.24 g, 2.0 mmol) and benzyl trichloroacetimidate (1.0 g, 4.0 mmol) in co-solvent (20 mL, $V_{cyclohexane}$: V_{DCM} = 2:1) was added triflic acid (30 uL, 0.30 mmol) at room temperature. Stirring was continued for 48 h. The reaction was quenched by addition of sat. $NaHCO_3$ (20 mL), followed by the separation of the organic phase. The aqueous phase was washed with dichloromethane (5 mL x 3), and the combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure ester as a clear oil in 60% isolated yield (0.25 g, 1.2 mmol). R_f = 0.20 (1:15 ethyl acetate /hexanes). *Spectral data*[68]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, 3H, *J* = 6.0), 2.43 (dd, 1H, *J* = 15, 6.0 Hz), 2.65 (dd, 1H, *J* = 15, 7.5 Hz), 3.66 (s, 3H), 3.99-4.03 (m, 1H), 4.50 (d, 1H, *J* = 11.5 Hz), 4.57 (d, 1H, *J* = 11.5 Hz), 7.25-7.33 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.65, 41.66, 51.32, 70.64, 71.72, 127.34, 127.44, 128.13, 138.38, 171.64.

The resulting ester (0.25 g, 1.2 mmol) was then subjected to the DIBAL-H reduction as described for the synthesis of (*R*)-**46b**. Purification of **46b** by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure **46b** as a clear oil in 63% isolated yield (0.12 g, 0.76 mmol). R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data*[69]: ^{1}H NMR (500 MHz, $CDCl_3$) δ1.34 (d, 3H, *J* = 6.0 Hz), 2.53-2.58 (m, 1H), 2.71-2.76 (m, 1H), 4.10-4.12 (m, 1H), 4.51 (d, 1H, *J* = 11.5 Hz), 4.64 (d, 1H, *J* = 11.5 Hz), 7.29-7.39 (m, 5H), 9.83 (t, 1H, *J* = 2.0 Hz).

6.3.3 Optimization of the alcohol protecting group

Diastereoselective aza-Cope rearrangement with (*R*)-3-((*tert*-butyldimethylsilyl)oxy) butanal **46a**



Preparation of catalyst stock solution. A 50 mL Schlenk flask was flame dried under high vacuum and cooled under a low flow of Nitrogen. To the flask was sequentially added (*R*)-VANOL (44 mg, 0.10 mmol), phenol (19 mg, 0.20 mmol), dry toluene (2.0 mL), BH_3•SMe_2 (2 *M* solution in toluene, 150 μL, 0.300 mmol) and water (5.4 μL, 0.30 mmol) under a low flow of Argon. The threaded Teflon valve on the Schlenck flask was then closed, and the mixture heated at 100 °C for 1 h. The valve was carefully and slowly opened to gradually apply high vacuum (0.1 mm Hg) and the solvent was removed. The vacuum was maintained for a period of 30 min at 100 °C. The flask was then removed from the oil bath and allowed to cool to room temperature under a low flow of Nitrogen. The residue was then completely dissolved in 2 mL of dry toluene to afford the stock solution of the catalyst.

aza-Cope rearrangement with (R)-VANOL catalyst. A 5 mL Schlenk test tube charged with 5Å powdered molecular sieves (50 mg) and fitted with a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Nitrogen. To the test tube was then added amine **22f** (28 mg, 0.10 mmol, 1.0 equiv), 0.10 mL of the catalyst stock solution (5 mol% catalyst) and *m*-xylene (0.35 mL) via a plastic syringe

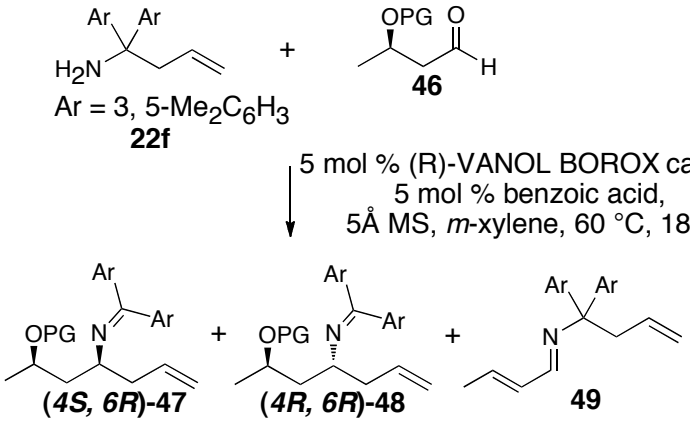
fitted with a metallic needle. The mixture was stirred for 30 min at 60 °C. At the same time, to an oven-dried 5 mL vial was added benzoic acid (12 mg, 0.10 mmol) and *m*-xylene (1 mL). Then (*R*)-**46a** (22 mg, 0.11 mmol) and 50 μL of the benzoic acid stock solution (5 mol%) were transferred to the above catalyst-amine complex under a high flow of Nitrogen via a plastic syringe fitted with a metallic needle. The test tube was closed and the reaction was stirred at 60 °C for 18 h. Purification by flash column chromatography on silica gel (1:40 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products **47a+48a** as a viscous oil in 48% (22 mg, 0.048 mmol) yield. The diastereoselective ratio of the reaction was determined to be 33:1 by ^{1}H NMR analysis on the crude material and this ratio was unchanged after purification. R_f = 0.20 (1:40 ethyl acetate /hexanes). The ^{1}H NMR analysis of the crude reaction mixture of aza-Cope rearrangement with **46a** suggests the formation of by-product **49**, which was lost on the column when purification of the products was carried out. The ratio of (**47a+48a**):**49** is 3:1. *Spectral data for major diastereomer **47a***: ^{1}H NMR (600 MHz, $CDCl_3$) δ –0.01 (s, 3H), 0.01 (s, 3H), 0.80 (s, 9H), 0.86-0.87 (d, 3H, *J* = 6.0 Hz), 1.62-1.64 (m, 1H), 1.78-1.79 (m, 1H), 2.23-2.33 (m, 2H), 2.26 (s, 6H), 2.30 (s, 6H), 3.34-3.36 (m, 1H), 3.73-3.74 (m, 1H), 4.97-5.02 (m, 2H), 5.70-5.74 (m, 1H), 6.70 (s, 2H), 6.98 (s, 2H), 7.19 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ -4.83, -4.43, 18.14, 21.27, 21.32, 23.30, 25.89, 41.09, 46.19, 58.87, 66.09, 116.34, 125.49, 126.25, 129.61, 131.34, 136.23, 137.40, 137.45, 137.60, 140.43, 167.41; IR (thin film) 2957, 1595,

1474, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3340; $[\alpha]^{23}_{D}$ = +16.1 (*c* = 1.0, CH_2Cl_2) on **47a**.

aza-Cope rearrangement with (S)-VANOL catalyst. Chiral aldehyde (*R*)-**46a** (22 mg, 0.11 mmol) was also subjected to the aza-Cope rearrangement with 5 mol% (*S*)-VANOL derived BOROX catalyst according to the procedure described for (*R*)-VANOL derived catalyst above. Purification by flash column chromatography on silica gel (1:40 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products **47a+48a** as a viscous oil in 44% yield (20 mg, 0.044 mmol). The diastereoselective ratio of the reaction with (*S*)-VANOL was determined to be 1:23 by ^{1}H NMR analysis fo the crude reaction mixture and the ratio is essentially the same after purification (1:20). The ^{1}H NMR analysis of the crude reaction mixture of aza-Cope rearrangement with **46a** suggests the formation of by-product **49**, which was lost on the column when purification of the products was carried out. The ratio of (**47a+48a**):**49** is 4:1. The ^{1}H NMR spectra of the major diastereomer matches that of the minor diastereomer obtained with (*R*)-VANOL derived BOROX catalyst. R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data for major diastereomer **47a**:* ^{1}H NMR (600 MHz, $CDCl_3$) δ -0.11 (s, 3H), -0.04 (s, 3H), 0.79 (s, 9H), 0.96 (d, 3H, *J* = 6.0 Hz), 1.22-1.26 (m, 1H), 1.58-1.63 (m, 1H), 1.88-1.91 (m, 1H), 2.26-2.32 (m, 1H), 2.26 (s, 6H), 2.31 (s, 6H), 3.38-3.40 (m, 1H), 3.69-3.70 (m, 1H), 4.96-5.01 (m, 2H), 5.67-5.72 (m, 1H), 6.72 (s, 2H), 6.97 (s, 1H), 6.98 (s, 1H), 7.16 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

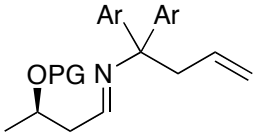
-4.75, -4.43, 18.06, 21.28, 21.32, 24.14, 25.84, 41.21, 46.54, 59.71, 67.24, 116.21, 125.55, 126.23, 129.61, 131.34, 136.30, 137.40, 137.62, 137.66, 140.57, 167.15; IR (thin film) 2957, 1595, 1474, 1199cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3335; $[\alpha]^{23}_{D}$ = –29.7 (*c* = 1.0, CH_2Cl_2) on **47a**.

Diastereoselective aza-Cope rearrangement with chiral aldehydes **46b** and **46c**



PG		(**47**+**48**):**49**
Bn	**46b**	4:1
TBDPS	**46c**	1:10

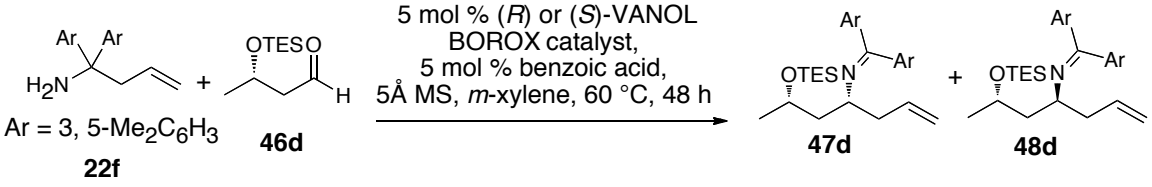
Further optimization of the alcohol protecting group were performed with **8b** and **46c** to minimize the formation of by-product **49**. Chiral aldehydes **46b** and **46c** were subjected to the diasteraoselective aza-Cope rearrangement according to the method described for aldehyde **46a**. The ^{1}H NMR analysis of the aza-Cope rearrangement with aldehydes **46b-c** were carried out on crude reaction mixture. As shown in Table 2, when the reactions were incomplete, in most cases, the unreacted material is in the form of amine **22f** but in some cases a small amount of imine **50** formed from **46** and **22f** is present.



Ar = 3, 5-$Me_2C_6H_3$

50

Diastereoselective aza-Cope rearrangement with (S)-3-((triethylsilyl)oxy) butanal **46d**



Ar = 3, 5-$Me_2C_6H_3$ **22f** **46d** **47d** **48d**

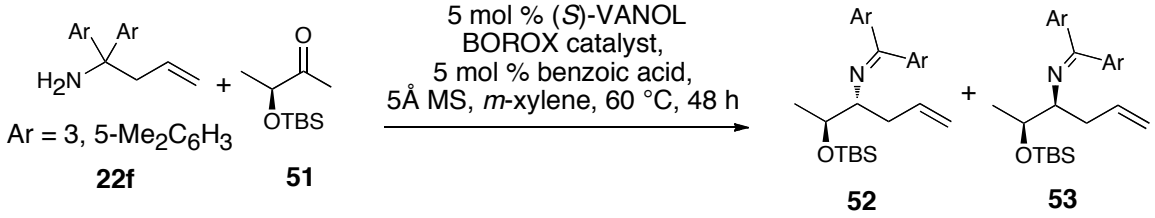
aza-Cope rearrangement with (R)-VANOL catalyst. (*S*)-3-((triethylsilyl)oxy)butanal **46d** (22 mg, 0.11 mmol) was subjected to the diastereoselective aza-Cope rearrangement according to the procedure for **46a**. Purification by column chromatography on silica gel (EtOAc/hexanes 1:30) afforded a mixture of the rearrangement products (*4R, 6S*)-**47d** and (*4S, 6S*)-**48d** as a viscous oil in 87% yield (40 mg, 0.087 mmol). The diastereoselective ratio of the reaction was determined to be 1:20 (**47d**:**48d**) by ^{1}H NMR analysis of the crude reaction mixture and was essentially the same after purification (1:22). R_f = 0.20 (1:30 ethyl acetate /hexanes). *Spectral data for major diastereomer* (*4S, 6S*)-**48d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.51-0.55 (q, 6H, *J* = 8.0 Hz), 0.89-0.92 (t, 9H, *J* = 8.0 Hz), 1.08-1.09 (d, 3H, *J* = 6.0 Hz), 1.67-1.71 (m, 1H), 1.92-1.97 (m, 1H), 2.34-2.42 (m, 2H), 2.32 (s, 6H), 2.36 (s, 6H), 3.45-3.48 (m, 1H), 3.74-3.77 (m, 1H), 5.01-5.07 (m, 2H), 5.73-5.79 (m, 1H), 6.78 (s, 2H), 7.03-7.05 (d, 2H, *J* = 8.0 Hz), 7.22 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.92, 6.83, 21.28, 21.31, 24.23, 41.20, 46.59, 59.66, 66.90, 116.23, 125.56, 126.23, 129.59, 131.33, 136.26, 137.40,

137.57, 137.65, 140.61, 167.20; ; IR (thin film) 2957, 1595, 1458, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3362; $[\alpha]^{23}_{D}$ = +15.8 (*c* = 1.0, CH_2Cl_2) on (*4S, 6S*)-**48d**.

aza-Cope rearrangement with (S)-VANOL catalyst. Chiral aldehyde (*R*)-**46d** (22 mg, 0.11 mmol) was also subjected to the aza-Cope rearrangement with 5 mol% (*S*)-VANOL derived BOROX catalyst **9** according to the procedure described for (*R*)-VANOL derived catalyst above. Purification by flash column chromatography on silica gel (1:30 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products (*4R, 6S*)-**47d** and (*4S, 6S*)-**48d** as a viscous oil in 74% yield (34 mg, 0.074 mmol). The diastereoselective ratio of the reaction with (*S*)-VANOL was determined to be 26:1 (47d:48d) by ^{1}H NMR analysis of the crude reaction mixture and the ratio was essentially unchanged after purification (23:1). The ^{1}H NMR spectra of the major diastereomer matches that of the minor diastereomer obtained with (*R*)-VANOL derived BOROX catalyst **9**. R_f = 0.20 (1:30 ethyl acetate /hexanes). *Spectral data for major diastereomer* (*4R, 6S*)-**47d***:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.58-0.63 (q, 6H, *J* = 8.0 Hz), 0.89-0.90 (d, 3H, *J* = 6.0 Hz), 0.96-0.99 (t, 9H, *J* = 8.0 Hz), 1.65-1.70 (m, 1H), 1.89-1.95 (m, 1H), 2.34-2.42 (m, 2H), 2.30 (s, 6H), 2.36 (s, 6H), 3.37-3.38 (m, 1H), 3.74-3.78 (m, 1H), 5.02-5.07 (m, 2H), 5.74-5.80 (m, 1H), 6.76 (s, 2H), 7.04 (s, 2H), 7.25 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.88, 6.88, 21.26, 21.31, 23.11, 41.47, 46.42, 58.96, 65.85, 116.41, 125.56, 126.26, 129.59, 131.37, 136.08, 137.38, 137.40, 137.59, 140.40,

167.47; IR (thin film) 2957, 1595, 1458, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{30}H_{46}NOSi$ *m/z* 464.3349 (M+1), meas 464.3363. $[\alpha]^{23}_{D}$ = –31.7 (*c* = 1.0, CH_2Cl_2) on (*4R, 6S*)-**47d**.

6.3.4 Diastereoselective aza-Cope rearrangement with (*S*)-2-((tert-butyldimethylsilyl) oxy)propanal 51



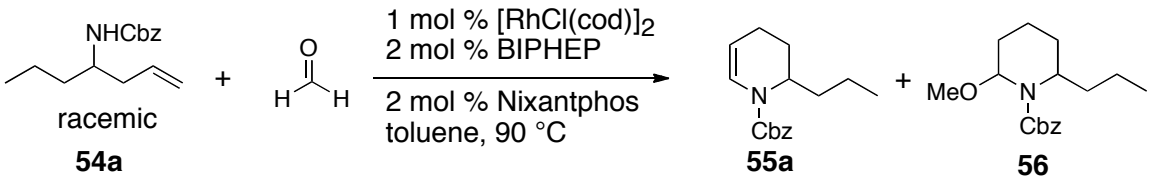
aza-Cope rearrangement with (S)-VANOL catalyst. (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal **51** (21 mg, 0.11 mmol) was subjected to the diastereoselective aza-Cope rearrangement according to the procedure for **46a** except (S)-VANOL was used. Purification by column chromatography on silica gel (EtOAc/hexanes 1:40) afforded a mixture of the rearrangement products **52+53** as a viscous oil in 71% yield (32 mg, 0.071 mmol). The diastereoselective ratio of the reaction was determined to be 12:1 by ^{1}H NMR analysis of the crude reaction mixture and the ratio was unchanged after purification. The following spectral data were collected on a 12:1 ratio of isomers. R_f = 0.20 (1:40 ethyl acetate /hexanes). *Spectral data for diastereomer **52***: ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.15 (s, 3H), 0.02 (s, 3H), 0.84 (s, 9H), 1.23-1.25 (d, 3H, *J* = 6.5 Hz), 2.31 (s, 6H), 2.35 (s, 6H), 2.42-2.44 (m, 2H), 3.40-3.42 (m, 1H), 3.77-3.79 (m, 1H), 4.95-5.03 (m, 2H), 5.67-5.72 (m, 1H), 6.80 (s, 2H), 7.02 (s, 2H), 7.24 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (C=N missing) δ -4.99, -4.72, 17.99, 18.15, 19.02, 21.30, 25.83, 35.10, 67.47, 71.29, 115.66, 125.91, 126.27, 127.73,

129.37, 131.24, 133.90, 137.23, 137.39, 137.84, 140.59; IR (thin film) 2958, 1594, 1462, 1199 cm^{-1}; HRMS (ES+) calcd for $C_{29}H_{44}NOSi$ *m/z* 450.3192 (M+1), meas 450.3181. $[\alpha]^{23}_{D}$ = +14.2 (*c* = 1.0, CH_2Cl_2) on **52**.

aza-Cope rearrangement with (R)-VANOL catalyst. Chiral aldehyde (*S*)-**51** (21 mg, 0.11 mmol) was also subjected to the aza-Cope rearrangement with 5 mol% (*S*)-VANOL derived BOROX catalyst according to the procedure described for (*S*)-VANOL derived catalyst above. Purification by flash column chromatography (1:40 EtOAc/hexanes) was complete in 5 min and gave a mixture of the rearrangement products **52+53** as a viscous oil in 71% yield (32 mg, 0.071 mmol). The diastereoselective ratio of the reaction with (*R*)-VANOL was determined to be 2.5:1 by ^{1}H NMR analysis of the crude reaction mixture and was not changed after purification. R_f = 0.20 (1:30 ethyl acetate /hexanes). The following spectral data for **53** was extracted from the spectra data of the 2.5:1 mixture with the aid of the 12:1 mixture described above. *Spectral data for diastereomer **53**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.12-1.13 (d, 3H, *J* = 6.5 Hz), 2.31 (s, 6H), 2.35 (s, 6H), 2.42-2.44 (m, 2H), 3.29-3.32 (m, 1H), 3.96-3.99 (m, 1H), 4.95-5.03 (m, 2H), 5.67-5.72 (m, 1H), 6.78 (s, 2H), 7.00 (s, 2H), 7.23 (s, 2H).

6.3.5 Optimization of the intramolecular amidocarbonylation with formaldehyde

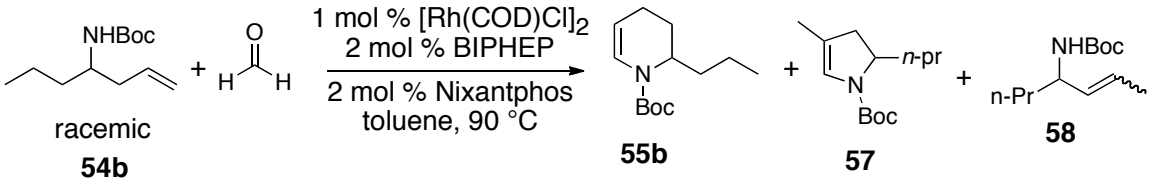
I. Typical procedure for intramolecular amidocarbonylation with formalin



To a 50 mL Schlenk flask equipped with a T-shaped threaded high vacuum Teflon valve, containing a stirring bar, was added $[RhCl(cod)]_2$ (2.5 mg, 0.0050 mmol), BIPHEP (5.5 mg, 0.010 mmol), Nixantphos (6.0 mg, 0.010 mmol) and 3 mL of toluene under nitrogen. After adding racemic **54a**[70] (0.12 g, 0.50 mmol) and 37% formalin (0.19 mL, 2.5 mmol), the mixture was deoxygenated by the freeze-pump-thaw method (–196 °C to 25 °C, 3 cycles). The Schlenk flask was sealed under vacuum with Teflon valve at –196 °C and then warmed to room temperature. The flask was then heated to 90 °C and stirring continued for 22 h. Upon completion, ^{1}H NMR analysis on the crude reaction mixture showed the formation of the desired product **55a** and the by-product **56** with a ratio of 5:3. The formation of **56** was due to the presence of 15% methanol as a stabilizer in the commercial formalin. The mixture was concentrated and the major product purified by column chromatography on silica gel (1:12 EtOAc/hexanes) to afford compound **55a** as a viscous oil in 46% yield (60 mg, 0.23 mmol). R_f = 0.20 (1:12 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H NMR spectrum. *Spectral data for **55a**:* ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.84-0.94 (m, 3H), 1.24-1.40 (m, 3H), 1.49-1.53 (m, 1H), 1.69-1.83 (m, 1H), 1.91-1.96 (m, 1H), 2.02-2.07 (m, 1H), 4.24 (brs, 0.4H), 4.33 (brs, 0.5H), 4.81 (brs, 0.5H), 4.92 (brs, 0.4H), 5.16 (s, 2H), 6.72-6.74 (d, 0.5H, *J* = 6.5 Hz). 6.82-6.83 (d, 0.4H, *J* = 6.5 Hz), 7.30-7.37 (m, 5H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 13.92, 13.99, 17.37, 17.54, 19.11, 23.90, 24.03, 32.63, 33.05, 50.16, 50.38, 67.25, 105.84, 106.21, 123.52, 123.99, 127.89, 127.99, 128.29, 128.42, 136.35, 136.43, 152.92, 153.45. IR (thin film) 3020, 2872, 1705, 1415, 1327 cm^{-1}. HRMS (ES+) calcd for $C_{16}H_{22}NO_2$ *m/z* 260.1651 (M+1), meas 260.1659. Compound **56** was observed in the ^1H NMR spectrum of the crude reaction mixture but was not isolated, but the following absorptions have been reported for this compound: d = 3.25 (s, 1.5H), 3.32 (s, 1.5H), 4.19 (s, 0.5H), 4.27 (s, 0.5 H).[70]

II. Typical procedure for intramolecular amidocarbonylation with paraformaldehyde

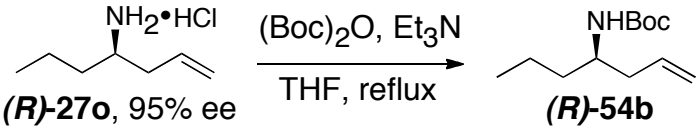


To a 50 mL Schlenk flask, containing a stirring bar, was added $[RhCl(cod)]_2$ (10 mg, 0.020 mmol), BIPHEP (22 mg, 0.040 mmol), Nixantphos (24 mg, 0.040 mmol) and 12 mL of toluene under nitrogen. After adding racemic **54b**[71] (0.42 g, 2.0 mmol) and paraformaldehyde (0.30 g, 10 mmol), the mixture was deoxygenated by the freeze-pump-thaw method (–196 °C to 25 °C, 3 cycles). The Schlenk flask was sealed under vacuum with the Teflon valve at –196 °C and then warmed to room temperature. The flask was then heated to 90 °C and stirring continued for 24 h. Upon completion, the mixture was concentrated and the products purified by column chromatography on silica gel (1:40 EtOAc/hexanes). Compound **55b** was obtained as a viscous oil in 73% yield

(0.33 g, 1.5 mmol). R_f = 0.25 (1:40 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H NMR spectrum. *Spectral data for **55b**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz), 1.24-1.42 (m, 4H), 1.46 (s, 9H), 1.63-1.78 (m, 2H), 1.88-2.06 (m, 2H), 4.13 (brs, 0.44H), 4.26 (brs, 0.5H), 4.73 (bs, 0.55H), 4.84 (brs, 0.40H), 6.64 (d, 0.5H, *J* = 7.0 Hz), 6.78 (d, 0.4H, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.06, 19.21, 23.99, 24.27, 28.35, 32.74, 33.22, 49.42, 50.33, 80.21, 104.61, 105.08, 123.96, 124.33; IR (thin film) 2961, 1703, 1653, 1410 cm^{-1}; HRMS (ES+) calcd for $C_{13}H_{24}NO_2$ *m/z* 226.1729 (M+1), meas 226.1723. Compound **57** was isolated as a viscous oil in 13% yield (58 mg, 0.26 mmol). R_f = 0.18 (1:40 ethyl acetate /hexanes) and the ^{1}H NMR spectrum revealed the presence of a 2:3 mixture of rotamers. *Spectral data for **57**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.5 Hz), 0.95-1.78 (m, 4H), 1.45 (s, 9H), 1.65 (s, 3H), 2.08 (brs, 1H), 2.73 (brs, 1H), 4.02 (brs, 0.4H), 4.10 (brs, 0.6H), 6.10 (brs, 0.6H), 6.22 (brs, 0.4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.02, 18.05, 28.49, 36.45, 37.10, 40.45, 41.34, 57.46, 79.45, 117.1, 123.96; IR (thin film) 2965, 1704, 1653, 1418 cm^{-1}; HRMS (ES+) calcd for $C_{13}H_{24}NO_2$ *m/z* 226.1729 (M+1), meas 226.1732. Compound **58** was isolated as a viscous oil in 12% yield (51 mg, 0.24 mmol). *Spectral data for **58**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.0 Hz), 1.32-1.39 (m, 4H), 1.47 (s, 9H), 1.69 (d, 3H, *J* = 7.0 Hz), 4.03 (brs, 1H), 4.43 (brs, 1H), 5.32-5.36 (m, 1H), 5.56-5.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.87, 17.60, 18.96, 28.41, 37.88,

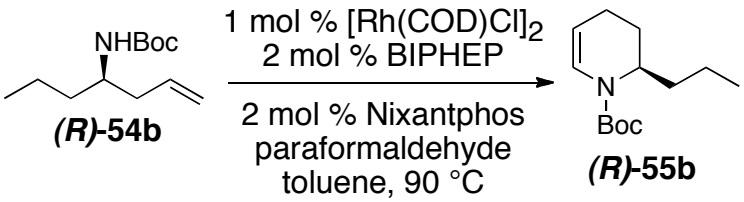
52.12, 78.99, 125.55, 132.11, 155.34; IR (thin film) 3342, 3005, 2964, 1690, 1522 cm^{-1}; HRMS (ES+) calcd for $C_{12}H_{24}NO_2$ *m/z* 214.1729 (M+1), meas 214.1725.

6.3.6 Total synthesis of (-)-Coniine



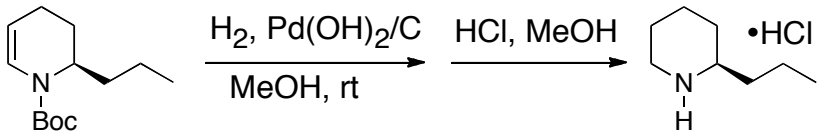
***(R)*-27o**, 95% ee ***(R)*-54b**

To a 100 mL round-bottomed flask was added amine **27o** (0.34 g, 3.0 mmol) and $(Boc)_2O$ (0.75 g, 3.3 mmol). The mixture was dissolved in THF (30 mL), followed by the addition of triethylamine (0.9 mL, 6 mmol). The mixture was stirred at room temperature for 24 hours. Upon completion, the mixture was concentrated and the product was purified by column chromatography on silica gel (1:12 EtOAc/hexanes) to afford (*R*)-*tert*-butyl hept-1-en-4-ylcarbamate **(*R*)-54b** in 76% yield (0.46 g, 2.3 mmol) as a colorless oil. R_f = 0.20 (1:12 ethyl acetate /hexanes). *Spectral data for (**R**)-**54b**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 8.0 Hz), 1.26-1.40 (m, 13H), 2.11-2.22 (m, 2H), 3.60 (brs, 1H), 4.30 (brs, 1H), 5.01-5.05 (m, 2H), 5.70-5.76 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.92, 19.11, 28.37, 36.84, 39.53, 49.77, 78.84, 117.45, 134.56, 155.54. IR (thin film) 3341, 3005, 2961, 1687, 1525 cm^{-1}. $[\alpha]^{23}_D$ = +15.8 (*c* = 1.0, $CDCl_3$) on material derived from 95% ee (***R*)-27o.**



***(R)*-54b** ***(R)*-55b**

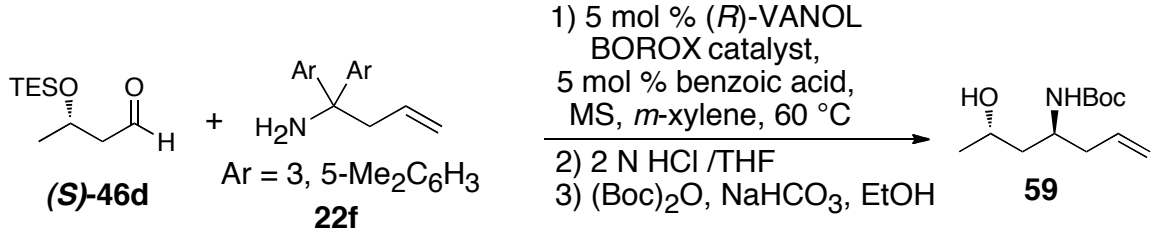
(*R*)-*tert*-butyl hept-1-en-4-ylcarbamate **(*R*)-54b** (0.250 g, 1.25 mmol) was reacted with paraformaldehyde according to the general procedure described in 6.3.5. The reaction was complete in 40 hours. Upon completion, the reaction mixture was concentrated and the product was purified by column chromatography on silica gel (1:40 EtOAc/hexanes) to afford (*R*)-**55b** in 71% yield (0.20 g, 0.89 mmol) as a colorless oil. R_f = 0.20 (1:40 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H and ^{13}C NMR spectrum. *Spectral data for* (*R*)-**55b***:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz), 1.24-1.42 (m, 4H), 1.46 (s, 9H), 1.63-1.78 (m, 2H), 1.88-2.06 (m, 2H), 4.13 (brs, 0.44H), 4.26 (brs, 0.5H), 4.73 (brs, 0.55H), 4.84 (brs, 0.40H), 6.64 (d, 0.5H, *J* = 7.0 Hz), 6.78 (d, 0.4H, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (carbonyl missing) δ 14.06, 17.62, 19.21, 23.99, 24.27, 28.35, 32.74, 33.22, 49.42, 50.33, 80.21, 104.61, 105.08, 123.96, 124.33. IR (thin film) 2961, 1703, 1653, 1410 cm^{-1}. $[\alpha]^{23}_D$ = –60.3 (*c* = 1.0, $CDCl_3$) on material derived from 95% ee (***R*)-54b**.



***(R)*-55b** (*R*)-Coniine **35**

To a 100 mL round bottom flask fitted with a magnetic stir bar was added (*R*)-**55b** (0.2 g, 0.9 mmol), $Pd(OH)_2$ (0.400 g, 0.225 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, *ca*. 60% moisture) and methanol (27 mL). The flask was then equipped with a 3-way valve connected to vacuum and a hydrogen balloon. The flask was opened to vacuum for a few seconds, and then switched to the hydrogen balloon; this manipulation was repeated three times. The reaction mixture was allowed to stir at room temperature for 12 h. It was then filtered through a Celite pad and to the methanol solution was then added 2 mL of 2N HCl at room temperature. Stirring was continued for 6 hours and the mixture was concentrated thereafter by rotary evaporation to give (*R*)-Coniine hydrochloride salt **35** which was further dried at 40 °C under vacuum until no weight loss was observed to give a white solid in 91 % yield (0.13 g, 0. 82 mmol, mp 213-215 °C, lit.[23] 215-216 °C). *Spectral data for **35**[23]:* ^{1}H NMR (DMSO, 500 MHz) δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.29-1.49 (m, 5H), 1.59-1.82 (m, 5H), 2.81 (dd, 1H, *J* = 22.5, 11.0 Hz), 2.95 (brs, 1H), 3.15 (d, 1H, *J* = 12.5 Hz), 8.46 (d, 2H, *J* =9.3 Hz); ^{13}C NMR (125 MHz, DMSO) δ 13.74, 17.78, 21.71, 21.81, 27.76, 34.94, 43.68, 55.39. $[\alpha]^{23}_D$ = – 6.3 (*c* = 1.0, EtOH) on material derived from 95% ee (***R***)**-55b**. These data match that previously reported[23] for this compound.

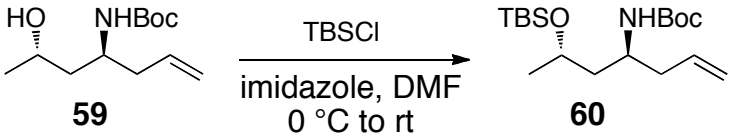
6.3.7 Total synthesis of (+)-Sedridine



***(S)*-46d** **22f** **59**

(*S*)-3-((Triethylsilyl)oxy)butanal **46d** (0.70 g, 2.5 mmol) was subjected to the aza-Cope rearrangement according to the general procedure described in section III except that 0.7 g of 5Å MS was used. Upon completion, *m*-xylene was removed by rotary evaporation and the reaction mixture was dissolved in THF (10 mL) and 2N HCl (5.0 mL) was added for hydrolysis. Hydrolysis was finished in 12 h and THF was then removed by rotary evaporation. To the residue was added another 4 mL of H_2O and the aqueous phase was washed with EtOAc (3 mL x 3). The aqueous phase was concentrated to give an off-white solid which was dissolved in EtOH (20 mL). $NaHCO_3$ and $(Boc)_2O$ were added at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then the ice-bath was removed. Stirring was maintained for 24 h at room temperature. Upon completion, EtOH was removed and the residue was dissolved in 20 mL of H_2O. The aqueous phase was extracted with EtOAc (10 mL x 3). The organic phases were combined and dried over Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel (1:4 EtOAc/hexanes) to give *tert*-butyl ((4*S*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **59** as a light yellow viscous oil and as a single diastereomer in 72% yield (0.41 g, 1.8 mmol) over three steps. R_f = 0.20 (1:4 ethyl acetate /hexanes). *Spectral data for **59**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, 3H, *J* = 6.0 Hz), 1.29-1.53 (m, 11 H), 2.16-2.23 (m, 2H), 3.76 (brs, 1H), 3.86 (brs, 1H), 4.50 (brs, 1H), 5.05-5.10 (m, 2H), 5.70-5.77 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.70, 28.31, 39.71, 45.58, 46.88, 63.58, 79.85, 118.06, 134.08, 157.08. IR (thin film)

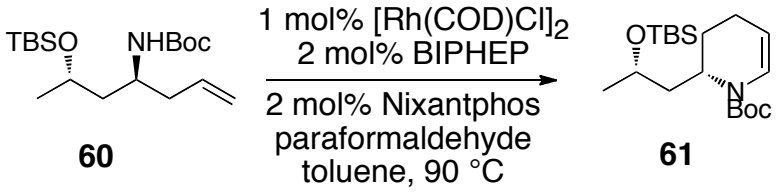
3339, 3078, 2976, 1684, 1531 cm^{-1}. HRMS (ES+) calcd for $C_{12}H_{24}NO_3$ *m/z* 230.1756 (M+1), meas 230.1752. $[\alpha]^{23}_D$ = +22.9 (*c* = 1.0, CH_2Cl_2) on **59**.



59 **60**

tert-Butyl ((4*S*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **59** (0.62 g, 2.7 mmol) and TBSCl (0.48 g, 3.2 mmol) were dissolved in 7 mL of dry DMF. Imidazole (0.23 g, 3.2 mmol) was added at 0 °C. The ice-bath was then removed and the reaction mixture was stirred at room temperature for 18 h. Upon completion, 40 mL of brine was added to quench the reaction. Stirring was maintained for 5 minutes and the aqueous phase was extracted with hexanes (8 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel (1:8 EtOAc/hexanes) to give *tert*-butyl ((4*S*, 6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **60** in 86% yield (0.80 g, 2.3 mmol) as a white solid (mp 63-64 °C). R_f = 0.50 (1:8 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in ^{1}H NMR spectra. *Spectral data for **60**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (t, 6H, *J* = 4.5 Hz), 0.87 (s, 9H), 1.12 (d, 3H, *J* = 6.0 Hz), 1.40 (s, 9H), 1.57-1.61 (m, 1H), 2.19-2.23 (m, 1H), 2.30 (brs, 2H), 3.71, (brs, 1H), 3.98 (brs, 1H), 4.97 (brs, 1H), 5.01-5.05 (m, 2H), 5.72-5.77 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.91, -4.17, 17.93, 23.94, 25.90, 28.41, 39.64, 42.67, 47.80, 66.10, 78.63, 117.22, 134.90, 155.38. IR (thin film) 3316, 2926, 1691, 1531, 1365 cm^{-1}. HRMS (ES+) calcd for

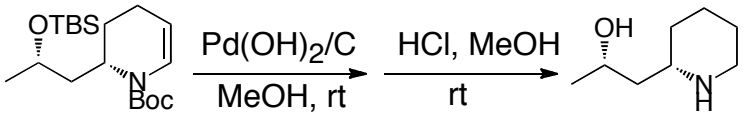
$C_{18}H_{38}NO_3Si$ *m/z* 344.2621 (M+1), meas 344.2625. $[\alpha]^{23}_D$ = +49.4 (*c* = 1.0, CH_2Cl_2) on **60**.



60 **61**

tert-Butyl ((4*S*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **60** (0.51 g, 1.5 mmol) was subjected to the intramolecular amidocarbonylation with paraformaldehyde according to the typical procedure in 6.3.5. Purification by column chromatography on silica gel (1:30 EtOAc/hexanes) afforded (*S*)-*tert*-butyl 2-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2*H*)-carboxylate **61** in 78% yield (0.410 g, 1.17 mmol) as a colorless oil. R_f = 0.30 (1:30 ethyl acetate /hexanes). A 5:4 mixture of rotamers was observed in the ^{1}H NMR spectrum. *Spectral data for **61**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (t, 6H, *J* = 4.5 Hz), 0.87 (s, 9H), 1.14 (d, 3H, *J* = 4.0 Hz), 1.45-1.52 (m, 10H), 1.64-1.68 (m, 2H), 1.77-1.83 (m, 1H), 1.90-1.94 (m, 1H), 2.02-2.09 (m, 1H), 3.87 (t, 1H, *J* = 6.0 Hz), 4.07 (brs, 0.4H, rotamer), 4.28 (brs, 0.5H), 4.73 (brs, 0.5H), 4.84 (brs, 0.4H, rotamer), 6.62 (d, 0.5H, *J* = 8.0 Hz), 6.76 (d, 0.4H, *J* = 8.0 Hz, rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.71, -4.66, -4.48, 17.33, 17.66, 18.04, 23.44, 23.77, 23.87, 24.39, 25.84, 25.87, 28.30, 28.44, 40.73, 40.95, 47.70, 48.85, 66.63, 80.24, 80.38, 104.47, 104.71, 123.97, 124.35, 151.80, 152.26 . IR (thin film) 2927,

1699, 1367, 1169 cm^{-1}. HRMS (ES+) calcd for $C_{19}H_{38}NO_3Si$ *m/z* 356.2621 (M+1), meas 356.2606. $[\alpha]^{23}_D$ = – 7.5 (*c* = 1.0, CH_2Cl_2) on **61**.

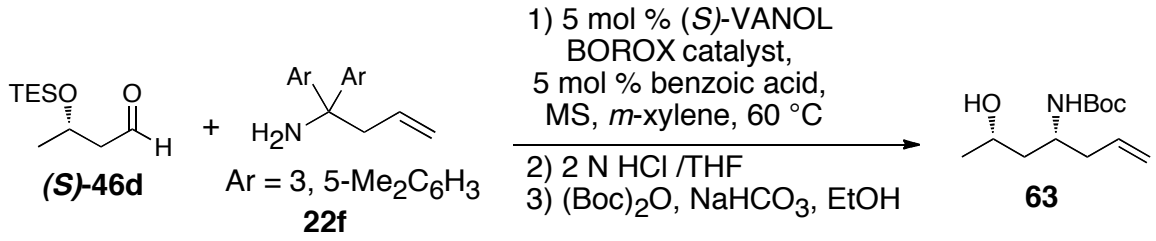


61 (+)-Sedridine, **62**

To a 100 mL round bottom flask fitted with a magnetic stir bar was added (*S*)-*tert*-butyl 2-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2*H*)-carboxylate **61** (0.39 g, 1.1 mmol), $Pd(OH)_2$ (0.49 g, 0.27 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, *ca*. 60% moisture) and methanol (32 mL). The flask was then equipped with a 3-way valve connected to vacuum and a hydrogen balloon. The flask was opened to vacuum for a few seconds, and then switched to the hydrogen balloon; this manipulation was repeated three times. The reaction mixture was allowed to stir at room temperature for 12 h. It was then filtered through a Celite pad and to the methanol solution was then added 2 mL of 2N HCl at room temperature. Stirring was continued for 6 hours and the mixture was concentrated thereafter by rotary evaporation to give (+)-Sedridine hydrochloride salt as a white solid which was dissolved in 10 mL of 1N NaOH and extracted with EtOAc (3 mL x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give (+)-Sedridine in 83% yield (0.13 g, 0.91 mmol) as a white solid (mp 82-83 °C, lit. 83-84 °C[72]). *Spectral data for **(+)-Sedridine**[72]:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 6.0 Hz), 1.31-1.35 (m, 3H), 1.7-1.43 (m, 1H), 1.50-1.55 (m, 3H), 1.76-1.77 (m, 1H), 2.58 (td, 1H, *J* =12.0, 3.0 Hz), 2.81-2.83 (m,

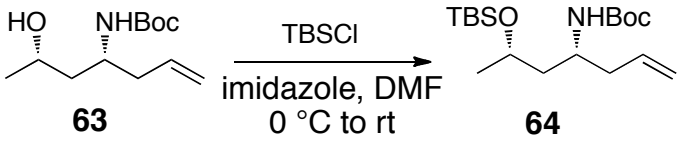
1H), 3.01 (dd, 1H, *J* = 11.5, 2.5 Hz), 3.05-3.35 (brs, 1H), 4.04-4.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.57, 24.73, 26.10, 31.38, 43.81, 46.90, 54.74, 65.04; $[\alpha]^{23}_{D}$ = +20.8 (*c* = 1.0, EtOH), Lit.[73] $[\alpha]^{25}_{D}$ = +28.36, (*c* = 1.13, EtOH). These spectral data match that reported for this compound.[73]

6.3.8 Total synthesis of (+)-Allosedridine



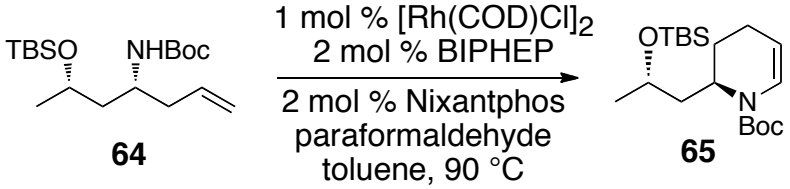
(+)-Allosedridine was obtained in a similar manner to that described for (+)-sedridine utilizing the boroxinate catalyst **9** derived from (*S*)-VANOL. (*S*)-3-((Triethylsilyl)oxy)butanal (0.56 g, 2.0 mmol) was subjected to the aza-Cope rearrangement according to the general procedure described for the synthesis of compound **59** except that (*S*)-VANOL BOROX catalyst was used. Purification by column chromatography on silica gel (1:2 EtOAc/hexanes) afforded *tert*-butyl ((4*R*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **63** in 60% yield (0.28 g, 1.2 mmol) and as a single diastereomer as a light yellow viscous oil. R_f = 0.20 (1:2 ethyl acetate /hexanes). *Spectral data for **63**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, 3H, *J* = 6.0 Hz), 1.45 (s, 9H), 1.53-1.65 (m, 2H), 2.24-2.31 (m, 2H), 2.48 (brs, 1H), 3.76 (brs, 1H), 3.94 (t, 1H, *J* =5.0 Hz), 4.61 (brs, 1H), 5.09-5.13 (m, 2H), 5.74-5.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.81, 28.38, 40.21, 44.31, 48.69, 66.48, 79.50, 118.10, 134.11, 156.2. IR (thin film)

3339, 2978, 1686, 1527 cm^{-1}. HRMS (ES+) calcd for $C_{12}H_{24}NO_3$ *m/z* 230.1756 (M+1), meas 230.1765. $[\alpha]^{23}_D$ = – 7.4 (*c* = 0.5, CH_2Cl_2) on **63**.



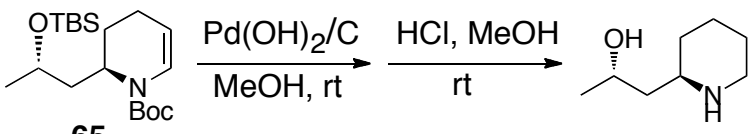
63 **64**

tert-Butyl ((4*R*,6*S*)-6-hydroxyhept-1-en-4-yl)carbamate **63** (0.25 g, 1.1 mmol) was reacted with TBSCl as described for the synthesis of compound **60**. Purification of the product by column chromatography on silica gel (1:8 EtOAc/hexanes) afforded *tert*-butyl ((4*R*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **64** in 74% yield (0.28 g, 0.82 mmol) as a clear viscous oil. R_f = 0.40 (1:8 ethyl acetate /hexanes). *Spectral data for **64**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.02 (s, 6H), 0.81 (s, 9H), 1.10 (d, 3H, *J* = 6.0 Hz), 1.35 (s, 9H), 1.48 (brs, 2H), 2.18 (brs, 2H), 3.56-3.58 (m, 1H), 3.82 (q, 1H, *J* = 6.0 Hz), 4.55 (brs, 1H), 4.99 (d, 2H, *J* = 12.5 Hz), 5.66-5.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.82, -4.38, 17.93, 23.81, 25.83, 28.31, 39.79, 44.37, 48.27, 66.82, 78.67, 117.51, 134.38, 155.29. IR (thin film) 2959, 1705, 1498, 1174 cm^{-1}. HRMS (ES+) calcd for $C_{18}H_{38}NO_3Si$ *m/z* 344.2621 (M+1), meas 344.2631. $[\alpha]^{23}_D$ = – 10.2 (*c* = 1.0, CH_2Cl_2) on **64**.



64 **65**

tert-Butyl ((4*R*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)hept-1-en-4-yl)carbamate **64** (0.26 g, 0.75 mmol) was subjected to intramolecular amidocarbonylation with paraformaldehyde according to the typical procedure in 6.3.5. Purification of the product by column chromatography on silica gel (1:30 EtOAc/hexanes) afforded *(R)-tert-butyl 2-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2H)-carboxylate* **65** in 72% yield (0.19 g, 0.54 mmol) as a clear viscous oil. R_f = 0.30 (1:30 ethyl acetate /hexanes). A 1:1 mixture of rotamers was observed in the ^{1}H NMR spectrum. *Spectral data for **65**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.007 (s, 6H), 0.85 (s, 9H), 1.18-1.23 (m, 3H), 1.36-1.42 (m, 1H), 1.46 (s, 9H), 1.65-2.35 (m, 5H), 3.86 (d, 1H, *J* = 5.5 Hz), 4.23 (brs, 0.6H), 4.33 (brs, 0.4H), 4.77 (brs, 0.5H), 4.85 (brs, 0.5H), 6.62 (d, 0.4H, *J* = 7.0 Hz), 6.77 (d, 0.5H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.85, -4.55, -4.29, 17.61, 17.84, 18.10, 23.49, 24.07, 24.19, 25.34, 25.88, 28.38, 28.51, 29.68, 40.30, 41.14, 46.69, 47.84, 65.50, 66.26, 80.23, 80.36, 104.87, 105.15, 124.08, 152.11, 152.46. IR (thin film) 2957, 1705, 1653, 1410 cm^{-1}. HRMS (ES+) calcd for $C_{19}H_{38}NO_3Si$ *m/z* 356.2621 (M+1), meas 356.2629 $[\alpha]^{23}_D$ = +25.1 (*c* = 0.5, CH_2Cl_2) on **65**.



65 (+)-Allosedridine, **66**

*(R)-tert-Butyl-2-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-3,4-dihydropyridine-1(2H)-carboxylate **65*** (0.17 g, 0.50 mmol) was subjected to the reduction conditions followed

by hydrolysis to remove the protecting groups as described for the synthesis of (+)-Sedridine. The product was obtained in 74% yield (52 mg, 0.37 mmol) as white crystals (mp 65-66 °C, lit. 62 °C[73]). *Spectral data for **(+)-Allosedridine**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01-1.06 (m, 1H), 1.08 (d, 3H, *J* = 6.0 Hz), 1.11-1.26 (m, 2H), 1.41-1.49 (m, 2H), 1.53-1.59 (m, 2H), 1.74-1.78 (m, 1H), 2.50-2.56 (m, 1H), 2.63-2.68 (m, 1H), 2.98 (dd, 1H, *J* = 10, 4.5 Hz), 3.93-3.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.80, 24.48, 27.36, 34.37, 44.40, 45.99, 58.14, 69.03. $[\alpha]^{23}_{D}$ = +15.0 (*c* = 1.0, MeOH), Lit.[73] $[\alpha]^{25}_{D}$ = +17.10, (*c* = 1.55, MeOH).

6.4 Supporting information for chapter 5

6.4.1 General information

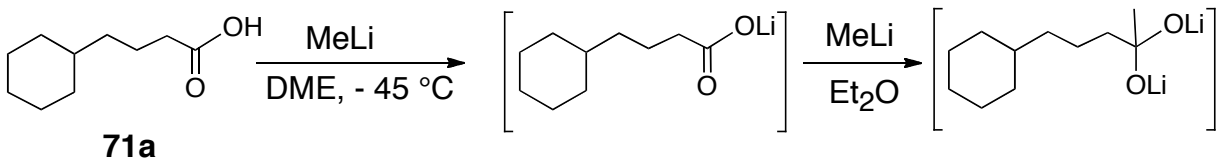
All experiments were performed under an argon atmosphere. Flasks were flame-dried and cooled under argon before use. All solvents such as benzene, dichloromethane, ether, triethylamine, toluene, THF, DMF and CH3CN were dried if used in the reaction. ACS-grade hexanes and ethyl acetate were used as purchased. Triphenylborate and trimethylsilyldiazomethane were used as purchased from Aldrich. Cyclohexanebutyric acid, hex-5-ynoic acid, 5-ethoxy-5-oxopentanoic acid, 4-bromobutanoic acid, and levulinic acid were used as purchased. VAPOL and VANOL were purified by column chromatography with 9:1 hexanes/ethyl acetate.

Melting points were measured on a Thomas Hoover capillary melting point apparatus. 1H NMR and 13C NMR were recorded on a Varian 300 MHz or VXR-500 MHz instrument in CDCl3 unless otherwise noted. CHCl3 was used as the internal standard for both 1H NMR (δ = 7.24) and 13C NMR (δ = 77.0). Column chromatography

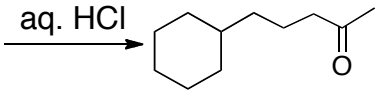
was performed with silica gel 60 (230–450 mesh). Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol.

HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation.

6.4.2 General procedure for the preparation of diazoketones with the azide transfer method



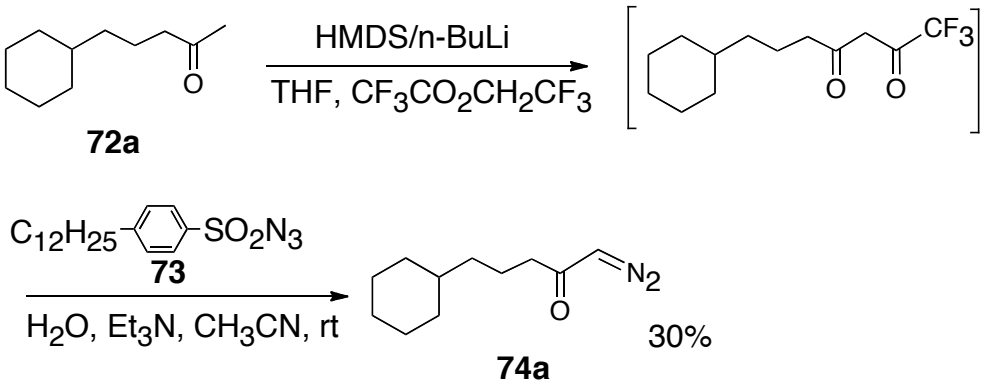
71a



72a

Procedure for the synthesis of 5-cyclohexylpentan-2-one **72a***:* The following procedure is adapted from one for related methyl ketones.[74] To a flame-dried 100 mL round-bottomed flask, fitted with a magnetic stirrer and an argon balloon was added DME (7.5 mL) and MeLi (7.5 mL, 12 mmol) at – 45°C. A solution of cyclohexanebutyric acid **71a** (1.7 g, 10 mmol) in DME (7.5 mL) was added dropwise. The mixture was allowed to stir for 2 h, followed by the addition of MeLi (7.5 mL, 12 mmol) at 0°C. Stirring was continued at room temperature for 3 hours. Then the mixture was siphoned into a vigorously stirred flask charged with conc HCl (1.8 mL) and H_2O (30 mL). The mixture was stirred for about 30 min, and then NaCl was added to saturate the solution,

followed by the separation of the organic and aqueous phases. The aqueous phase was washed with Et_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the product by column chromatography on silica gel (1:25 ether /pentane) gave the pure methyl ketone **72a** as a clear oil in 49% isolated yield (0.82 g, 4.9 mmol). *Spectral data for **72a**:* R_f = 0.25 (1:25 ether /pentane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70–0.88 (m, 2H), 1.02–1.22 (m, 6H), 1.43–1.62 (m, 7H), 2.03 (s, 3H), 2.36–2.40 (t, 2H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.83, 27.12, 26.94, 31.22, 32.28, 36.63, 38.45, 40.55, 208.12.

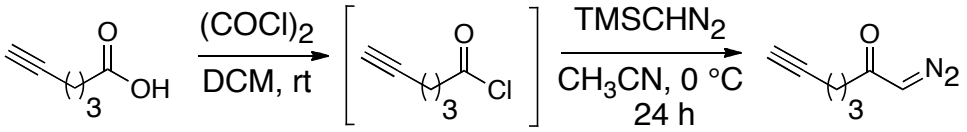


*Procedure for the synthesis of 5-cyclohexyl-1-diazopentan-2-one **74a**:* The following procedure is adapted from one for related diazoketone.[75] To a 250 mL round bottomed flask was added dry tetrahydrofuran (25 mL) and 1,1,1,3,3,3-hexamethyldisilazane (16.5 mmol, 3.89 mL). The mixture was then cooled to 0 °C while n-butyllithium (16.5 mmol, 7.01 mL) in hexane was added dropwise. After stirring for 10 min, the resulting solution was cooled to –78°C, and a solution of methyl ketone (2.52 g, 15.0 mmol) in dry tetrahydrofuran (25 mL) was added slowly over 10 min. Stirring was continued for 30 min at –78°C, and then 2,2,2-trifluoroethyl trifluoroacetate (16.5 mmol, 2.48 mL) was

added rapidly via syringe (over 5 sec). After 10 min, the reaction mixture was poured into a separatory funnel containing 5% aqueous hydrochloric acid (50 mL) and diethyl ether (25 mL). The aqueous layer was separated and extracted with diethyl ether. The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude product was immediately dissolved in acetonitrile (23 mL). Water (0.25 mL), triethylamine (22.5mmol, 3.20 mL), and a solution of 4-dodecylbenzenesulfonyl azide[76] (7.88 g, 22.5 mmol) in acetonitrile (23 mL) were then added to the solution. The mixture was allowed to stir at room temperature for 12 h and then was poured into a separatory funnel containing diethyl ether (23 mL) and aqueous 5% sodium hydroxide. The organic phase was separated, washed successively with 5% aq NaOH, water and saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. Purification of the product by column chromatography on silica gel (1:4 ethyl acetate/hexane) gave 5-cyclohexyl-1-diazopentan-2-one **74a.** Pure product is only obtained if the column chromatography is repeated at least two times which then gives **74a** as a yellow oil in 30% isolated yield (0.87 g, 4.5 mmol). *Spectral data for **74a**[77]:* R_f = 0.25 (1:4 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75–0.83 (m, 2H), 1.01–1.20 (m, 6H), 1.50–1.63 (m, 7H), 2.21 (bs, 2H), 5.21 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.82, 26.52, 26.84, 33.42, 37.13, 37.65, 41.55, 54.32, 195.53.

6.4.3 General procedure for the synthesis of diazo ketone 8a-k with trimethylsilyldiazomethane ($TMSCHN_2$) as a stable and safe substitute for

diazomethane – Illustrated for the synthesis of 5-cyclohexyl-1-diazopentan-2-one 74d.

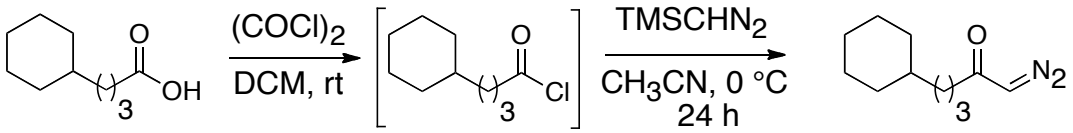


71d **74d**

The following procedure is one that is modified from that reported by Shroiri in that it uses only 1.1 equiv of $TMSCHN_2$ and workup with sat aq $NaHCO_3$ is not employed.[78,79] A 250 mL flame-dried round-bottomed flask with stir bar was charged with hex-5-ynoic acid **71d** (1.7 g, 15 mmol) and CH_2Cl_2 (15 mL). Oxalyl chloride $(COCl)_2$ (2.85 g, 22.5 mmol) was then added slowly at room temperature. Stirring was continued for 1 h, and then the reaction mixture was concentrated by rotary evaporation to give a brown liquid which can be used for the next step without further purification.

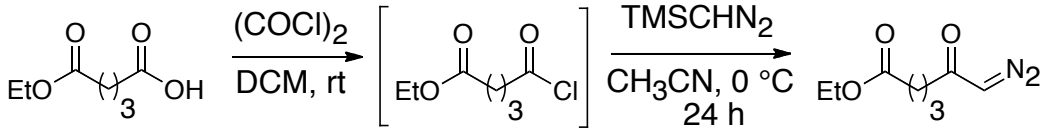
The residual from the above step was dissolved in CH_3CN (75 mL), followed by the addition of $TMSCHN_2$ (16.5 mmol, 8.3 mL) at 0°C. The reaction mixture was allowed to stir for 24 h. Volatiles were then removed by rotary evaporation. Purification of the product by column chromatography on silica gel (1:6 ethyl acetate/hexane) gave the pure 1-diazohept-6-yn-2-one **74d** as a yellow oil in 66% isolated yield (1.35 g, 9.9 mmol). When the reaction was run at room temperature according to the general procedure described above, a 60% yield of compound **74d** was obtained. *Spectral data for **74d***[80]: R_f = 0.2 (1:6 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, CDCl3) δ 1.57–

1.61 (m, 2H), 1.82–1.83 (m, 1H), 2.00-2.03 (m, 2H), 2.23 (bs, 2H), 5.24 (bs, 1H); ^{13}C NMR (125 MHz, CDC_{l3}) δ 17.24, 32.10, 38.67, 53.94, 68.87, 82.82, 193.76.



71a **74a**

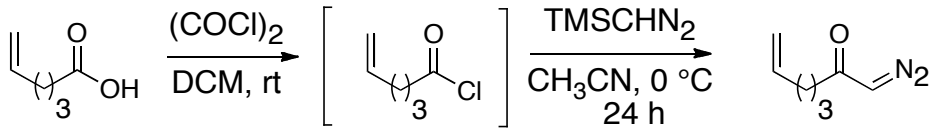
*5-cyclohexyl-1-diazopentan-2-one **74a**:* cyclohexanebutyric acid **71a** (0.34g, 2.0 mmol) was reacted according to the general procedure described above except that the reaction mixture from the second step was quenched with sat. $NaHCO_3$, extracted with ether and dried over $NaSO_4$. Purification of **74a** by column chromatography on silica gel (1:4 ethyl acetate/hexane) gave the pure *5-cyclohexyl-1-diazopentan-2-one **74a*** as a yellow oil in 73% isolated yield (0.28 g, 1.5 mmol). The same reaction at room temperature gave **74a** in 59% yield and the same reaction at 25 °C with 2.0 equiv of $TMSCHN_2$ gave 62% yield.



71b **74b**

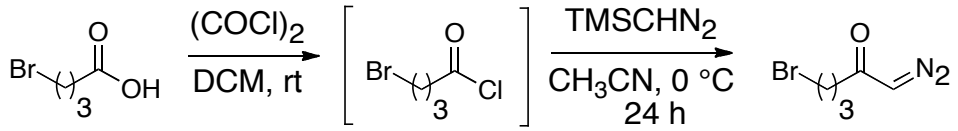
*ethyl 6-diazo-5-oxohexanoate **74b***: 5-ethoxy-5-oxopentanoic acid **71b** (0.32g, 2.0 mmol) was reacted according to the general procedure described above except that the reaction mixture from the second step was quenched with sat. $NaHCO_3$, extracted with ether and dried over $NaSO_4$. Purification of **74b** by column chromatography on silica gel

(1:3 ethyl acetate/hexane) gave the pure ethyl 6-diazo-5-oxohexanoate **74b** as a yellow oil in 70% isolated yield (0.26 g, 1.4 mmol). When the reaction was run at room temperature according to the same procedure, a 91% yield of compound **74b** was obtained. *Spectral data for **74b***[81]: R_f = 0.2 (1:3 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14–1.17 (t, 3H, *J* = 7.0 Hz), 1.82–1.88 (m, 2H), 2.25-2.29 (m, 4H), 4.00-4.05 (q, 2H, *J* = 7.0 Hz), 5.23 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.00, 20.03, 33.08, 39.47, 54.27, 60.16, 172.77, 193.88.



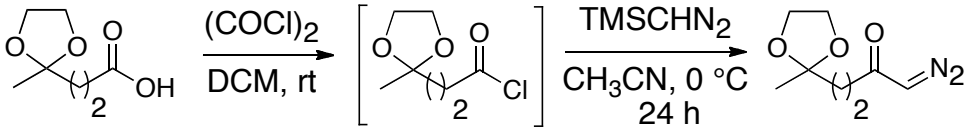
71c **74c**

*1-diazohept-6-en-2-one **74c**:* Hex-5-enoic acid[82] **71c** (1.6 g, 14 mmol) was reacted according to the general procedure described above. Purification of **74c** by column chromatography on silica gel (1:6 ethyl acetate/hexanes) gave the pure diazoketone as a clear yellow liquid in 69% isolated yield (1.28 g, 9.00 mmol). When the reaction was run at room temperature according to the general procedure described above, a 65% yield of compound **74c** was obtained. *Spectral data for **74c***[83]: R_f = 0.2 (1:6 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56–1.62 (m, 2H), 1.93–1.97 (m, 2H), 2.19 (bs, 2H), 4.83-4.91 (m, 2H), 5.21 (bs, 1H), 5.96-5.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.88, 32.72, 39.78, 53.75, 114.53, 137.28, 194.66. These data match that reported for this compound.



71e **74e**

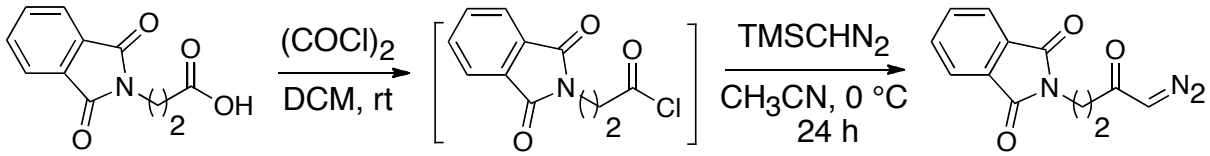
*5-bromo-1-diazopentan-2-one **74e**:* 4-bromobutanoic acid **71e** (0.33 g, 2.0 mmol) was reacted according to the general procedure described above. Purification of **74e** by column chromatography on silica gel (1:6 ethyl acetate/hexanes) gave the pure diazoketone as a clear yellow liquid in 78% isolated yield (0.30 mg, 1.6 mmol). Compound **74e** gradually turned orange at room temperature after evaporation of solvent by rotary evaporator to remove most of the solvent. The yield was calculated from the ^{1}H NMR spectrum after integration of solvent peaks. Removing all solvents by high vacuum was detrimental to the compound. Therefore, this compound should be used immediately after purification by column chromatography. *Spectral data for **74e**[84]*: R_f = 0.2 (1:6 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13-2.18 (m, 2H), 2.48 (bs, 2H), 3.41-3.44 (m, 2H), 5.27 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.55, 33.07, 37.75, 54.68, 193.21.



71f **74f**

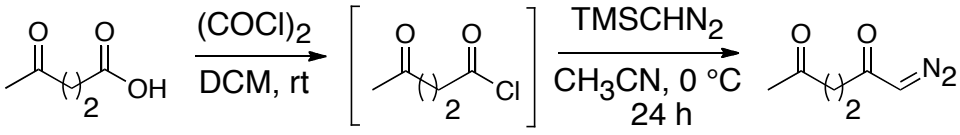
*1-diazo-4-(2-methyl-1,3-dioxolan-2-yl)butan-2-one **74f**: tert*-butyldimethylsilyl 3-(2-methyl-1,3-dioxolan-2-yl)propanoate[85] (0.15 g, 1.8 mmol) was reacted according to the general procedure described above with the exception that a few drops of DMF were

added for the preparation of acid chloride. Purification of **74f** by column chromatography on silica gel (1:1 ethyl acetate/hexanes) gave the pure diazoketone as a clear yellow liquid in 52% isolated yield (170 mg, 0.920 mmol). *Spectral data for **74f***[86]: R_f = 0.20 (1:1 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.93–1.96 (t, 2H, *J* = 7.5 Hz), 2.35 (bs, 2H), 3.83-3.91 (m, 4H), 5.21 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.37, 24.09, 33.89, 54.45, 64.91, 109.40, 194.63.



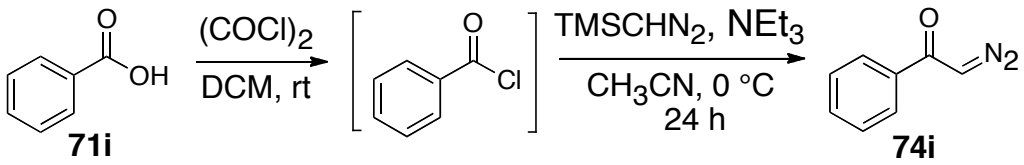
71g **74g**

2-(4-diazo-3-oxobutyl)isoindoline-1,3-dione ***74g****:* 3-(1,3-dioxoisoindolin-2-yl)propanoic acid[87] **71g** (0.88 g, 4.0 mmol) was reacted according to the general procedure described above. Purification of **74g** by column chromatography on silica gel (1:9 ethyl acetate/dichloromethane) gave the pure diazoketone as a light yellow solid (mp 126-128 ^{o}C) in 82% isolated yield (0.8 g, 3.3 mmol). *Spectral data for **74g***[88]: R_f = 0.2 (1:9 ethyl acetate /dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72 (bs, 2H), 3.96-3.99 (t, 2H, *J* = 7.5 Hz), 5.29 (bs, 1H), 7.66-7.70 (m, 2H), 7.78-7.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.70, 38.53, 55.25, 123.27, 131.96, 133.99, 167.97, 191.26.



71h **74h**

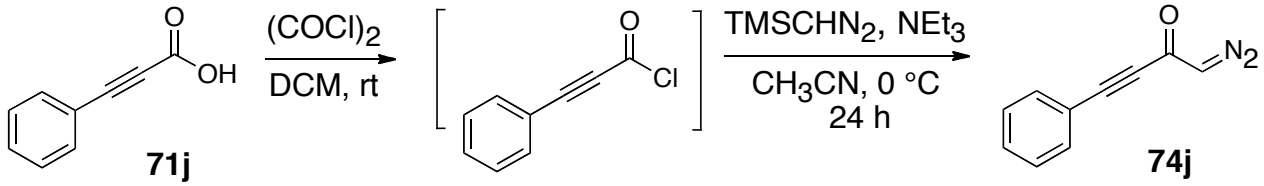
*1-diazohexane-2,5-dione **74h** was prepared as follow*: A flame-dried flask was charged with levulinic acid **71h** (0.23 g, 2.0 mmol) and THF (10 mL). Then 1.05 eq. of TEA was added at 0°C, followed by the addition of 1.05 eq of ethyl chloroformate. The mixture was stirred for 2 h. After filtration and concentration at reduced pressure, the anhydride was obtained which could be used in the next step without further purification. The anhydride was dissolved in CH_3CN (10 mL) at 0°C, followed by the addition of $TMSCHN_2$ (2.2 mmol, 1.1 mL). Stirring was continued overnight. The solvent was then removed by rotary evaporator. The residual was dissolved in ether, and washed with sat. $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated. Purification of **74h** by column chromatography on silica gel (1:1 ethyl acetate/hexanes) gave the pure diazoketone as a clear yellow liquid in 30% isolated yield (84 mg, 0.60 mmol). *Spectral data for **74h***[89]: R_f = 0.30 (1:1 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.56 (s, 2H), 2.75-2.78 (t, *J* = 6.0 Hz, 2H), 5.28 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.03, 35.41, 39.49, 53.94, 194.83, 207.82.



71i **74i**

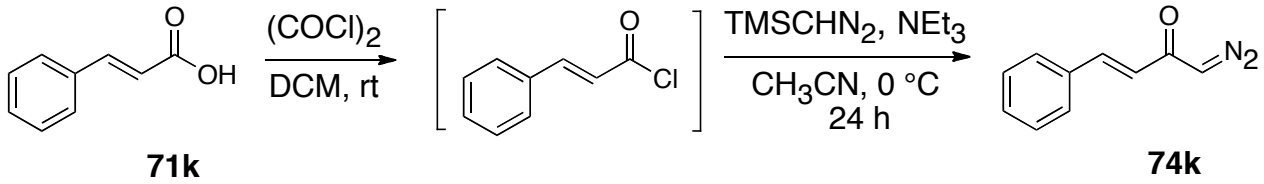
*2-diazo-1-phenylethanone **74i***: Benzoic acid **71i** (0.24 g, 2.0 mmol) was reacted according to the general procedure described above with the exception that 1.2 eq. of triethylamine was added after the addition of $TMSCHN_2$ (2.2 mmol, 1.1 mL). Purification

of **74i** by column chromatography on silica gel (1: 6 ethyl acetate/hexanes) gave the pure diazoketone as a yellow solid (mp 52-54 °C) in 55% isolated yield (160 mg, 1.10 mmol). *Spectral data for **74i**[90]:* R_f = 0.2 (1:6 ethyl acetate) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (bs, 1H), 7.37-7.41 (m, 2H), 7.47-7.50 (m, 1H), 7.71- 7.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.42, 126.89, 128.89, 132.95, 136.87, 186.61.



71j **74j**

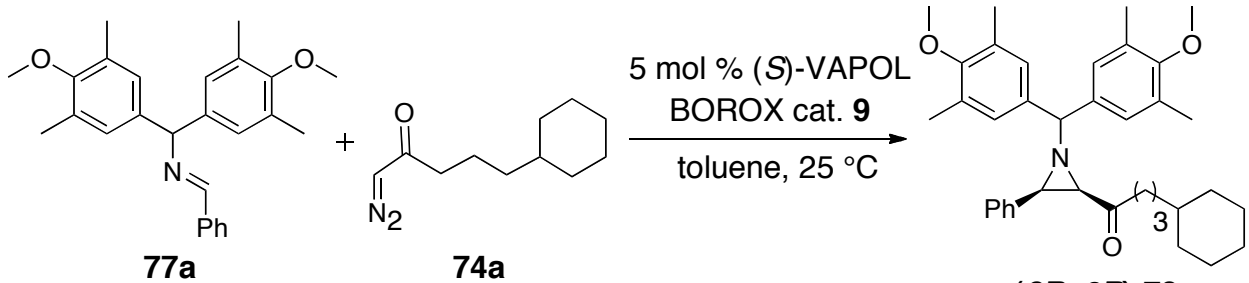
*1-diazo-4-phenylbut-3-yn-2-one **74j**:* Phenylpropiolic acid **71j** (0.29 g, 2.0 mmol) was reacted according to the general procedure described above with the exception that 1.2 eq. of triethylamine was added after the addition of $TMSCHN_2$. Purification of **74j** by column chromatography on silica gel (1: 9 ethyl acetate/hexanes) gave the pure diazoketone as a clear yellow liquid in 15% isolated yield (51 mg, 0.3 mmol). *Spectral data for **74j**[91]*: R_f = 0.2 (1:3 ethyl acetate /hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (bs, 1H), 7.34-7.42 (m, 3H), 7.51-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.92, 89.92, 96.34, 127.99, 128.83, 133.84, 135.82, 184.21.



71k **74k**

(E)-1-diazo-4-phenylbut-3-en-2-one ***74k***: (E)-cinnamic acid **71k** (0.3 g, 2 mmol) was reacted according to the general procedure described above with the exception that 1.2 eq. of triethylamine was added after the addition of $TMSCHN_2$. The ^1H NMR spectrum of the crude reaction mixture indicated that the desired diazo compound **74k** was not present due to the absence of the characteristic diazo methine peak at δ 5.6 that has been reported for this compound.[92]

6.4.5 General procedure for the catalytic asymmetric aziridination of diazo ketones 74a-g, j – Illustrated for the preparation of 1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethyl-phenyl)methyl)-3-phenylaziridin-2-yl)-4-cyclohexylbutan-1-one 78a



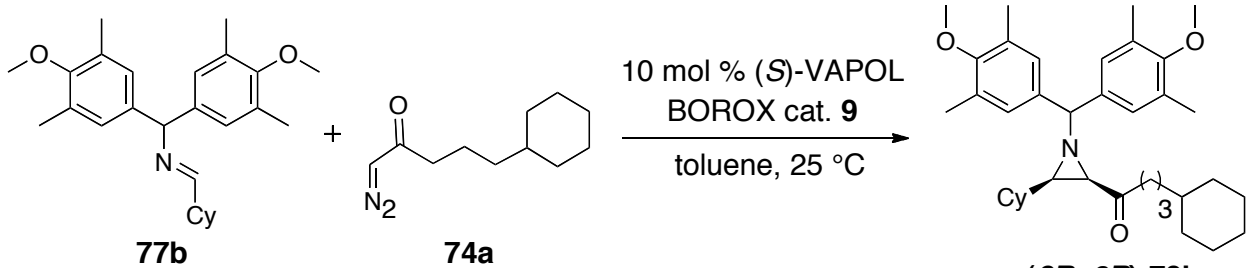
77a **74a** **(*2R, 3R*)-78a**

Procedure for catalyst preparation[93]*:* To a flame-dried 50 mL Schlenk flask, fitted with a magnetic stirrer and filled with argon, was added (*S*)-VAPOL (26.9 mg, 0.0500 mmol) and triphenylborate (58 mg, 0.20 mmol). Dry toluene (2 mL) was added under an argon flow, followed by the addition of water (0.9 µL, 0.05 mmol). After capping the flask, the mixture was heated at 80 ºC for 1 h with stirring. Thereafter a vacuum was gradually applied to remove solvent (0.05 mm Hg). The vacuum was maintained for 30 min at 80 ºC. Then the flask was cooled down under argon flow to room temperature.

Procedure for the aziridination reaction[93]*:* Aldimine **77a** (387 mg, 1.00 mmol) and dry toluene (2 mL) were added to this Schlenk flask under an argon flow. Thereafter, 5-

cyclohexyl-1-diazopentan-2-one **74a** (232 mg, 1.20 mmol) was added via syringe. Stirring was continued at room temperature for 24 h. The mixture was then diluted with 15 mL of hexanes and transferred to a 100 mL round bottom flask. The Schlenk flask was rinsed with dichloromethane. Concentration of the solvent followed by applying high vacuum (0.05 mm Hg) for 30 minutes provided the crude aziridine as an off-white solid. The *cis/trans* ratios were determined by the ^{1}H NMR spectrum of the crude reaction mixture by integration of the aziridine methine protons. The coupling constants of the cis (7-8 Hz) and the trans (2-3 Hz) were used to differentiate the two isomers. Purification of the product by column chromatography (35 mm x 400 mm column) on silica gel with an elutant mixture of ethyl acetate:hexanes (1:9) gave the pure aziridine (mp 45-47 °C) as a white solid in 72% isolated yield (400 mg, 0.72 mmol). *Cis/trans* ratio: 100:1. The optical purity of **78a** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 8.24 min (major enantiomer) and R_t = 6.70 min (minor enantiomer). *Spectral data for (2R, 3R)-**78a***: R_f = 0.15 (1:9 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60-1.30 (m, 11H), 1.45-1.65 (m, 5H), 1.85-2.00 (m, 1H), 2.21 (s, 6H), 2.24 (s, 6H), 2.56-2.59 (d, 1H, *J* = 7 Hz), 3.12-3.20 (d, 1H, *J* = 7 Hz), 3.59 (s, 1H), 3.63 (s, 3H), 3.67 (s, 3H), 7.12-7.14 (d, 4H, *J* = 7 Hz), 7.16-7.25 (m, 3H), 7.27-7.30 (d, 2H, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (1 sp^3 carbon missing) δ 16.09, 16.15, 20.09, 26.19, 26.56, 33.01,33.03, 36.58, 37.21, 40.87, 49.17, 52.74, 59.40, 59.43, 77.64, 127.23, 127.35, 127.65, 127.72, 127.90, 130.56, 130.58, 135.36, 137.71, 137.87, 155.98, 156.05, 207.09; IR (thin film) 2922s, 1697m, 1483s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel

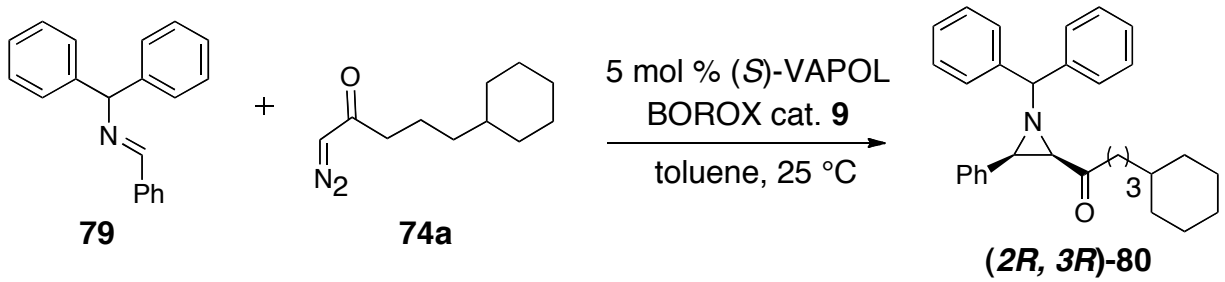
intensity) 553 M^+ (2), 283 (100), 269 (100), 238 (46); Anal calcd for $C_{37}H_{47}NO_3$: C, 80.25; H, 8.55; N, 2.53. Found: C, 79.73; H, 8.55; N, 2.32; $[\alpha]^{23}_D$ = +54.0 (*c* 1.0, CH_2Cl_2) on 99% ee material (HPLC).



77b **74a** (***2R, 3R***)**-78b**

1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridin-2-yl)-4-cyclohexylbutan-1-one ***78b***: Aldimine **77b** (275 mg, 0.700 mmol) was reacted with 5-cyclohexyl-1-diazopentan-2-one **74a** (163mg, 0.840 mmol) according to the general procedure described above with the exception that the catalyst loading was 10 mol%. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure aziridine as a viscous oil in 82% isolated yield (319 mg, 0.570 mmol). The optical purity of **78b** was determined to be 95% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 5.05 min (major enantiomer) and R_t = 5.98 min (minor enantiomer). *Spectral data for (2R, 3R)-****78b***: R_f = 0.15 (1:15 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.42-0.58 (m, 1H), 0.70-1.70 (m, 25H), 1.40-1.58 (t, 1H, *J* = 7.5 Hz), 2.21(s, 6H), 2.22 (s, 6H), 2.26-2.27 (d, 1H, *J* = 7.5 Hz), 2.40-2.50 (m, 2H), 3.30 (s, 1H), 3.64 (s, 3H), 3.66 (s, 3H), 6.96 (s, 2H), 7.03 (s, 2H); ^{13}C NMR (125 MHz,

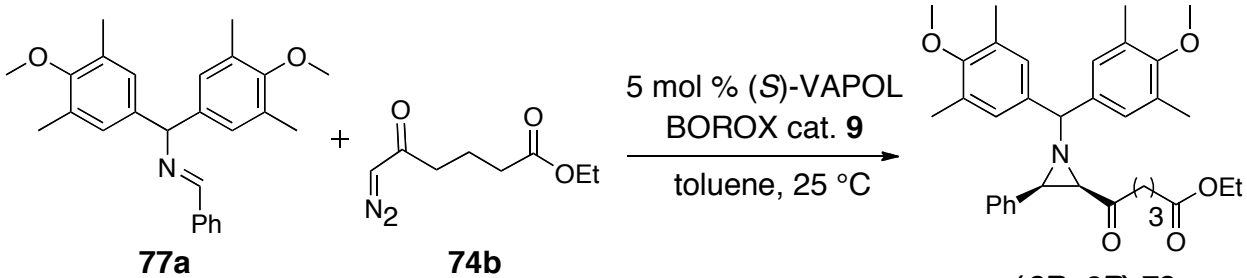
$CDCl_3$) (1 sp^3 carbon missing) δ 16.08, 16.19, 21.20, 25.40, 25.52, 26.13, 26.34, 26.65, 30.44, 30.98, 33.22, 33.24, 36.07, 37.01, 37.48, 42.41, 49.99, 54.85, 59.58, 59.66, 78.11, 127.35, 128.38, 130.34, 130.50, 137.77, 138.12, 155.83, 156.22, 207.77; IR (thin film) 2924s, 1701w, 1483s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 559 M^+ (0.77), 283 (100), 95 (16), 55 (38); Anal calcd for $C_{37}H_{53}NO_3$: C, 79.38; H, 9.54; N, 2.50. Found: C, 79.11; H, 9.26; N, 2.41; $[\alpha]^{23}_D$ = +91.8 (*c* 1.0, CH_2Cl_2) on 95% ee material (HPLC).



79 **74a** **(*2R, 3R*)-80**

*1-((2R,3R)-1-benzhydryl-3-phenylaziridin-2-yl)-4-cyclohexylbutan-1-one **80***: Aldimine **79** (271 mg, 1.00 mmol) was reacted with 6-diazo-5-oxohexanoate **74a** (232 mg, 1.20 mmol) according to the above mentioned procedure. Purification of the product by column chromatography on silica gel (1:15 ethyl acetate/hexanes) gave the pure aziridine (mp 138-139 °C) as a white solid in 66% isolated yield (289 mg, 0.66 mmol). The optical purity of **80** was determined to be 92% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 6.92 min (major enantiomer) and R_t = 10.64 min (minor enantiomer). *Spectral data for (2R, 3R)–**80***: R_f = 0.15 (1:15 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60-0.90 (m, 4H), 1.01-1.37 (m, 7H), 1.58-1.71 (m, 4H), 2.00-2.07 (m, 1H), 2.28-2.34 (m,

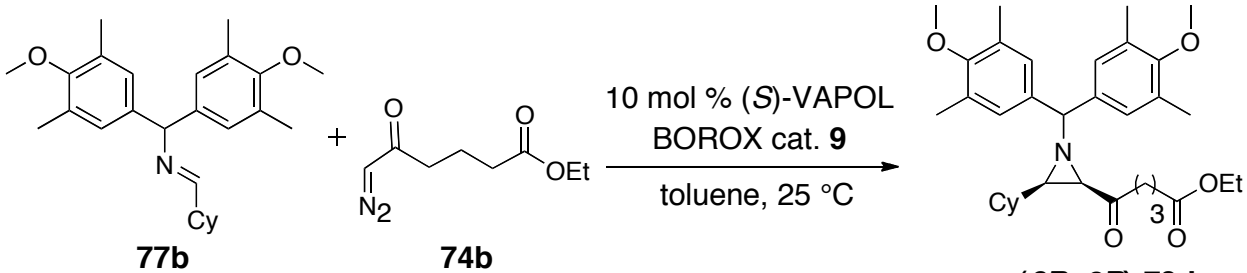
1H), 2.77-2.79 (d, 1H, *J* = 7 Hz), 3.33-3.52 (d, 1H, *J* = 7 Hz), 3.96 (s, 1H), 7.23-7.40 (m, 11H), 7.60-7.63 (t, 4H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (1 sp^2 and sp^3 carbon missing) δ 20.16, 26.29, 26.66, 33.07, 33.13, 36.60, 37.25, 40.95, 49.20, 52.85, 78.45, 127.25, 127.38, 127.43, 127.49, 127.53, 127.75, 128.07, 128.55, 135.19, 142.33, 142.50, 206.82; IR (thin film) 2918m, 1709s, 1653s, 1456w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 437 M^+ (1.82), 270 (100), 167 (95), 118 (43); Anal calcd for $C_{31}H_{35}NO$: C, 85.08; H, 8.06; N, 3.20. Found: C, 85.00; H, 7.89; N, 3.22; $[\alpha]^{23}_D$ = +55.5 (*c* 1.0, CH_2Cl_2) on 92% ee material (HPLC).



77a **74b** **(*2R, 3R*)-78c**

ethyl-5-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)-5-oxopentanoate ***78c****:* Aldimine **77a** (387 mg, 1.00 mmol) was reacted with *ethyl 6-diazo-5-oxohexanoate* **74b** (222 mg, 1.20 mmol) according to the above mentioned procedure. Purification of the product by column chromatography on silica gel (1:6 ethyl acetate/hexanes) gave the pure aziridine as a viscous oil in 76% isolated yield (412 mg, 0.760 mmol). The optical purity of **78c** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow 0.7mL/min). Retention times: R_t = 19.36 min (major enantiomer) and R_t = 28.56 min (minor

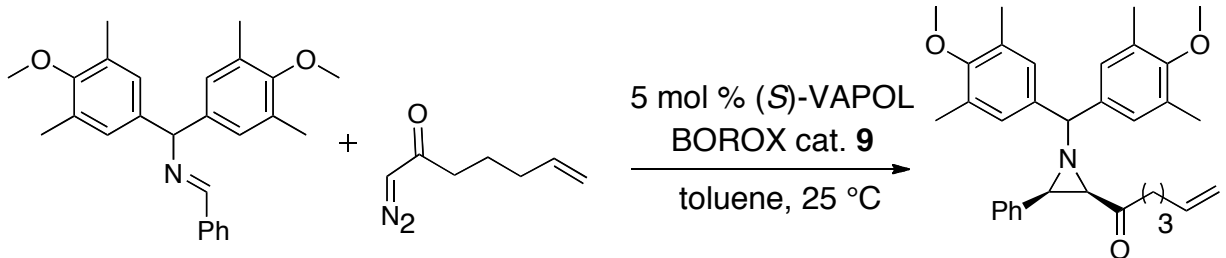
enantiomer). *Spectral data for (2R, 3R)–**78c***: R_f = 0.15 (1:6 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18-1.22 (t, 3H, *J* = 7 Hz), 1.40-1.65 (m, 2H), 1.80-2.15 (m, 3H), 2.24 (s, 6H), 2.26 (s, 6H), 2.27-2.30 (m, 1H), 2.61-2.63 (d, 1H, *J* = 7.5 Hz), 3.20-3.21 (d, 1H, *J* = 7.5 Hz), 3.63 (s, 1H), 3.65(s, 3H), 3.69 (s, 3H), 4.01-4.07 (q, 2H, *J* = 7 Hz), 7.15-7.31 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.11, 16.13, 16.16, 18.05, 33.02, 39.68, 49.20, 52.55, 59.48, 59.50, 60.04, 77.67, 127.34, 127.36, 127.65, 127.73, 128.00, 130.65, 130.71, 135.23, 137.65, 137.80, 156.06, 156.12, 172.95, 206.21; IR (thin film) 2934m, 1734s, 1653m, 1456s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 543 M^+ (0.12), 283 (100), 91 (24), 55 (14); Anal calcd for $C_{34}H_{41}NO_5$: C, 75.11; H, 7.60; N, 2.58. Found: C, 74.77; H, 7.71; N, 2.35; $[\alpha]^{23}_D$ = –52.4 (*c* 1.0, CH_2Cl_2) on 99% ee material (HPLC).



77b **74b** (***2R, 3R***)**-78d**

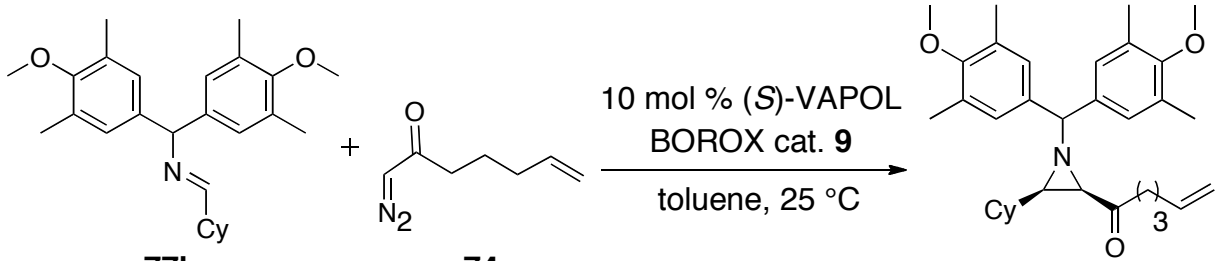
*ethyl5-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridin-2-yl)-5-oxopentanoate **78d*****:** Aldimine **77b** (196.5 mg, 0.5000 mmol) was reacted with *ethyl 6-diazo-5-oxohexanoate* **74b** (111 mg, 0.600 mmol) according to the above mentioned procedure with the exception that the catalyst loading was 10 mol%. Purification of the product by column chromatography on silica gel (1:5 ethyl acetate/hexanes) gave the

pure aziridine as a colorless viscous oil in 92% isolated yield (254 mg, 0.460 mmol). The optical purity of **78d** was determined to be 97% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow 0.7mL/min). Retention times: R_t = 8.37 min (major enantiomer) and R_t = 11.04 min (minor enantiomer). *Spectral data for (2R, 3R)–**78d***: R_f = 0.20 (1:5 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40-0.60 (m, 1H), 0.80-1.40 (m, 11H), 1.40-1.60 (m, 3H), 1.85-1.95 (m, 3H), 2.19 (s, 6H), 2.20 (s, 6H), 2.10-2.27 (m, 2H), 2.53-2.55 (m, 2H), 3.29 (s, 1H), 3.61 (s, 3H), 3.64 (s, 3H), 4.04-4.09 (q, 2H, *J* = 7 Hz), 6.96 (s, 2H), 7.02 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.06, 15.92, 16.00, 18.76, 25.22, 25.35, 25.96, 30.28, 30.83, 33.11, 36.04, 40.80, 49.77, 54.71, 59.40, 59.47, 60.12, 77.93, 127.17, 128.19, 130.21, 130.41, 137.61, 137.90, 155.72, 156.10, 172.91, 206.60; IR (thin film) 2928m, 1734s, 1485m, 1375w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 549 M^+ (0.62), 283 (100), 268 (14), 55 (10); Anal calcd for $C_{34}H_{47}NO_5$: C, 74.28; H, 8.62; N, 2.55. Found: C, 74.05; H, 8.78; N, 2.34; $[\alpha]^{23}_D$ = +86.3 (*c* 1.0, CH_2Cl_2) on 97% ee material (HPLC).



*1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)hex-5-en-1-one **78e***: Aldimine **77a** (387 mg, 1.00 mmol) was reacted with 1-diazohept-6-en-2-

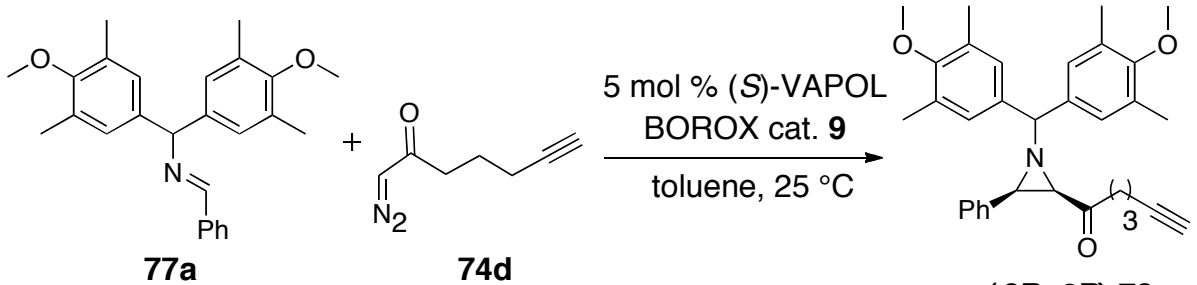
one **74c** (166 mg, 1.20 mmol) according to the general procedure described above. Purification of the product by column chromatographyon silica gel (1:12 ethyl acetate/hexanes) gave the pure aziridine as a colorless viscous oil in 77% isolated yield (380 mg, 0.770 mmol). The optical purity of **78e** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexanes:2-propanol, 222 nm, flow 0.5 mL/min). Retention times: R_t = 9.89 min (major enantiomer) and R_t = 8.22 min (minor enantiomer). *Spectral data for (2R, 3R)–**78e***: R_f = 0.15 (1:12 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27-1.31 (m, 1H), 1.39-1.43 (m, 1H), 1.73-1.79 (m, 2H), 1.99-2.06 (m, 1 H), 2.26-2.37 (m, 1 H), 2.28 (s, 6H), 2.31 (s, 6H), 2.65-2.67 (d, 1H, *J* = 7.5 Hz), 3.24-3.25 (d, 1H, *J* = 7.5 Hz), 3.67 (s, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 4.86-4.90 (m, 2H), 5.57-5.64 (m, 1H), 7.20-7.24 (m, 5H), 7.26-7.30 (m, 2H), 7.36-7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.15, 16.18, 21.96, 32.76, 39.91, 49.27, 52.76, 59.48, 59.51, 76.75, 114.67, 127.30, 127.40, 127.66, 127.75, 127.98, 130.64, 130.67, 135.34, 137.72, 137.85, 137.96, 156.03, 156.08, 206.91; IR (thin film) 3060w, 2934m, 1699m, 1485s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 497 M^+ (0.27), 283 (100), 91 (27), 41 (16); Anal calcd for $C_{33}H_{39}NO_3$: C, 79.64; H, 7.90; N, 2.81. Found: C, 79.37; H, 7.61; N, 2.67; $[\alpha]^{23}_D$ = +52.1 (*c* 1.0, CH_2Cl_2) on 99% ee material (HPLC).



77b **74c** **(*2R, 3R*)-78f**

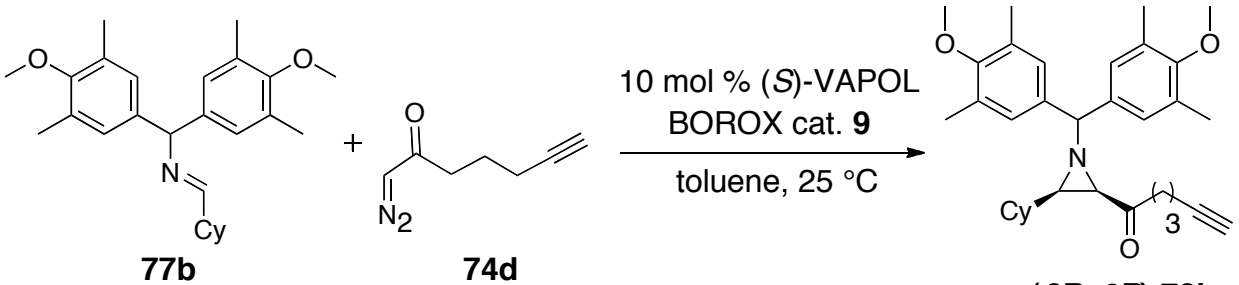
*1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridin-2-yl)hex-5-en-1-one **78f*****:** Aldimine **77b** (196.5 mg, 0.5000 mmol) was reacted with 1-diazohept-6-en-2-one **74c** (83 mg, 0.60 mmol) according to the general procedure described above with the exception that the catalyst loading was 10 mol%. Purification of the product by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure aziridine as a colorless viscous oil in 72% isolated yield (182 mg, 0.360 mmol). The optical purity of **78f** was determined to be 95% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 4.42 min (major enantiomer) and R_t = 5.47 min (minor enantiomer). *Spectral data for (2R, 3R)–**78f***: R_f = 0.2 (1:12 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.44-0.56 (m, 1H), 0.91-1.30 (m, 7H), 1.40-1.63 (m, 5H), 1.75-1.78 (t, 1H, *J* = 7.5 Hz), 1.98-2.00 (m, 2H), 2.21 (s, 6H), 2.22 (s, 6H), 2.27-2.28 (d, 1H, *J* = 7.5 Hz), 2.47-2.50 (t, 2H, *J* = 7.5 Hz), 3.30 (s, 1H), 3.64 (s, 3H), 3.65 (s, 3H), 4.91-4.96 (m, 2H), 5.68-5.74(m, 1H), 6.98 (s, 2H), 7.04 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.03, 16.12, 22.90, 25.34, 25.48, 26.08, 30.38, 30.94, 33.00, 36.05, 41.22, 49.92, 54.90, 59.53, 59.59, 78.08, 115.07, 127.32, 128.31, 130.30, 130.47, 137.73, 137.91, 138.02, 155.80, 156.18, 207.42; IR (thin film) 2928m, 1699m, 1483m, 1221m

cm^{-1}; mass spectrum, *m/z* (% rel intensity) 503 M^+ (0.82), 283 (100), 95 (30), 55 (59); Anal calcd for $C_{33}H_{45}NO_3$: C, 78.69; H, 9.00; N, 2.78. Found: C, 79.09; H, 8.89; N, 2.73; $[\alpha]^{23}_D$ = +96.4 (*c* 1.0, CH_2Cl_2) on 95% ee material (HPLC).



*1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)hex-5-yn-1-one **78g**:* Adimine **77a** (387 mg, 1.00 mmol) was reacted with 1-diazohept-6-yn-2-one **74d** (164 mg, 1.20 mmol) according to the general procedure described above. Purification of the product by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure aziridine as a colorless viscous oil in 89% isolated yield (440 mg, 0.890 mmol). The optical purity of **78g** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow 0.5 mL/min). Retention times: R_t = 15.61 min (major enantiomer) and R_t = 7.92 min (minor enantiomer). *Spectral data for (2R, 3R)–**78g***: R_f = 0.15 (1:12 ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 1.40-1.48 (m, 1H), 1.52-1.62 (m, 1H), 1.82-2.02 (m, 3H), 2.14-2.22 (m, 1H), 2.31 (s, 6H), 2.34 (s, 6H), 2.46-2.54 (m, 1H), 2.71-2.73 (d, 1H, *J* = 7.5 Hz), 3.29-3.31 (d, 1H, *J* = 7.5 Hz), 3.71 (s, 3H), 3.73 (s, 1H), 3.75 (s, 3H), 7.25-7.26 (m, 5H), 7.29-7.32 (m, 2H), 7.39-7.41(m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.05,

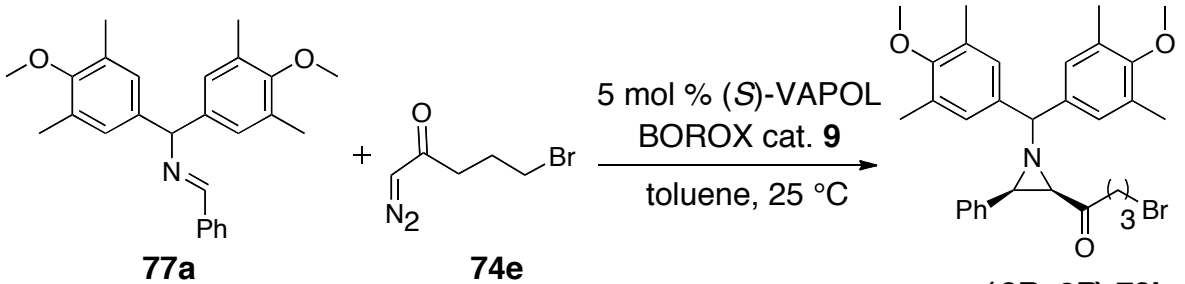
16.10, 17.42, 21.63, 39.31, 49.16, 52.52, 59.34, 59.37, 68.57, 77.55, 83.55, 127.25, 127.29, 127.57, 127.62, 127.93, 130.54, 130.61, 135.15, 137.62, 137.75, 155.96, 156.01, 206.18; IR (thin film) 2947m, 2118w, 1695s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 495 M^+ (0.18), 283 (100), 118 (79), 91 (77); HRMS (ES+) calcd for $C_{33}H_{38}NO_3$ *m/z* 496.2852 (M^++1), meas 496.2852; $[\alpha]^{23}_D$ = +45.6 (*c* 1.0, CH_2Cl_2) on 99% ee material (HPLC).



77b **74d** (***2R, 3R***)**-78h**

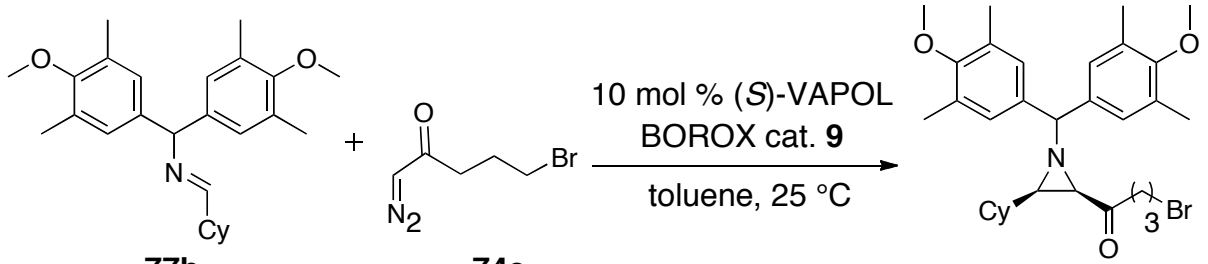
1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridin-2-yl)hex-5-yn-1-one ***78h****:* Aldimine **77b** (196.5 mg, 0.5000 mmol) was reacted with 1-diazohept-6-yn-2-one **74d** (82 mg, 0.60 mmol) according to the general procedure described above with the exception that the catalyst loading was 10 mol%. Purification of the product by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure aziridine as a colorless viscous oil in 79% isolated yield (199 mg, 0.390 mmol). The optical purity of **78h** was determined to be 96% ee by HPLC analysis (CHIRALCEL OD-H column, 99.5:0.5hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 9.24 min (major enantiomer) and R_t = 14.86 min (minor enantiomer). *Spectral data for (2R, 3R)–****78h***: R_f = 0.15 (1:12 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.46-0.58 (m, 1H), 0.84-1.22 (m, 5H), 1.26-1.38 (m, 2H),

1.40-1.60 (m, 3H), 1.69-1.82 (m, 3H), 1.85-1.90 (t, 1H, *J* = 7.5 Hz), 2.12-2.19 (m, 2H), 2.21 (s, 6H), 2.22 (s, 6H), 2.29-2.31 (d, 1H, *J* = 7.0 Hz), 2,63-2.64 (m, 2H), 3.31 (s, 1H), 3.64 (s, 3H), 3.65 (s, 3H), 6.99 (s, 2H), 7.05 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.96, 16.06, 17.60, 22.25, 25.25, 25.40, 25.99, 30.31, 30.87, 36.06, 40.33, 49.85, 54.79, 59.44, 59.50, 68.91, 77.96, 83.45, 127.22, 128.21, 130.24, 130.45, 137.67, 137.93, 155.71, 156.07, 206.98. IR (thin film) 2928m, 2118w, 1697w, 1483m, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 501 M^+ (0.19), 283 (100), 95 (26), 55 (33); HRMS (ES+) calcd for $C_{33}H_{44}NO_3$ *m/z* 502.3321(M^++1), meas 502.3287; $[\alpha]^{23}_D$ = +96.8 (*c* 1.0, CH_2Cl_2) on 96% ee material (HPLC).



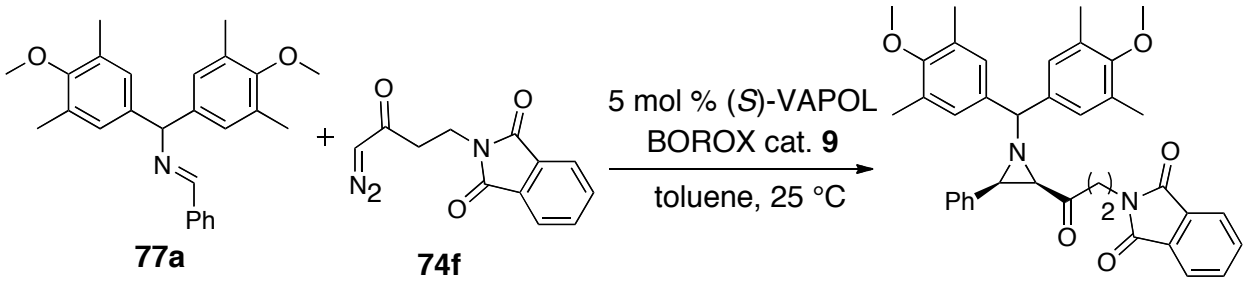
*1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)-4-bromobutan-1-one **78i**:* Aldimine **77a** (387 mg, 1.00 mmol) was reacted with 5-bromo-1-diazopentan-2-one **74e** (230 mg, 1.20 mmol) according to the general procedure described above. Purification of the product by column chromatography on silica gel (1:9 ethyl acetate/hexanes) gave the pure aziridine (mp 42-44°C) as a white solid in 85% isolated yield (469 mg, 0.850 mmol). The optical purity of **78i** was determined to be 95% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222

nm, flow 0.7 mL/min). Retention times: R_t = 14.06 min (major enantiomer) and R_t = 10.57 min (minor enantiomer). *Spectral data for (2R, 3R)–**78i***: R_f = 0.2 (1:9 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67-1.73 (m, 1H), 1.81-1.86 (m, 1H), 2.12-2.18 (m, 1H), 2.27 (s, 6H), 2.29 (s, 6H), 2.48-2.55 (m, 1H), 2.64-2.66 (d, 1H, *J* = 7.5 Hz), 3.03-3.14 (m, 2H), 3.24-3.26 (d, 1H, *J* = 7.0 Hz), 3.64 (s, 1H), 3.68 (s, 3H), 3.71 (s, 3H), 7.27-7.24 (m, 5H), 7.26-7.29 (m, 2H), 7.33-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.12, 16.20, 25.83, 32.93, 38.88, 49.18, 52.50, 59.43, 59.46, 77.62, 127.29, 127.39, 127.56, 127.65, 128.05, 130.64, 130.74, 135.07, 137.57, 137.70, 156.01, 156.04, 205.88; IR (thin film) 2880w, 1701s, 1485s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 551 M^+ (0.15, Br^{81}), 549 M^+ (0.28, Br^{79}), 283 (100), 253 (54), 118 (100); Anal calcd for $C_{31}H_{36}BrNO_3$: C, 67.63; H, 6.59; N, 2.54. Found: C, 67.28; H, 6.42; N, 2.40; $[\alpha]^{23}_D$ = –42.0 (*c* 1.0, CH_2Cl_2) on 95% ee material (HPLC).



*1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridin-2-yl)-4-bromobutan-1-one **78j***: Aldimine **77b** (196.5 mg, 0.5000 mmol) was reacted with 5-bromo-1-diazopentan-2-one **74e** (115 mg, 0.600 mmol) according to the general

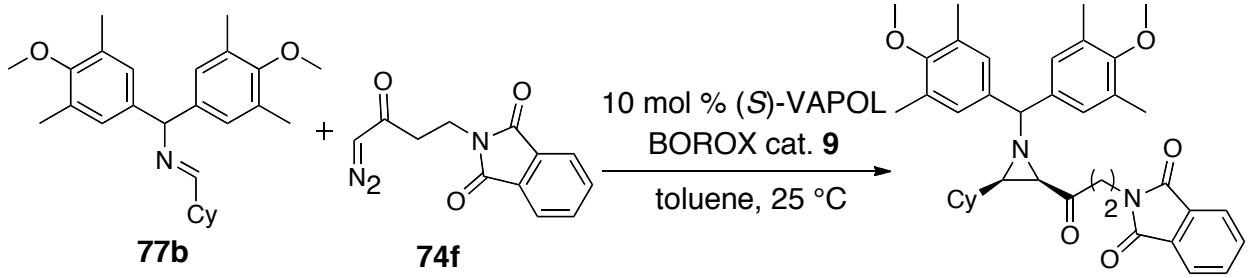
procedure described above with the exception that the catalyst loading was 10 mol%. Purification of the product by column chromatography on silica gel (1:12 ethyl acetate/hexanes) gave the pure aziridine as a colorless viscous oil in 61% isolated yield (170 mg, 0.310 mmol). The optical purity of **74e** was determined to be 92% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 6.58 min (major enantiomer) and R_t = 8.02 min (minor enantiomer). *Spectral data for (2R, 3R)–**74e***: R_f = 0.2 (1:15 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.51-0.53 (m, 1H), 0.90-1.1.16 (m, 5H), 1.28-1.1.59 (m, 5H), 1.77-1.81 (t, 1H, *J* = 7.0 Hz), 2.04-2.09 (m, 2H), 2.22 (s, 12H), 2.28-2.30 (d, 1H, *J* = 7.0 Hz), 2.67-2.71 (m, 2H), 3.31 (s, 1H), 3.37-3.39 (m, 2H), 3.67 (s, 3H), 3.73 (s, 3H), 6.98 (s, 2H), 7.05 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.02, 16.15, 25.28, 25.43, 26.37, 29.61, 30.34, 30.91, 33.18, 36.26, 39.81, 49.90, 54.81, 59.51, 59.57, 78.02, 127.23, 128.18, 130.32, 130.55, 137.63, 137.87, 155.77, 156.11, 206.44; IR (thin film) 2926s, 1701m, 1485s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 557 M^+ (0.06, ^{81}Br), 555 M^+ (0.11, ^{79}Br), 283 (100), 192 (39), 55 (39). Anal calcd for $C_{31}H_{42}BrNO_3$: C, 66.90; H, 7.61; N, 2.52. Found: C, 66.88; H, 7.96; N, 2.39. $[\alpha]^{23}_D$ = +85.6 (*c* 1.0, CH_2Cl_2) on 92% ee material (HPLC).



77a **74f** **(*2R, 3R*)-78k**

2-(3-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)-3-oxopropyl)-1H-indene-1,3(2H)-dione ***78k***: Aldimine **77a** (379 mg, 1.00 mmol) was reacted with 2-(4-diazo-3-oxobutyl)isoindoline-1,3-dione **74f** (292 mg, 1.20 mmol) according to the general procedure described above. Purification of the product by column chromatography on silica gel (1:2 ethyl acetate/hexanes) gave the pure aziridine (mp 134-136 ^{o}C) as a white solid in 85% isolated yield (550 mg, 0.850 mmol). The optical purity of **78k** was determined to be 98% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 38.18 min (major enantiomer) and R_t = 78.62 min (minor enantiomer). *Spectral data for (2R, 3R)–**78k***: R_f = 0.2 (1:2 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 6H), 2.29 (s, 6H), 2.40-2.47 (m, 1H), 2.70-2.71 (d, 1H, *J* = 7.0 Hz), 2.80-2.87 (m, 1H), 3.26-3.27 (d, 1H, *J* = 7.0 Hz), 3.58-3.71 (m, 3H), 3.65 (s, 3H), 3.69 (s, 3H), 7.07-7.10 (m, 1H), 7.17-7.21 (m, 6H), 7.30-7.32 (d, 2H, *J* = 7.5 Hz), 7.63-7.66 (m, 2H), 7.75-7.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.73, 31.93, 38.83, 49.06, 52.15, 59.25, 59.27, 60.07, 77.44, 122.81, 127.14, 127.23, 127.36, 127.46, 127.91, 130.46, 130.64, 131.77, 133.51, 134.72, 137.41, 137.60, 155.91, 155.92, 167.39, 204.02; IR (thin film) 2928m, 1716s, 1653m, 1485m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 602 M^+

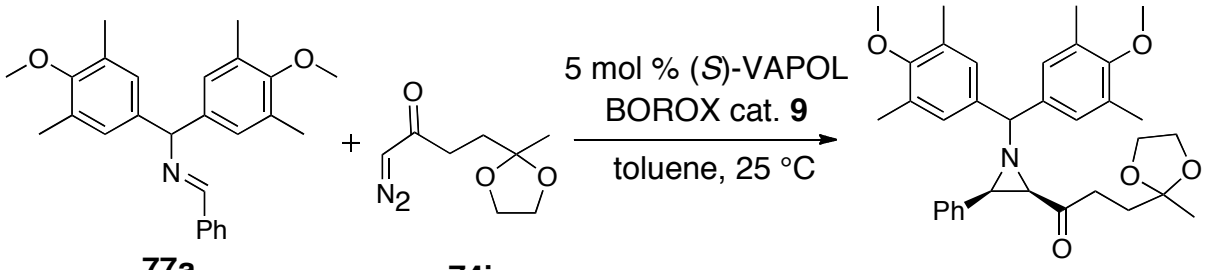
(1.03), 283 (100), 160 (75), 55 (62); Anal calcd for $C_{38}H_{38}N_2O_5$: C, 75.72; H, 6.35; N, 4.65. Found: C, 76.09; H, 6.68; N, 4.54; $[\alpha]^{23}_D$ = +50.9 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC).



77b **74f** (***2R, 3R***)**-78l**

2-(3-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridin-2-yl)-3-oxopropyl)-1H-indene-1,3(2H)-dione ***78l***: Aldimine **77b** (160 mg, 0.400 mmol) was reacted with 2-(4-diazo-3-oxobutyl)isoindoline-1,3-dione **74f** (97 mg, 0.48 mmol) according to the general procedure described above with the exception that the catalyst loading was 10 mol%. Purification of the product by column chromatography on silica gel (2:7 ethyl acetate/hexanes) gave the pure aziridine (mp 63-65 °C) as a white foamy solid in 63% isolated yield (150 mg, 0.25 mmol). The optical purity of **78l** was determined to be 87% ee by HPLC analysis (CHIRALCEL OD-H column, 97:3 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 13.18 min (major enantiomer) and R_t = 18.47 min (minor enantiomer). *Spectral data for (2R, 3R)–****78l***: R_f = 0.2 (2:7 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.45-0.47 (m, 1H), 0.82-1.08 (m, 6H), 1.20-1.29 (m, 2H), 1.37-1.49 (m, 2H), 1.71-1.74 (t, 1H, *J* = 7.0 Hz), 2.17 (s, 6H), 2.18 (s, 6H), 2.24-2.25 (d, 1H, *J* = 7.0 Hz), 2.92-2.97 (m, 2H), 3.28 (s, 1H),

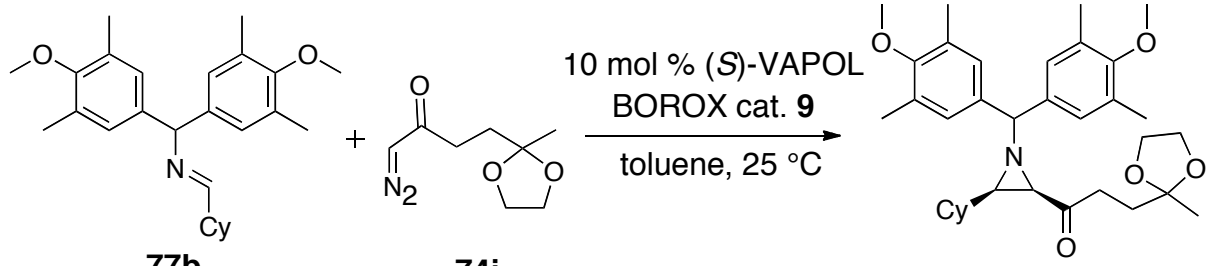
3.62 (s, 3H), 3.65 (s, 3H), 3.84-3.90 (m, 2H), 6.96 (s, 2H), 7.03 (s, 2H), 7.67-7.68 (m, 2H), 7.79-7.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.33, 16.41, 25.54, 25.65, 26.31, 30.62, 31.26, 33.05, 36.79, 40.09, 50.28, 54.95, 59.82, 59.89, 78.35, 123.45, 127.51, 128.48, 130.63, 130.95, 132.33, 134.18, 137.86, 138.23, 156.15, 156.45, 168.19, 205.18; IR (thin film) 2828m, 1772m, 1717s, 1485m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 608 M^+ (1.79), 283 (100), 160 (75), 55 (74); Anal calcd for $C_{38}H_{44}N_2O_5$: C, 74.97; H, 7.29; N, 4.60. Found: C, 75.06; H, 7.54; N, 4.50; $[\alpha]^{23}_D$ = +72.6 (*c* 1.0, CH_2Cl_2) on 87% ee material (HPLC).



77a **74j** **(*2R, 3R*)-78m**

1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)-3-(2-methyl-1,3-dioxolan-2-yl)propan-1-one ***78m****:* Aldimine **77a** (38.7mg, 0.100 mmol) was reacted with 1-diazo-4-(2-methyl-1,3-dioxolan-2-yl)butan-2-one **74j** (22.0 mg, 0.120 mmol) according to the general procedure described above. Purification of the product by column chromatography on silica gel (1:3 ethyl acetate/hexanes) gave the pure aziridine as a colorless viscous oil in 88% isolated yield (48 mg, 0.090 mmol). The optical purity of **78m** was determined to be 97% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t

= 13.31 min (major enantiomer) and R_t = 29.99 min (minor enantiomer). *Spectral data for (2R, 3R)–**78m***: R_f = 0.15 (1:3 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.42-1.48 (m, 1H), 1.60-1.66 (m, 1H), 2.01-2.07 (m, 1H), 2.24 (s, 6H), 2.25 (s, 6H), 2.32-2.39 (m, 1H), 2.62-2.63 (d, 1H, *J* = 7.5 Hz), 3.17-3.18 (d, 1H, *J*=7.0 Hz), 3.61 (s, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 3.68-3.70 (m, 2H), 3.80-3.82 (m, 2H), 7.14-7.20 (m, 5H), 7.21-7.24 (m, 2H), 7.30-7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.44, 16.46, 23.81, 31.92, 36.11, 49.50, 53.16, 59.80, 59.81, 64.70, 64.72, 78.07, 109.48, 127.57, 127.78, 127.98, 128.06, 128.29, 130.93, 130.98, 135.70, 137.99, 138.11, 156.36, 156.40, 206.51; IR (thin film) 2942m, 1653s, 1485s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 543 M^+ (0.42), 283 (100), 91 (71), 87 (90). Anal calcd for $C_{34}H_{41}NO_5$: C, 75.11; H, 7.60; N, 2.58. Found: C, 74.06 ; H, 7.89; N, 2.47. $[\alpha]^{23}_D$ = +42.1 (*c* 1.0, CH_2Cl_2) on 97% ee material (HPLC).

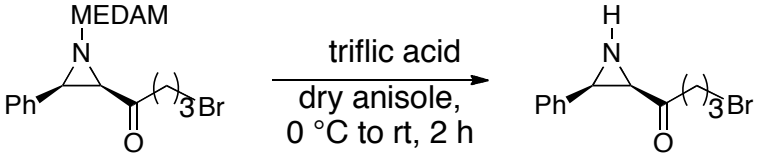


77b **74j** **(*2R, 3R*)-78n**

*1-((2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridin-2-yl)-3-(2-methyl-1,3-dioxolan-2-yl)propan-1-one **78n*:** Aldimine **77b** (79 mg, 0.20 mmol) was reacted with 1-diazo-4-(2-methyl-1,3-dioxolan-2-yl)butan-2-one **74j** (44 mg, 0.24 mmol) according to the general procedure described above with the exception that the catalyst

loading was 10 mol%. Purification of the product by column chromatography on silica gel (2:9 ethyl acetate/hexanes) gave the pure aziridine as a viscous oil in 64% isolated yield (70 mg, 0.13 mmol). The optical purity of **78n** was determined to be 91% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow 0.7 mL/min). Retention times: R_t = 9.47 min (major enantiomer) and R_t = 14.11 min (minor enantiomer). *Spectral data for (2R, 3R)–**78n***: R_f = 0.2 (2:9 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.48-0.50 (m, 1H), 0.86-1.15 (m, 5H), 1.26 (s, 3H), 1.27-1.32 (m, 2H), 1.41-1.57 (m, 3H), 1.74-1.77 (t, 1H, *J* = 7.0 Hz), 1.85-1.90 (m, 2H), 2.20 (s, 6H), 2.21 (s, 6H), 2.29-2.30 (d, 1H, *J* = 7.0 Hz), 2.51-2.61 (m, 2H), 3.30 (s, 1H), 3.64 (s, 3H), 3.66 (s, 3H), 3.82-3.90 (m, 4H), 6.97 (s, 2H), 7.04 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.04, 16.13, 23.82, 25.34, 25.51, 26.11, 30.38, 30.94, 32.51, 36.06, 36.88, 50.03, 54.70, 59.54, 59.61, 64.57, 64.60, 78.15, 109.27, 127.36, 128.35, 130.30, 130.48, 137.73, 138.07, 155.81, 156.20, 206.67; IR (thin film) 2928s, 1701m, 1650s, 1558m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 549 M^+ (0.23), 283 (100), 87 (87), 43 (50); HRMS (ES+) calcd for $C_{34}H_{48}NO_5$ *m/z* 550.3532 (M^++1), meas 550.3546; $[\alpha]^{23}_D$ = +79.4 (*c* 1.0, CH_2Cl_2) on 91% ee material (HPLC).

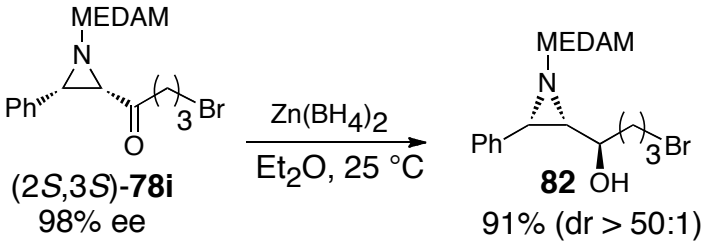
6.4.6 General procedure for the deprotection of the *N*-MEDAM aziridine 78i.



(2*R*,3*R*)-**78i** **81i**, 84% yield

To a 25 mL flame-dried round bottom flask filled with argon was added compound **78i** (110 mg, 0.200 mmol, 99% ee) and 2.2 mL of freshly distilled anisole at room temperature.[94] The flask was cooled to 0 ºC and triflic acid (88 μL, 1.0 mmol) was added. The ice-bath was removed and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched by addition of saturated aq Na_2CO_3 until the pH was greater than 9. After addition of 3 mL ether and 1 mL water, the organic layer was separated and the water layer was extracted with ether (5 mL × 3). The combined organic layer was washed with NaCl (aq. sat.) (2 x 10 mL) and dried over $MgSO_4$. The ether was removed by rotary evaporation. Purification of the product by column chromatography on silica gel (1:1 ether/hexanes as eluent) afforded **81i** as a clear viscous oil in 84% isolated yield (45 mg, 0.17 mmol). *Spectral data for (2R, 3R)–**81i***: R_f = 0.2 (1:1 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89-2.01 (m, 3H), 2.59 (bs, 2H), 3.01-3.09 (m, 1H), 3.19-3.27 (m, 2H), 3.62-3.64 (d, 1H, *J* = 6.0 Hz), 7.26-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) (1 sp^3 carbon and 1 carbonyl carbon missing) δ 25.92, 32.81, 39.67, 43.90, 127.35, 127.79, 127.99, 128.20; IR (thin film) 3310m, 2922m, 1701s, 1385m cm^{-1}; HRMS (ES+) calcd for $C_{12}H_{14}{}^{79}BrNO$ *m/z* 268.0377 (M^++1), meas 268.0328.

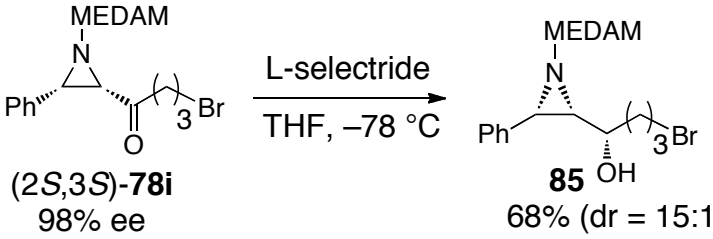
6.4.7 General procedure for preparation of (*R*)-1-((2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)-4-bromobutan-1-ol 82 via reduction of 78i with zinc borohydride.



An ethereal solution of zinc chloride (1.36 g, 10.0 mmol) was added dropwise to a stirred suspension of sodium borohydride (25 mmol) in dry diethyl ether (60 mL).[95] The mixture was stirred at room temperature under argon atmosphere for 12 h. The solid that formed (NaCl) was allowed to settle and the liquid was removed and stored in a stoppered bottle under argon atmosphere at –18 °C and was used as a 0.144 M zinc borohydride solution in diethyl ether. To an ice-cold solution of the compound **78i** (55 mg, 0.1 mmol, 98% ee) in dry diethyl ether (40 mL) was dropwise added a solution of zinc borohydride (0.30 mL). After 2 h, the reaction was quenched with water, and then the solution was stirred for another 30 min. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum to afford a light-yellow oil. Purification of the product by silica gel chromatography (1:4 ethylacetate/hexanes as eluent) gave **82** as a white foamy solid (mp 55-57 °C) in 91 % isolated yield (50 mg, 0.91 mmol). No trace of the diastereomer **85** could be observed by ^{1}H NMR in the crude reaction mixture (dr ≥50:1). The stereochemistry of the product was assigned based on a related reduction of an aziridinyl ketone reported previously.[94] *Spectral data for (1R, 2S, 3S)–**82***: R_f = 0.2 (1:4 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08-1.09 (d, 1H, *J* = 3.0 Hz), 1.12-1.20 (m, 1H), 1.24-1.32 (m, 1H), 1.56-1.68 (m, 2H), 1.91-

1.94 (dd, 1H, *J* = 6.5 Hz, 8.5 Hz), 2.16 (s, 6H), 2.27 (s, 6H), 2.82-2.83 (d, 1H, *J* = 6.0 Hz), 3.10-3.12 (t, 2H, *J* = 6.5 Hz), 3.16-3.18 (m, 1H), 3.57 (s, 1H), 3.62 (s, 3H), 3.69 (s, 3H), 7.04 (s, 2H), 7.10 (s, 2H), 7.21-7.23 (t, 1H, *J* = 7.5 Hz), 7.29-7.32 (t, 2H, *J* = 7.5 Hz), 7.43-7.45 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.43, 16.54, 28.63, 33.55, 34.05, 46.60, 50.89, 59.79, 59.91, 68.96, 78.31, 127.19, 127.64, 127.71, 128.51, 128.54, 130.65, 130.89, 137.08, 138.29, 138.75, 156.10, 156.57; IR (thin film) 3466m, 2920s, 1483s, 1221s cm^{-1}; HRMS (ES+) calcd for $C_{31}H_{39}NO_3{}^{79}Br$ *m/z* 552.2113 (M^++1), meas. 552.2092; $[\alpha]^{23}_D$ = +112.3 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC).

6.4.8 General procedure for preparation of (*S*)-1-((2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)-4-bromobutan-1-ol 85 via reduction of 78i with L-selectride.



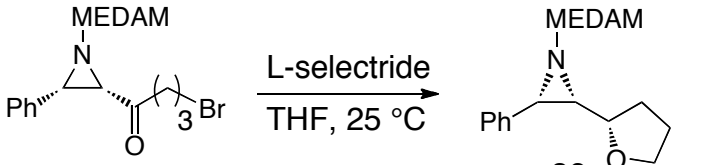
(2*S*,3*S*)-**78i**
98% ee

85
68% (dr = 15:1)

To a solution of ketoaziridine **78i** (55 mg, 0.10 mmol) in 1 mL of THF under argon at –78 °C was added L-Selectride (1M solution in THF, 0.20 mL, 0.20 mmol).[95] The mixture was stirred for 60 min at –78 °C and then the reaction mixture was treated with 10% aqueous sodium hydroxide and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 X 3 mL) and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under vacuum. Purification of the product by silica gel chromatography (1:4 ethylacetate/hexanes as eluent) gave **85** as a viscous oil in 68 % yield (37 mg, 0.068 mmol). The ratio of the two

diastereomers **82** and **85** was 1:15 observed by ^{1}H NMR in the crude reaction mixture. The stereochemistry of the products was assigned based on a related reduction of aziridinyl ketone reported previously.[95] *Spectral data for (1S, 2S, 3S)–**85***: R_f = 0.2 (1:4 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30-1.39 (m, 2H), 1.59-1.65 (m, 2H), 1.86-1.89 (dd, 1H, *J* = 7.0 Hz, 8.0 Hz), 2.16 (s, 6H), 2.27 (s, 6H), 2.89-2.90 (d, 1H, *J* = 7.0 Hz), 3.05-3.12 (m, 3H), 3.59 (s, 1H), 3.62 (s, 3H), 3.67 (s, 3H), 7.11 (s, 2H), 7.12 (s, 2H), 7.20-7.22 (t, 1H, *J* = 7.5 Hz), 7.27-7.30 (t, 2H, *J* = 7.5 Hz), 7.39-7.40 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.45, 16.56, 28.60, 32.71, 33.80, 47.45, 51.75, 59.79, 59.90, 68.81, 78.03, 127.18, 127.57, 127.65, 127.83, 128.32, 130.76, 131.58, 136.76, 138.17, 139.47, 156.09, 156.69; IR (thin film) 3422s, 2924s, 1483s, 1221s cm^{-1}; HRMS (ES+) calcd for $C_{31}H_{39}NO_3{}^{79}Br$ *m/z* 552.2113 (M^++1), meas 552.2092; $[\alpha]^{23}_{D}$ = +83.2 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC).

6.4.9 Preparation of (2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-2-phenyl-3-((*S*)-tetrahydrofuran-2-yl)aziridine 86.



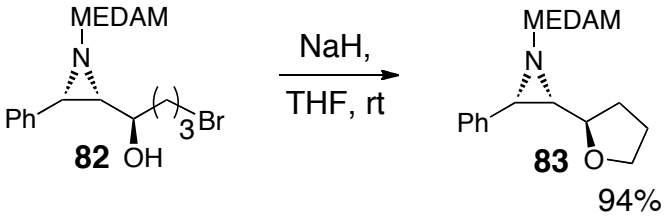
(2*S*,3*S*)-**78i**
98% ee

86
83% (dr = 11:1)

When the above mentioned L-selectride reduction of compound **78i** (0.275 g, 0.500 mmol) was carried out at room temperature for 24 h, compound **86** was isolated after silica gel chromatography (1:5 ethylacetate / hexanes as eluent) as a white foamy solid

(mp 110-112 °C) in 83% yield (0.190 g, 0.415 mmol). *Spectral data for (S, S, S)–**86***: R_f = 0.2 (1:5 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41-1.54 (m, 2H), 1.59-1.76 (m, 2H), 1.90-1.93 (dd, 1H, *J* = 6.5 Hz, 8.5 Hz), 2.20 (s, 6H), 2.27 (s, 6H), 2.75-2.76 (d, 1H, *J* = 6.5 Hz), 3.31-3.36 (q, 1H, 7.5 Hz), 3.56-3.60 (m, 1H), 3.64 (s, 1H), 3.64-3.70 (m, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 7.10 (s, 2H), 7.12 (s, 2H), 7.14-7.17 (m, 1H), 7.21-7.25 (m, 2H), 7.33-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.14, 16.15, 25.36, 28.76, 44.59, 50.13, 59.52, 59.57, 67.43, 76.75, 78.72, 126.41, 127.65, 127.77, 127.95, 128.19, 129.98, 130.24, 137.47, 138.18, 138.78, 155.62, 155.79; IR (thin film) 2963s, 1485s, 1221s,1016s cm^{-1}; HRMS (ES+) calcd for $C_{31}H_{38}NO_3$ *m/z* 472.2852 (M^++1), meas 472.2840; $[\alpha]^{23}_D$ = +28.6 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC).

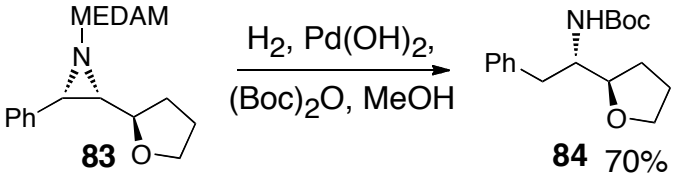
6.4.10 Preparation of (2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-2-phenyl-3-((*R*)-tetrahydrofuran-2-yl)aziridine 83.



(2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-2-phenyl-3-((*R*)-tetrahydro furan-2-yl)aziridine **83** was prepared by treating compound **82** (83 mg, 0.15 mmol) with NaH (60%, 12 mg, 0.30 mmol) in THF (6 mL) at room temperature for 24 h. The reaction mixture was quenched by addition of 10 mL of H_2O. The aqueous layer was extracted with ethyl acetate (3 X 3 mL) and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum. Purification of the

product by silica gel chromatography (1:3 ethylacetate/hexanes as eluent) gave **83** as a white foamy solid (mp 54-56 °C) in 94 % yield (65 mg, 0.14 mmol). *Spectral data for (S, S, R)–**83***: R_f = 0.25 (1:3 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05-1.09 (m, 1H), 1.57-1.67 (m, 3H), 1.84-1.87 (dd, 1H, *J* = 6.5 Hz, 8.0 Hz), 2.18 (s, 6H), 2.27 (s, 6H), 2.83-2.84 (d, 1H, *J* = 6.5 Hz), 3.29-3.31 (q, 1H, 7.5 Hz), 3.48-3.52 (m, 1H), 3.56 (s, 1H), 3.63 (s, 3H), 3.68 (s, 3H), 3.66-3.70 (m, 1H), 7.10 (s, 2H), 7.12 (s, 2H), 7.16-7.19 (m, 1H), 7.24-7.28 (m, 2H), 7.39-7.40 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.43, 25.85,30.61, 47.24, 49.69, 59.80, 59.94, 68.50, 76.33, 78.50, 126.82, 127.82, 128.13, 128.19, 128.50, 130.62, 130.63, 137.39, 138.62, 139.06, 156.03, 156.34; IR (thin film) 2947s, 1483s, 1221s,1016s cm^{-1}; HRMS (ES+) calcd for $C_{31}H_{38}NO_3$ *m/z* 472.2852 (M^++1), meas 472.2836; $[\alpha]^{23}_D$ = +73.4 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC).

6.4.11 Reductive ring-opening/deprotection/Boc-protection sequence for conversion of tetrahydrofurylaziridines to *tert*-butyl ((*S*)-2-phenyl-1-((*R*)-tetrahydrofuran-2-yl)ethyl)carbamate 84.

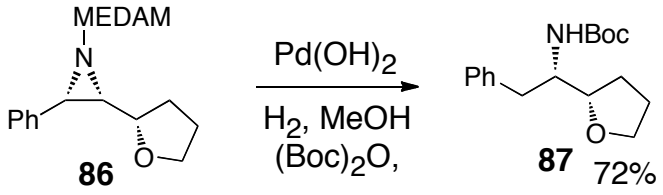


83 **84** 70%

To a 25 mL round bottom flask fitted with a magnetic stir bar was added tetrahydrufurylaziridine **83** (47 mg, 0.10 mmol), $Pd(OH)_2$ (44 mg, 0.025 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, *ca*. 60% moisture), $(Boc)_2O$ (65 mg, 0.30 mmol) and methanol (3 mL). The flask was then equipped with a 3-way valve connected to vacuum

and a hydrogen balloon. The flask was opened to vacuum for a few seconds, and then switched to the hydrogen balloon; this manipulation was repeated three times. The reaction mixture was allowed to stir at room temperature for 24 h. It was then filtered through a Celite pad and concentrated under vacuum. Purification of the product by silica gel chromatography (1:7 ethylacetate/hexanes as eluent) gave **84** as a white solid (mp 98-99 °C) in 70 % yield (20 mg, 0.070 mmol). *Spectral data for (1R, 2S)–**84***: R_f = 0.15 (1:7 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.77-1.78 (m, 1H), 1.89-1.98 (m, 3H), 2.82 (bs, 1H), 3.62-3.64 (dd, 1H, *J* = 4.5 Hz, 14.0 Hz), 3.76-3.83 (m, 2H), 3.87 (bs, 1H), 3.91-3.96 (m, 1H), 4.41 (bs, 1H), 7.20-7.23 (m, 3H), 7.28-7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.69, 28.29, 28.39, 36.94, 54.32, 68.44, 79.16, 80.31, 126.19, 128.27, 129.65, 137.90, 155.45; IR (thin film) 3370s, 3030m, 2964s, 1684s, 1525s, 1365m, 1262s cm^{-1}; HRMS (ES+) calcd for $C_{17}H_{26}NO_3$ *m/z* 292.1913 (M^++1), meas 292.1916; $[\alpha]^{23}_D$ = –5.6 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC).

6.4.12 Reductive ring-opening/deprotection/Boc-protection sequence for conversion of tetrahydrofurylaziridines to tert-butyl ((S)-2-phenyl-1-((S)-tetrahydrofuran-2-yl)ethyl)carbamate 87.



Tetrahydrufurylaziridine **86** (47 mg, 0.10 mmol), was subjected to the same ring-opening/deprotection/Boc-protection sequence to afford compound **87** as a viscous oil

in 72% yield (21 mg, 0.72 mmol). *Spectral data for (1R, 2R)–**87***: R_f = 0.17 (1:5 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.59-1.66 (m, 1H), 1.78-1.85 (m, 3H), 2.80-2.90 (m, 2H), 3.67-3.87 (m, 4H), 4.72-4.74 (d, 1H, *J* = 9.0 Hz), 7.17-7.27 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.04, 28.11, 28.35, 39.95, 54.09, 68.56, 78.47, 79.08, 126.17, 128.29, 129.46, 138.48, 155.93; IR (thin film) 3341m, 2976s, 1713s, 1496s, 1169s cm^{-1}; HRMS (ES+) calcd for $C_{17}H_{26}NO_3$ *m/z* 292.1913 (M^++1), meas 292.1924; $[\alpha]^{23}_D$ = –23.0 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC).

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