CATALYTIC ASYMMETRIC MULTI-COMPONENT KABACHNIK-FIELDS REACTION BY VANOL-DERIVED ZIRCONIUM COMPLEX AND TOTAL SYNTHESIS OF SPHINGOID BASES

By

Yijing Dai

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ABSTRACT

CATALYTIC ASYMMETRIC MULTI-COMPONENT KABACHNIK-FIELDS REACTION BY VANOL-DERIVED ZIRCONIUM COMPLEX AND TOTAL SYNTHESIS OF SPHINGOID BASES

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A highly efficient asymmetric catalytic approach to synthesize α-amino phosphonates by employing aldehydes, amines and diethyl phosphites under a chiral VANOL-derived zirconium complex was developed. The asymmetric induction of this direct three-component hydrophosphonylation reaction (Kabachnik-Fields reaction) of aliphatic aldehydes reaches over 90% *ee* for the first time. Broad scope of aromatic and aliphatic substrates bearing various functional groups including silyl ether, ester, amide, olefin, alkyne, azide etc. can be tolerated under the reaction conditions with good yield and *ee*. In the preliminary mechanism study, it was found that the 2-hydroxyl group on the aniline is crucial to the introduction of the enantioselectivity.

Sphingoid bases are backbones of new class sphingolipids and they have four different members present in two-headed family with similar structure, but with different stereochemistry. The key step in the synthesis of sphingoid bases are nucleophilic addition between two heads and highly enantioselective *trans-* / *cis*-asymmetric aziridination, which is for setting four chiral centers in the structure.

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I came to MSU in 2012 and after the Thanksgiving in this year I joined Dr. Wulff's group. Until now it has been almost 6 years. There is not many 6 years in our whole life, but when I am looking back of the past, this 6 year is the most important one. During those years, I had Dr. Wulff to be my advisor and systematically learned the organic chemistry from those excellent professors in MSU; I first time became a TA to teach undergrads chemistry classes; I met many good friends who helped me a lot in all aspects of my life. Although this is the time to farewell, I cannot stop thinking the first day when I stood in the front of the chemistry building. It was that moment I felt I can start chasing my dream from here and everything around me was so shining and beautiful under the big sunshine in July. 12th in 2012.

If I have to pick up the luckiest thing I did during my Ph.D. study, I would say that is I joined Dr. Wulff's lab. Dr. Wulff to me, is not only a PI, but also a hero in my life. He is the guy I never met that loves chemistry so much and makes all his efforts to it. He keeps writing down new organic reactions on blank cards during his career and he developed a system to keep tracking every single reaction in hundreds of total synthesis and record them in a systematic way. Even once I met him in Thai princess at lunch time, he was reading a JACS paper while waiting for his food. I learned a lot from Dr. Wulff, and am trying to become the person like him, who can always focus on what he likes and keep doing it perfectly all the time. By the way, he is also very smart, humorous and really loves wine.

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KEY TO ABBREVEDVIATIONS

Ac	acetyl
Bn	benzyl
BINAP	1,1’-binaphthyl-2,2’-bis(diphenylphosphine)
Bu	butyl
BUDAM	tetra-*tert*-butyldianisylmethyl
CAN	ceric ammonium nitrate
Cy	cyclohexyl
DCM	dichloromethane
DAM	dianisylmethyl
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EDA	ethyl diazoacetate
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
LDA	lithium diisopropylamide
LAH	lithium aluminium hydride
Me	methyl
MEDAM	tetramethyldianisylmethyl
M.S	molecular sieves
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NIS *N*-iodosuccinimide

NMI *N*-methylimidazole

PBB pyridinium bromide-perbromide

Ph phenyl

Piv pivaloyl

PMP *para*-methoxyphenyl

Pr propyl

TCCA trichloroisocyanuric acid

TEMPO 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl radical

Tf trifluoromethanesulfonyl

TFA trifluoroacetic acid

TLC Thin-layer chromatography

Ts 4-toluenesulfonyl

VANOL 3,3’-diphenyl-2,2’-bi(1-naphthol)

VAPOL 2,2’-diphenyl-(4-biphenanthrol)

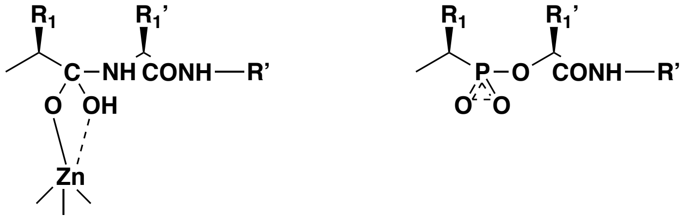
CHAPTER ONE

CATALYTIC ASYMMETRIC SYNTHESIS OF α-AMINO PHOPHOSPHONIC ACIDS BY HYDROPHOSPHONYLATION

1.1 Introduction

α-Amino phosphonic acids are important surrogates of α-amino carboxylic acids. With the replacement of the carboxyl function with a phosphonic acid, these amino acids have attracted great interest as a result of their wide range of biological activities.[1] The most significant application for α-amino phosphonic acids is serving as inhibitors of enzymes. This is due to the fact that the tetrahedral phosphonic moiety can mimic the putative tetrahedral transition state or intermediate in nucleophilic substitution reactions on the carbonyl group of the amino carboxylic acids.[2] Therefore, they could be incorporated *via* an amide linkage into a certain peptide to act as potent inhibitors of proteases and peptide ligases.

Figure 1.1 Tetrahedron states of phosphonopeptide



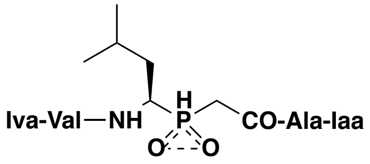
1
***gem*-diolate intermediate**

2
phosphonopeptide

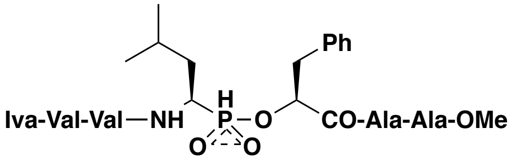
Figure 1.1 shows an example of synthetic analogs of peptides of the type **2**, in which the scissile peptide linkage is replaced by a tetrahedral phosphonate moiety providing good inhibitors of zinc protease[3]. The mechanism of this inhibition is because the presence of the phosphonate moiety, which mimics the presumed tetrahedral *gem*-diolate intermediate formed by the nucleophilic addition of water to the carbonyl group.

Thus, many α-amino phosphonic acids have very strong biological activities, such as the potent transition-state-analogue inhibitors **4** and **5**[4-5], the antibacterial agent alafosfalin **3**[6] for aspartic protease and crop desiccant glyphosate **6** (Roundup)[7] (Figure 1.2).

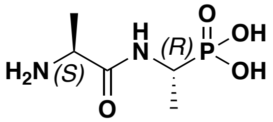
Figure 1.2 Bioactive α-amino phosphonic acids



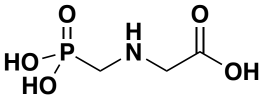
3
Iva: isovaleramido; Iaa: isoamylamide



4



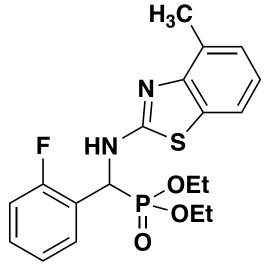
5, Alafosfalin



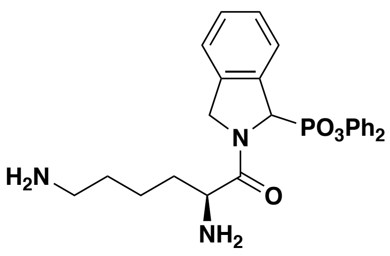
6, Glyphosate
Herbicide & crop desiccant

The diester derivatives of α-amino phosphonic acids, are more attractive as intermediates in multistep synthesis than their corresponding phosphonic acids.[3] The insolubility and high polarity of the phosphonic acids make the later functionalization of the amine and acid group more complicated than their diester derivatives.[8] In recent years, some α-amino phosphonates were also reported that have pharmaceutical and industrial applications. Dufulin **7**[9] now has been widely used as a pesticide product in preventing and controlling rice, vegetable and tobacco viral diseases in China; Dipeptidyl peptidases **8**[10-12] is an inhibitor of DPP8 for the treatment of type 2 diabetes; Analog **9**[13] of alkyl α-amino phosphonic acids can generate antibodies for dipeptide formation (Figure 1.3).

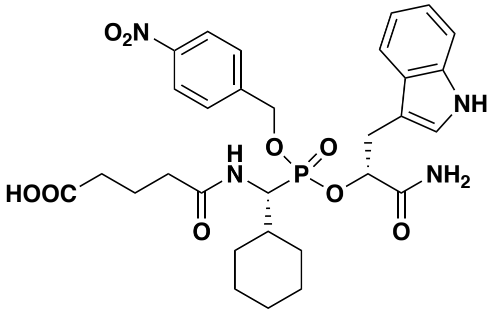
Figure 1.3 Useful α-amino phosphonic phosphonates



7, Dufulin



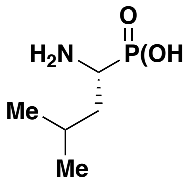
8, inhibitor of DPP 8
DPP: dipeptidyl peptidases



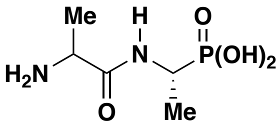
9, antibodies for coupling of amino acids

From the above examples, most have a chiral center at the α carbon. It is well known that the configuration of the α carbon has a big influence on the biological activity of α-amino phosphonic acids and their derivatives. For example, (*R*)-phospholeucine **10** [14-16]is a more potent inhibitor of the metalloenzyme leucine aminopeptidase from porcine kidney compared with its (*S*) isomer, and (*S, R*)-alaphosphalin **11**[17-18] has higher antibacterial activity than the other three diasteroisomers (Figure 1.4).

Figure 1.4 Chiral α-amino phosphonic acids



10, (*R*)-Phospholeucine



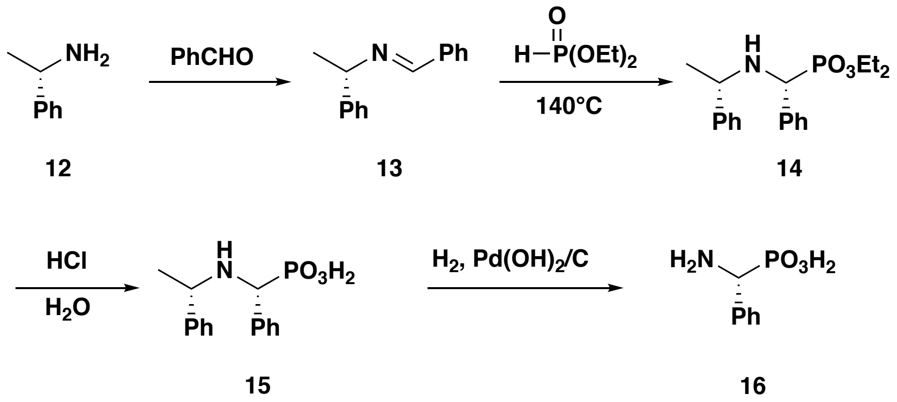
11, (*S, R*)-Alaphosphalin

As a result of the variety of biological activities and chemical applications of chiral α-amino phosphonic acids and their derivatives, many asymmetric methodologies for their synthesis have been developed. The history of catalytic asymmetric hydrophosphonylation by chiral catalysts, especially direct 3-component Kabachnik-Fields reaction will be described in this chapter.

1.2 Catalytic Asymmetric Hydrophosphonylation of imine

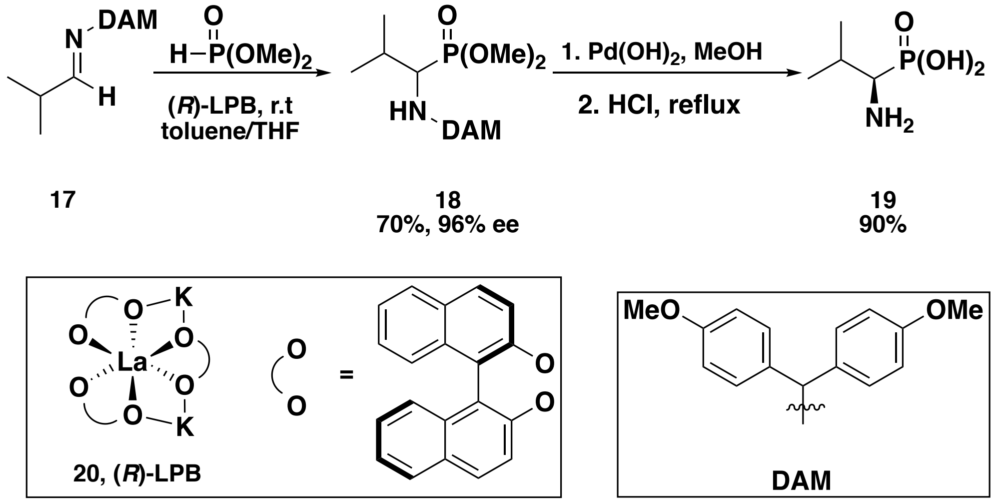
The first synthesis of optical pure α-amino phosphonic acids from imines (Pudovik reaction) was reported by Gilmore and McBride in 1972[19]. In their method, diethyl phosphite was added to benzyl imine **13** which was derived from the enantiomerically pure α-methylbenzylamine **12**. Subsequent esterhydrolysis with hydrochloric acid and then hydrogenloysis provided the product **16** in unspecified chemical and optical yields (Scheme 1.1).

Scheme 1.1 First asymmetric synthesis of α-amino phosphonic acids[19]



Shibasaki and his group reported the first example of a catalytic asymmetric hydrophosphonylation of an imine in 1995 by using a lanthanoid-potassium-BINOL heterobimetallic complex (LPB, **20**)[20], which gives optically active α-amino phosphonates in moderate to high enantiomeric excess. After cleavage of the dianisylmethyl group on the nitrogen and hydrolysis of the dimethyl phosphonate, the enantiomerically enriched α-amino phosphonic acid **19** can be obtained in 90% yield (Scheme 1.2).

Scheme 1.2 First catalytic asymmetric hydrophosphonylation with imines[20]



17

18
70%, 96% ee

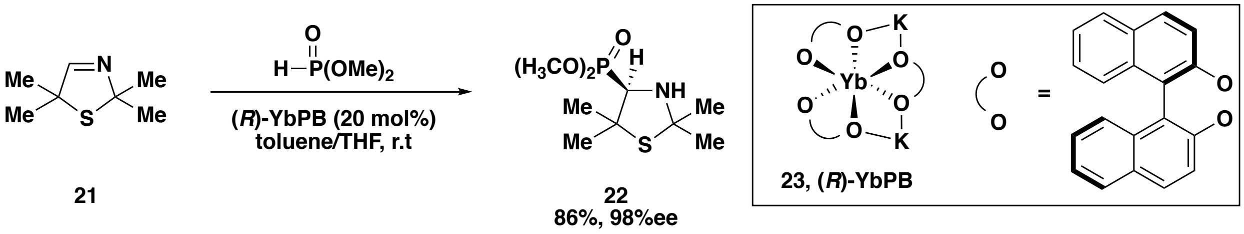
19
90%

20, (*R*)-LPB

DAM

One year later, the Shibasaki group published another example of asymmetric hydrophosphonylation of cyclic imines with chiral Ytterbium catalyst (**23**)[21], which delivered the 4-thiazolidinylphosphonates in up to 98% *ee* (Scheme 1.3). These two exceptional papers opened the gate of chiral catalyst controlled enantioselective hydrophosphonylation of imines for the preparation of a variety of α-amino phosphonates.

Scheme 1.3 Asymmetric hydrophosphonylation of cyclic imines[21]



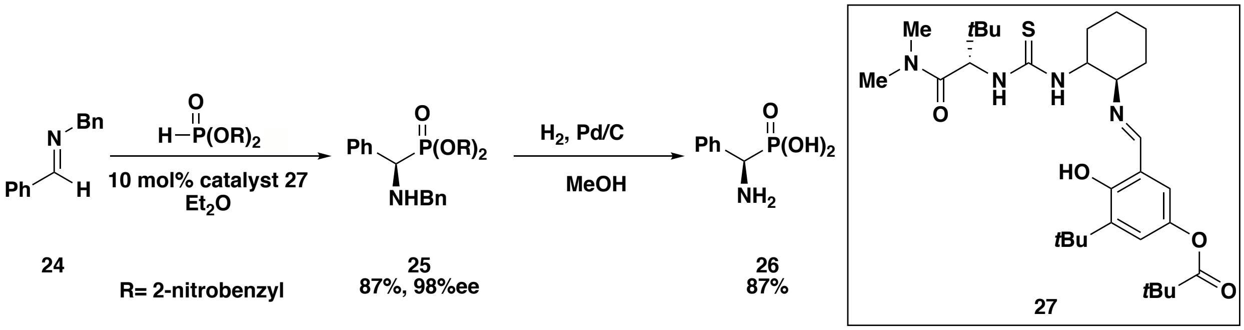
21

22
86%, 98%ee

23, (*R*)-YbPB

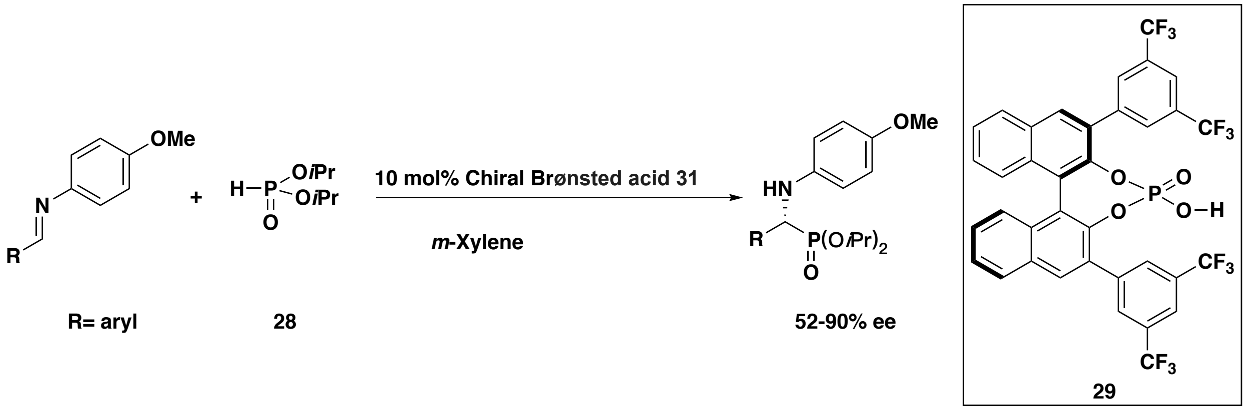
In 2004, Jacobsen and his group developed a unique chiral thiourea catalyst (**27**)[22], which can catalyze hydrophosphonylation of both aromatic and aliphatic imines with di-(2-nitrobenzyl) phosphite in excellent yield and *ee*. The benzyl group on nitrogen and the nitrobenzyl phosphite can be easily reductively cleaved under Pd/H_2 to give the enantiomeric enriched α-amino phosphonic acids (Scheme 1.4).

Scheme 1.4 Asymmetric hydrophosphonylation with a chiral thiourea catalyst[22]



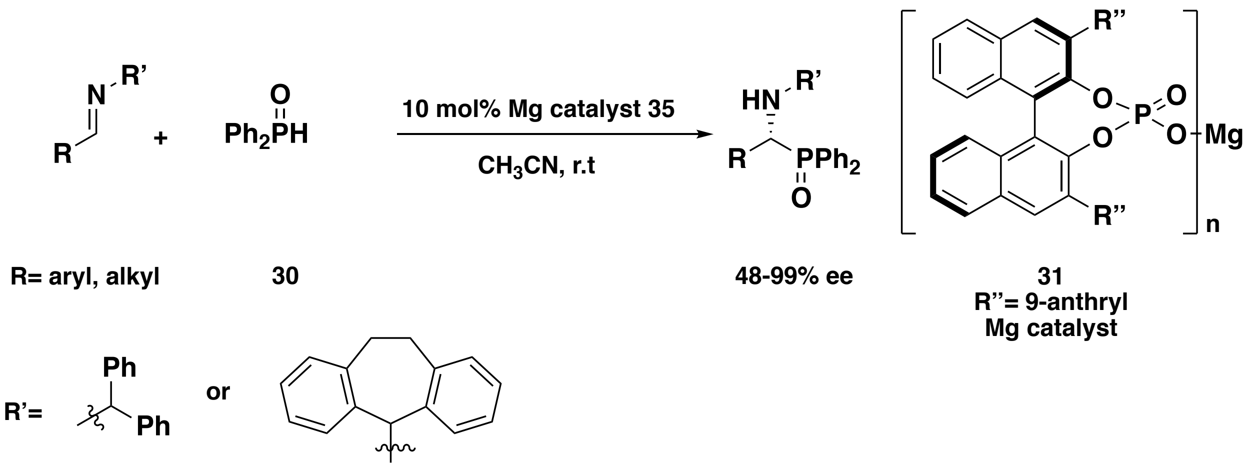
Another class of novel catalytic systems developed for this reaction employs chiral Brønsted acids, such as BINOL, SPINOL and other phosphonic acids[23-25]. These phosphonic acids can generally serve as bifunctional catalysts, by activating the imine and the phosphite by their Brønsted acidic and Lewis basic sites.[26] Scheme 1.5 shows one example by Fuchibe and his group[23].

Scheme 1.5 Asymmetric hydrophosphonylation with a chiral Brønsted acid[22],



Later in 2011, Antilla and his coworkers developed a highly enantioselective addition of diphenylphosphine oxide to *N*-substituted imines catalyzed by a chiral BINOL magnesium phosphate (**31**)[27]. This work further supports the idea that phosphonic acid can activate both the imine and also facilitate the nucleophilic addition of the phosphine (Scheme 1.6).

Scheme 1.6 Asymmetric hydrophosphonylation with a chiral Magnesium catalyst[27]



R= aryl, alkyl

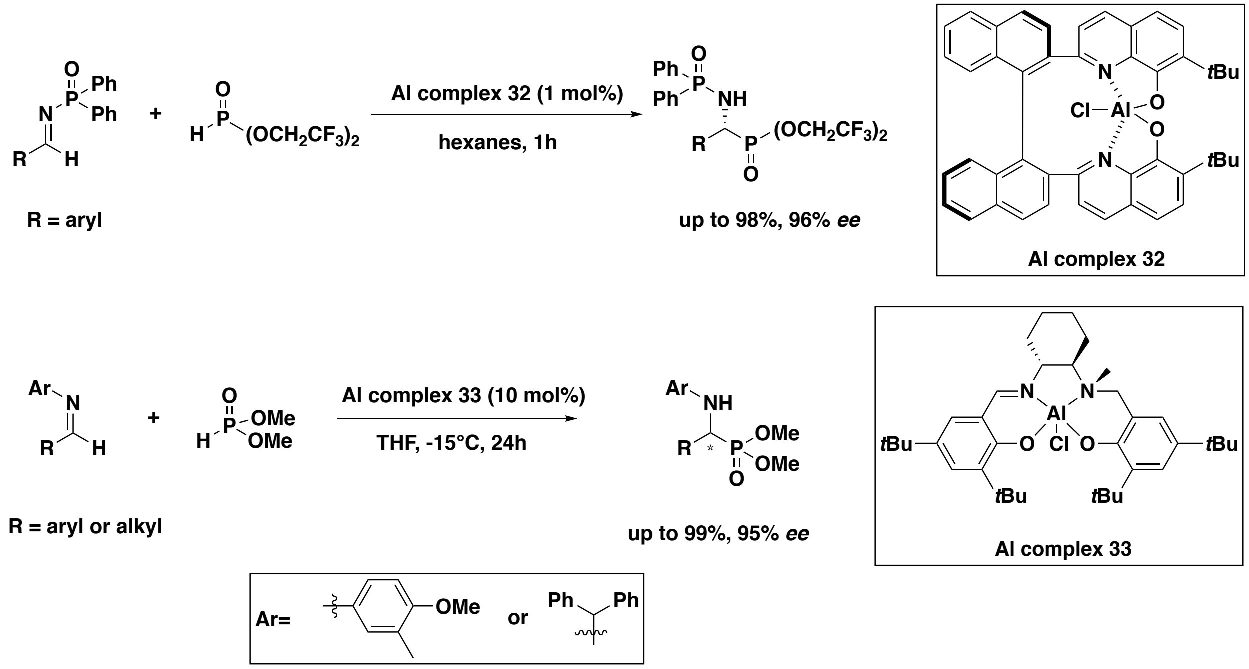
30

48-99% ee

31
R"= 9-anthryl
Mg catalyst

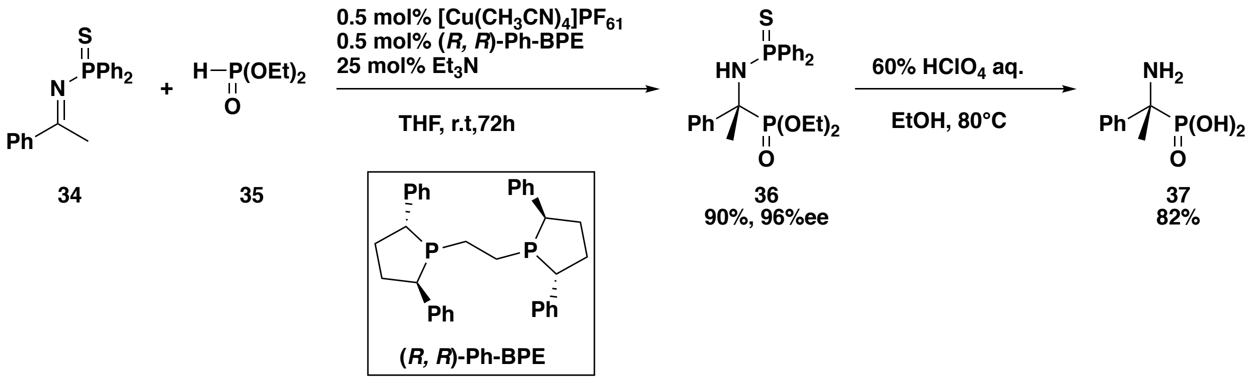
In 2007 and 2008, Katsuki's and Yamamoto's groups subsequently published two different methods about using chiral aluminum catalysts **32**[28] and **33**[29] for the hydrophosphonylation of aldimines in good yield and *ee*, respectively (Scheme1.7). In the mechanistic investigation in Katsuki's paper[28], it is revealed that the nitrogen of the imine is bound to the aluminum and the *N*-methyl group on the resulting chiral nitrogen atom is *cis* to the chloro ligand (Al complex **33**), which provides a unique asymmetric reaction site. It should be noted that Katsuki's reaction can be carried out in a one pot version. With the addition of amines and aldehydes with molecular sieves in THF for stirring 3-4 hours, dimethyl phosphite and the catalyst **32** was added to the reaction. The mixture was reacted at -15°C for 24 hours to furnish the desired α-amino phosphonates.

Scheme 1.7 Hydrophosphonylation of aldimines by chiral aluminum catalysts[28, 29]



The last example is the catalytic asymmetric construction of a tetrasubstituted stereogenic center in an α-amino phosphonates synthesis reported by Shibasaki and his group[30]. In 2013, they employed *N*-thiophosphinoyl ketimines **34** as suitable soft Lewis basic electrophile and secondary phosphites as nucleophile, providing tetrasubstituted α-amino phosphonates **36** as products. This process involves the action of a soft Lewis acid/hard Brønsted base cooperative catalyst consisting of copper and triethylamine. The subsequent removal of the thiophosphinoyl group can be easily carried out with perchloric acid (Scheme 1.8).

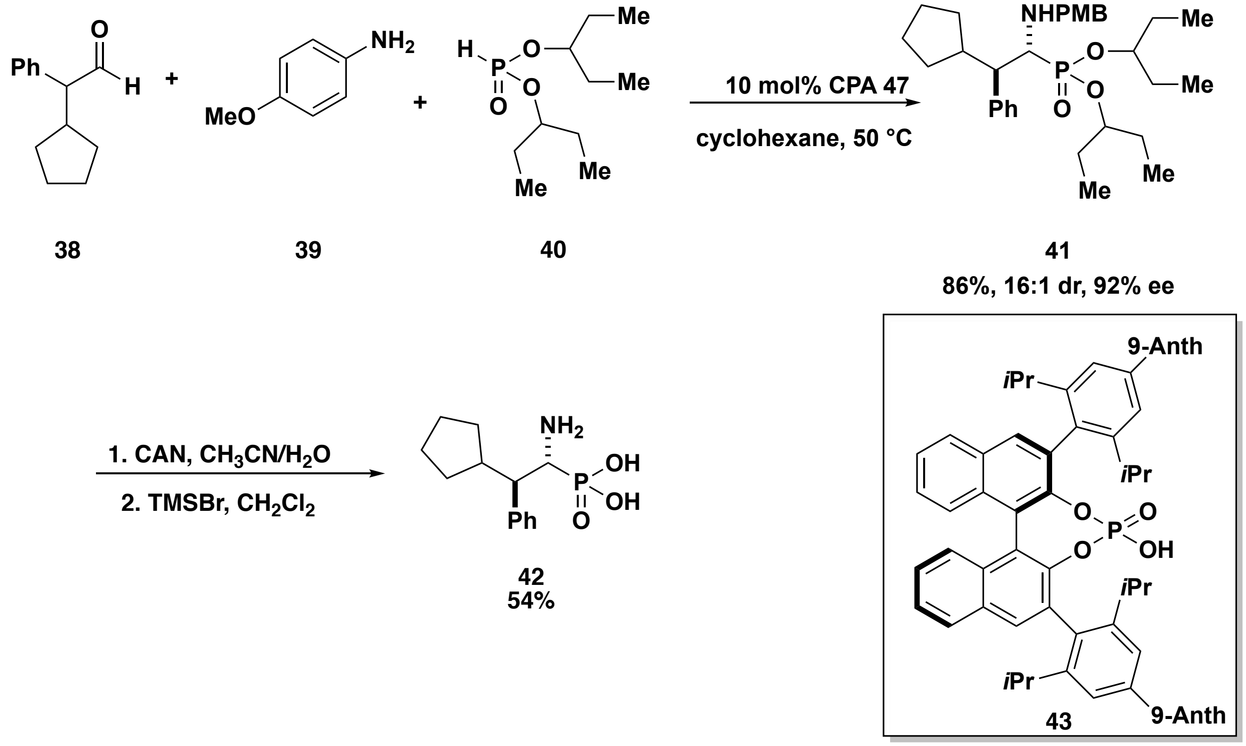
Scheme 1.8 Asymmetric hydrophosphonylation with ketimines[30]



1.3 Direct Three-Component Catalytic Asymmetric Hydrophosphonylation (Kabachnik-Fields Reaction)

The Kabachnik-Fields reaction was discovered in 1952 by Kabachnik and Fields[31]. It is a three-component reaction generating α-amino phosphonates from a amine, an aldehyde and a phosphonate. However, it wasn't until 2009 that List and his coworkers reported its first asymmetric version[32] . By employing racemic α-branched aldehydes, ρ-anisidine and dialkyl phosphonates in the presence of a new chiral phosphoric acid catalyst (CPA, **43**), the reaction produces β-branched α-amino phosphonates with high diastereoselectivity and enantioselectivity by a dynamic kinetic resolution. Removal of the PMP group with CAN followed by hydrolysis of the ester to the acid by TMSBr, produced the corresponding α-amino phosphonic acid with the retention of enantioselectivity. However, this reaction was limited to α-substituted phenyl acetaldehydes (Scheme1.9).

Scheme 1.9 First asymmetric Kabachnik-Fields reaction[32]


38 39 40 41

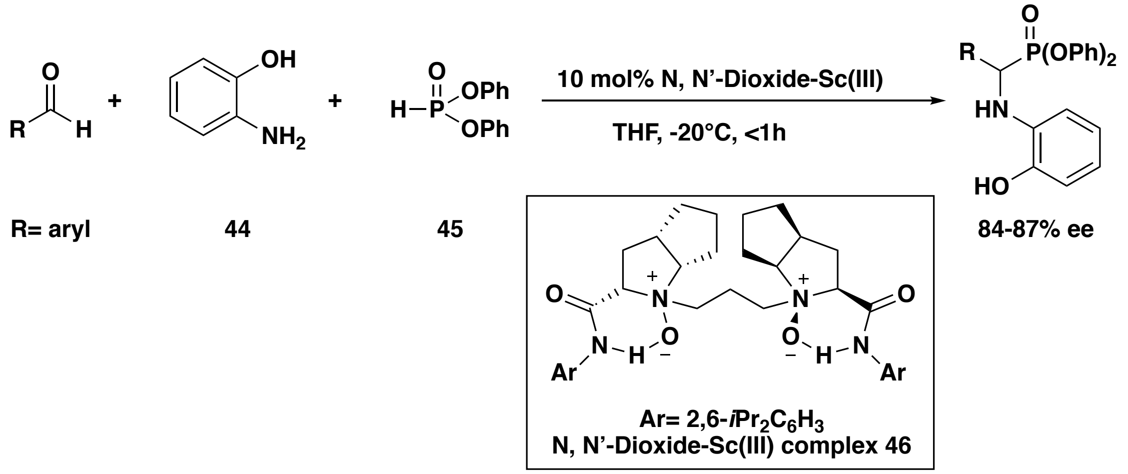
86%, 16:1 dr, 92% ee

42
54%

43

In 2009, Feng and his group developed a second novel catalyst (**46**)[33], which is a chiral scandium(III)- *N*, *N*'-dioxide complex. With a 10 mol% loading of scandium complex **46**, the three-component reaction reaction with aromatic aldehydes, 2-aminophenol and diphenyl phosphite gives the desired α-amnio phosphonate product in good yield and high enantioselectivity (up to 87% *ee*) (Scheme 1.10). During the optimization process, many lanthanides were also attempted in the reaction condition which have similar Lewis acidity, multifunctionality and coordination capability as scandium, however, none gave better results. Based on the procedure in their supporting information, it is not a multi-component reaction since the aldehyde, amine and catalyst are stirred for an hour in THF at room temperature followed by the addition of the diphenyl phosphites at -20°C.

Scheme 1.10 Asymmetric Kabachnik-Fields reaction with a scandium catalyst[33]



R= aryl

44

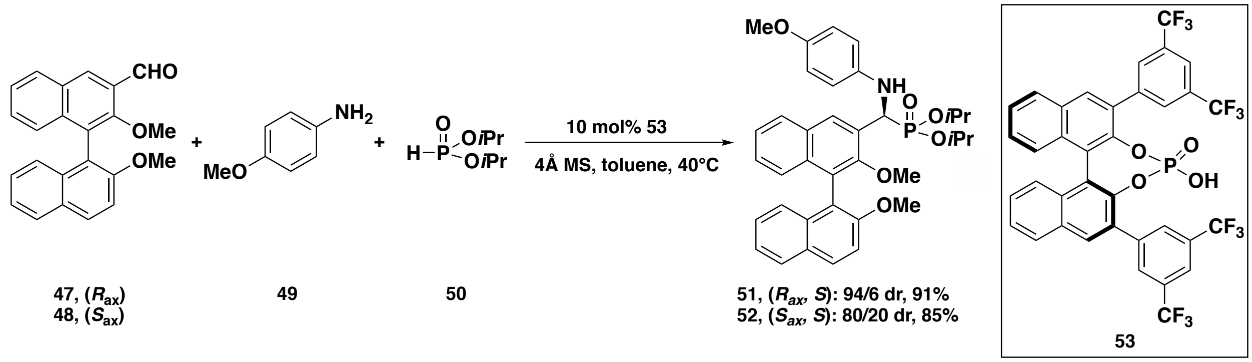
45

84-87% ee

Ar= 2,6-iPr$_2$C$_6$H$_3$
N, N'-Dioxide-Sc(III) complex 46

Another related example is from Ma and his coworkers[34]. In 2010, they described a direct organocatalytic three-component hydrophsophonylation with chiral phosphonic acid **53** as the catalyst. The enantioselectivity of this reaction is moderate to good (32-87% *ee*) and the reaction time is 168 hours on average. All the aldehyde substrates were limited to aromatic aldehydes. It is worth mentioning that they extended the reaction to the (*R*) and (*S*)-1,1'-binaphthyl-3-formaldehydes (**47** and **48**) to illustrate application of this methodology. The result shows that the (*R*)-binaphthyl aldehyde **47** gave higher stereoselectivity (dr: 94/6) than the (*S*)-enantiomer (dr: 80/20) (Scheme 1.11).

Scheme 1.11 Asymmetric Kabachnik-Fields reaction with binaphthyl aldehydes[34]



47, (R_{ax})
48, (S_{ax})

49

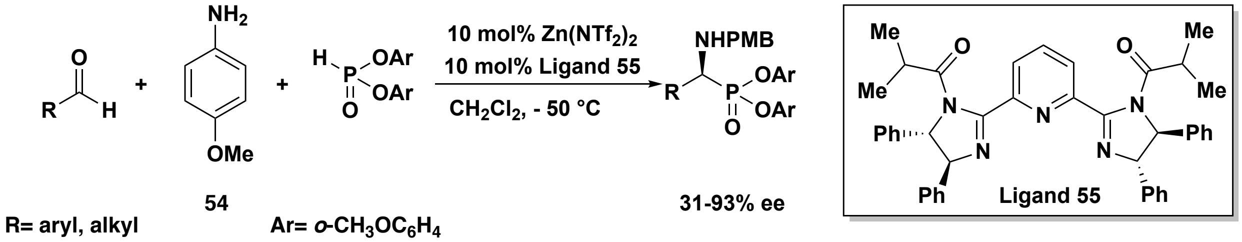
50

51, (R_{ax}, S): 94/6 dr, 91%
52, (S_{ax}, S): 80/20 dr, 85%

53

More recently, Shibata and his group discovered the combination of catalytic amounts of $Zn(NTf_2)_2$ and 1,3-bis(imidazolin-2-ly) pyridine (pybim) (**55**) as a C_2-symmetric ligand[35], produced a species that can catalyze direct Kabachnik-Fields reaction with aldehydes, ρ-anisidines **54** and diaryl phosphites in good yields and enantioselectivity (Scheme 1.12). It is to be noted that two aliphatic aldehydes (cyclohexyl and isobutyl carboxylic aldehyde) were also examined under the standard conditions. Although the enantioselectivity is only 61% and 31% *ee*, respectively, it is the first time that aliphatic aldehyde substrates were applied in the asymmetric Kabachnik-Fields reaction to provide simple α-amino phosphonates.

Scheme 1.12 Asymmetric Kabachnik-Fields reaction with a pybim ligand[35]



1.4 Summary

In this chapter, an overview of the two component catalytic asymmetric synthesis of α-amino phosphonic acids from imines and phosphites (Pudovik reaction) and the three-component synthesis from amines, aldehydes and phosphites (Kabachnik-Fields reaction) were described. Compared with the two-component reaction, the strategy of the multicomponent synthesis is more attractive. They have higher levels of atom efficiency and the simplicity of the reaction procedure of the work-up make the reaction environmentally friendly and more economical. However, to the best of our knowledge, there are only three reports on the direct three-component enantioselective reaction and these were described above. In addition, their substrate scope is very limited. List's work focuses on α-branched arylacetaldehydes and the reaction itself is a dynamic kinetic resolution. The other two methods target mostly aromatic aldehydes and the highest enantioselectivity reported the aliphatic aldehyde is only 61% *ee*. Moreover, the reaction temperature for Shibata's reaction is -50°C. Therefore, expanding the reaction substrate scope, especially for the aliphatic aldehydes and seeking much milder conditions for the asymmetric Kabachnik-Fields reaction is highly desirable and necessary.

CHAPTER TWO

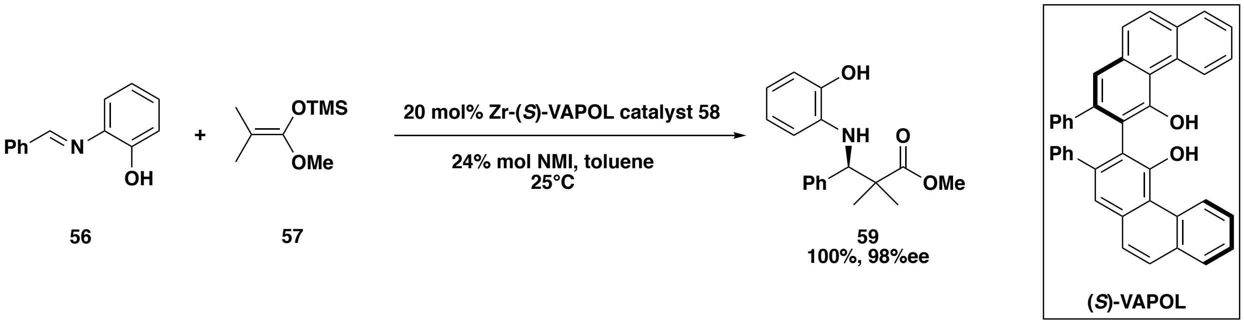
CATALYTIC ASYMMETRIC KABACHNIK-FIELDS REACTION WITH AROMATIC ALDEHYDES

2.1 Introduction

As outlined in the last chapter there are only four papers (List's, Ma, Feng and Shibata's group)[32, 34-35] have appeared in the past decade describing a catalytic asymmetric version of the Kabachnik-Fields reaction. In addition, in Feng's work[33], it is required that the imines be pre-formed from aldehydes and amines, followed by addition of diphenyl phosphites. Moreover, most of these studies are focused on aromatic aldehydes or other limited substrates, such as α-branched arylacetaldehydes, and reactions sometimes require harsh reaction conditions. In List's method, the reaction time is 168 hours. Therefore, seeking another more effective method for the direct asymmetric catalytic Kabachnik-Fields reaction which has wide range of aromatic and aliphatic aldehydes is highly desirable.

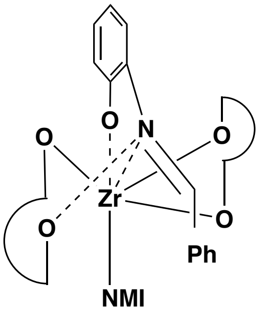
In 2001, a previous member Xue Song of our group published a Mukaiyama type condensation of ketene acetals with imines by employing a VAPOL-zirconium catalyst (**58**) with high asymmetric induction (Scheme 2.1)[36].

Scheme 2.1 Imino aldol reaction by VAPOL-zirconium catalyst



Following Kobayashi's[37] BINOL-zirconium complex generation protocol, Xue's catalyst is assembled by adding VAPOL, zirconium tetraalkoxide and *N*-methyl imidazole in 2:1:1.2 ratio in toluene stirring for 1 hour at room temperature. It is thought that this reaction involves a catalyst substrate complex **60** bearing two VAPOL ligands and a *o*-hydroxyphenylimine as another bidentate ligand on the zirconium (Figure 2.1). This key intermediate then is thought to react with ketene acetals to deliver the final β-amino esters as products.

Figure 2.1 Zirconium catalyst with two VAPOL and a *o*-hydroxyphenylimine



60

Thirteen years later, in 2014, another novel zirconium catalyst platform was developed by another group member Xin Zhang[38].The catalyst is prepared from 1.0 equivalent of zirconium tetraisopropoxide, 2.0 equivalents of (*S*)-VANOL in the presence of 1.0 equivalent of *N*-methyl imidazole as base at 60°C for 1 hour. This catalyst was found to be highly effective towards α-iminol rearrangement. With 2.5 mol% catalyst loading, the starting α-hydroxyl imines furnished the corresponding α-amino ketone with quantitative yields and over 99% *ee* (Scheme 2.2). From the crystal structure of the catalyst, it is revealed that the zirconium exists as a six-coordinate homoleptic complex with three VANOL ligands and is charge balanced with two protonated *N*-methyl imidazoles (Figure 2.2). Many rare earth metals have been reported to be bonded with three BINOL ligands in the past[39-41], but not with zirconium. It is the first time that zirconium has been found to exist as a homoleptic complex with three bis-phenol ligands.

Scheme 2.2 α-Iminol rearrangement with new chiral zirconium catalyst

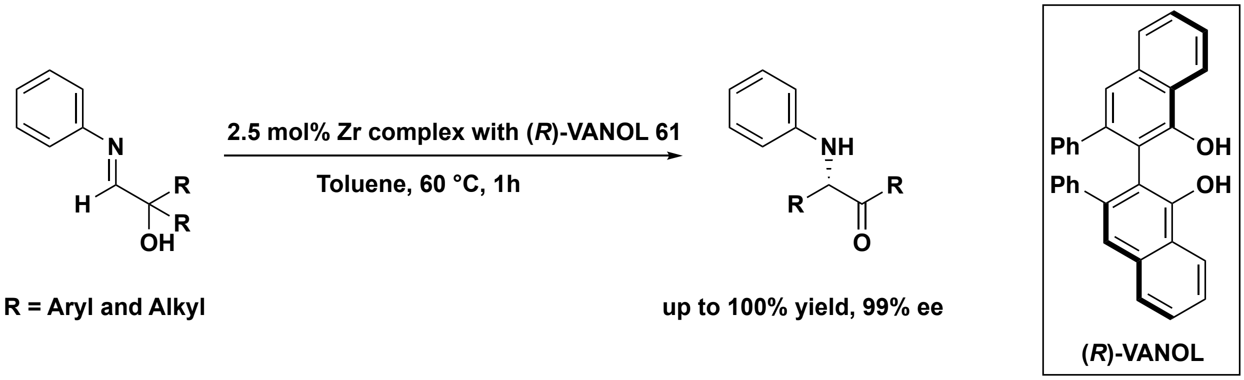
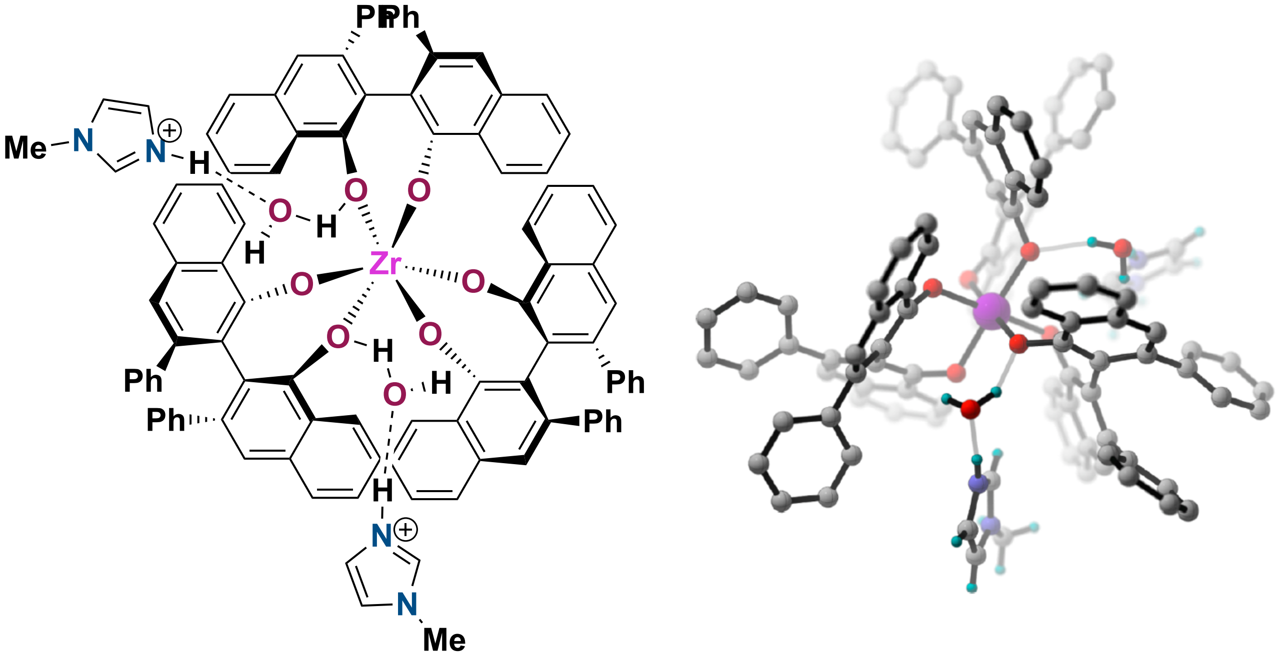


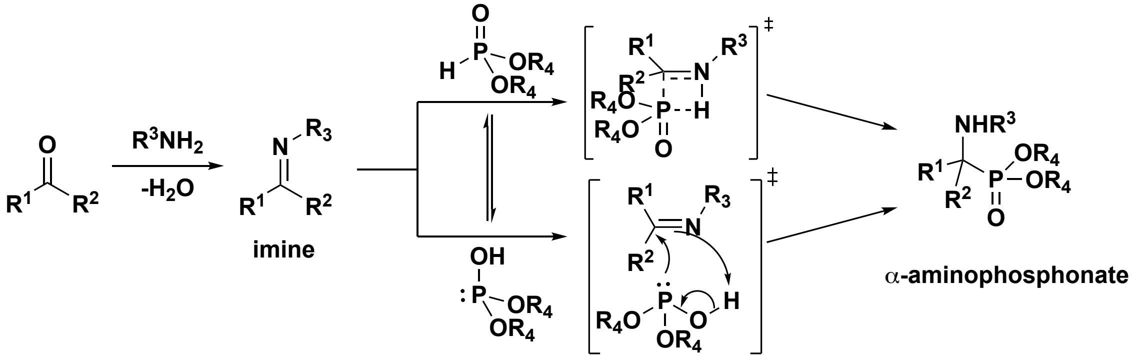
Figure 2.2 Crystal structure of the zirconium complex



61

Since above VAPOL and VANOL derived zirconium complexes both are very effective towards asymmetric catalytic reactions of imines, it was considered that perhaps they could be applied to the asymmetric Kabachnik-Fields reaction to generate α-amino phosphonates with high enantioselectivity. Theoretically, based on the mechanism of the Kabachnik-Fields reaction with aniline[42], imine formation could be followed by two different pathways in reaction with phosphite. In considering the two tautomers of phosphites, the reaction could either go through a four or five-membered ring transition state (Scheme 2.3). As the chiral borox and zirconium complexes were proved to be very effective toward reactions that involving imine intermediates, it might a good opportunity to exam these catalytic systems in Kabachnik-Fields reaction in its asymmetric version of both aromatic and aliphatic substrates.

Scheme 2.3 Two possible reaction pathways

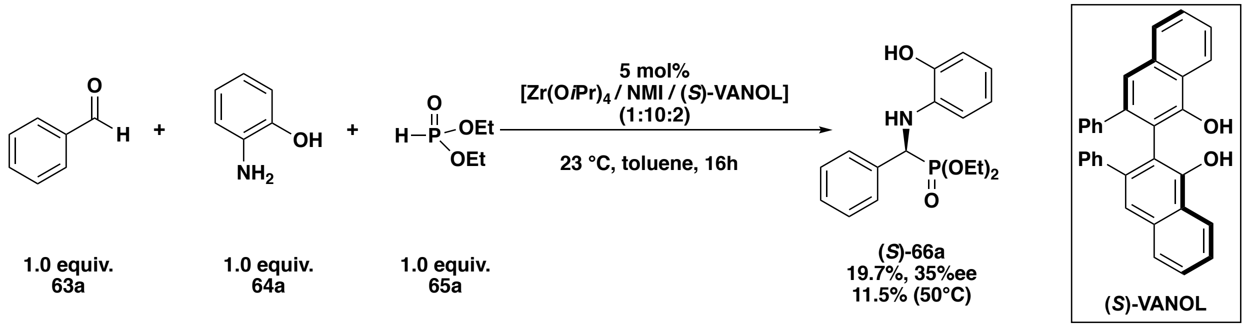


2.2 Initial results

2.2.1 First four trials

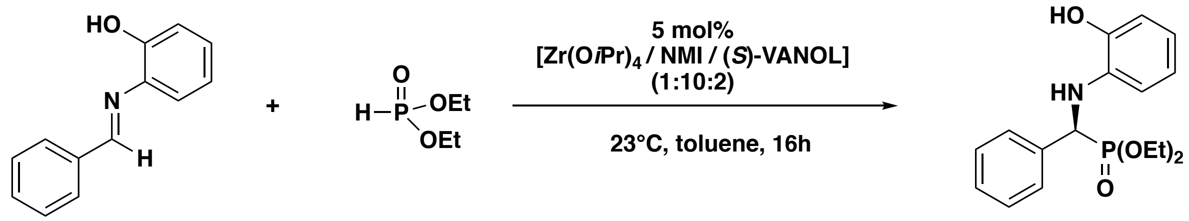
The first trial was done by using 1.0 equivalent of benzaldehyde **63a**, 1.0 equivalent of *o*-hydroxyl aniline **64a** and 1.0 equivalent of diethyl phosphite **65a** as the three starting materials with 5 mol% of the zirconium complex. The zirconium complex was prepared following Xin's protocol with 1.0 equivalent of the zirconium tetraisopropyloxide, 2.0 equivalents of the (*S*)-VANOL and 10 equivalents of the *N*-methyl imidazole (NMI), which were stirred at room temperature for 1 hour in toluene. After the reaction stirred overnight at room temperature, the desired α-amino phosphonate **66a** was obtained in 19.7% yield and 35% *ee*. In a second run at 50°C, the yield dropped to 11.5% (Scheme 2.4). Initially the absolute configuration of the product (*S*)-**66a** was assigned by comparing the HPLC retention time of the α-amino-di*i*sopropyl phosphonates, which is closely related[23].This assignment was ultimately confirmed by chemical correlation with a known compound (see chapter 3.7). All related structures from aromatic and aliphatic aldehyde were assume to be homo chiral.

Scheme 2.4 Initial two trials on the asymmetric Kabachnik-Fields reaction



For the control experiment, the imine (**67a’**) was generated from the benzaldehyde and *o*-hydroxyl aniline and was submitted to the reaction with the diethyl phosphite. Under the same reaction conditions as above, the yield of α-amino phosphonate (**66a**) jumped to 77% and 73% at room temperature and 60°C, respectively (Scheme 2.5).

Scheme 2.5 Control experiment with 2-component hydrophosphonylation (Pudorik reaction)



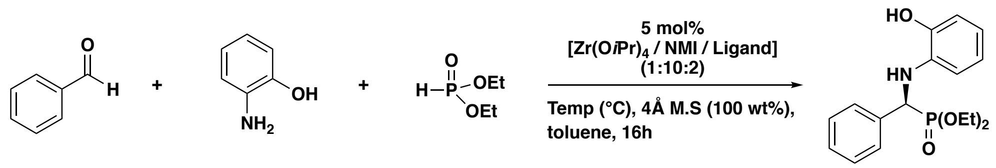
1.0 equiv.
67a’

1.0 equiv.
65a

(*S*)-66a
77.1% (isolated)
72.5% (60 °C, NMR yield)

2.2.2 Initial study on zirconium catalysts

Table 2.1 Zirconium complexes of VANOL and VAPOL at different temperatures[a]

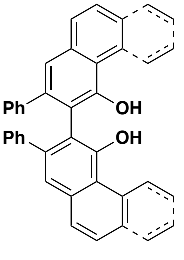


1.0 equiv.
63a

1.0 equiv.
64a

1.0 equiv.
65a

(*S*)-66a


VAPOL and VANOL

	Temperature (°C)	Ligand	% Yield[b]	% *ee*[c]
1	-45	(*S*)-VAPOL	0	-
2	-20	(*S*)-VAPOL	0	-
3	-10	(*S*)-VAPOL	40	25
4	0	(*S*)-VAPOL	44	9
5	23	(*S*)-VAPOL	94	21.5
6	-45	(*S*)-VANOL	-	-
7	-20	(*S*)-VANOL	0	-
8	-10	(*S*)-VANOL	71	19
9[d]	0	(*S*)-VANOL	89	-7
10[d]	23	(*S*)-VANOL	74	-6

[a] Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 100 wt% 4Å molecular sieves were added relative to the mass of **64a**; [b] Isolated yield; [c] *ee* was determined by HPLC; [d] (*R*)-isomer was observed.

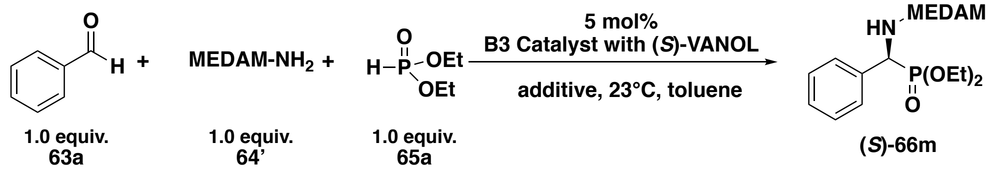
The control experiment revealed that the yield of the reaction by employing imines is much higher than for the direct three-component reaction. Therefore, in the following optimization, molecular sieves were added to promote the imine formation *in situ* in the reaction. VAPOL and VANOL zirconium complexes were examined at different reaction temperatures (Table 2.1).

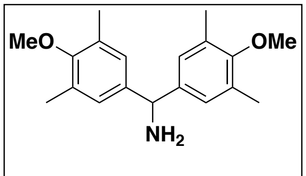
The best result was achieved by using VAPOL as ligand at room temperature, which gave the corresponding product **66a** in 94% yield and 21.5% *ee* (entry 5). The enantioselectivity was not impacted by decreasing of the temperature, but the reaction was much slower (entry 3, 4). When the temperature was -20°C, no product was detected. Compared to VAPOL, VANOL gave both slightly lower yields and *ee* in the reaction.

2.2.3 Studies with the other catalysts

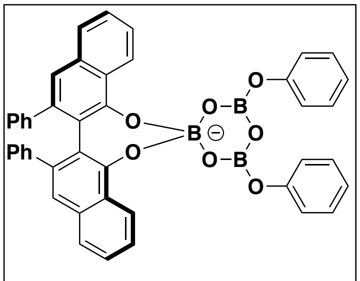
The B3 catalyst has been well developed by our group for a number of different asymmetric reactions of imines[43-47]. By switching the protecting group on the imines, high enantioselectivity can be obtained in *trans*-aziridinations, *cis*-aziridinations and asymmetric three-component Ugi reaction[48-49]. Therefore, in addition to zirconium catalysts, borox catalysts were also examined in the reaction on benzaldehyde **63a**, MEDAM amine **64’** and diethyl phosphite **65a** in the Kabachnik-Fields reaction (Table 2.2).

Table 2.2 Screen in the B3 catalyst in the Kabachnik-Fields reaction[a]





MEDAM amine 64'



B3 catalyst with (S)-VANOL

	4Å M.S (X wt%)	% Yield[b]	% *ee*[c]
1	0	0	-
2	2	50	29

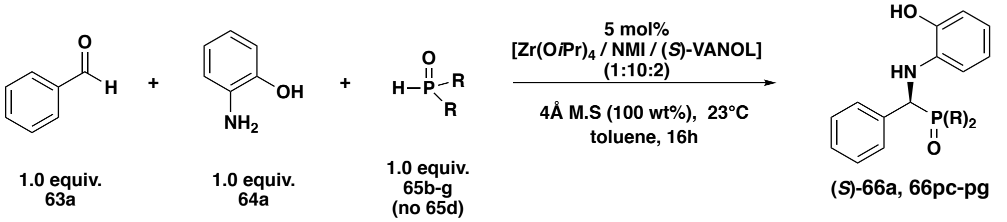
[a] 5 mol% of (*S*)-VANOL, 15 mol% of triphenylborane and 100 mol% of **64'** were added to dry toluene and the mixture was stirred 30 minutes at 80°C, followed by the addition of **63a**, **65a** and 4Å M.S (mass equivalents of **64'**). The reaction was stirred at 23°C overnight; [b] Isolated yield; [c] *ee* was determined by HPLC.

The reaction with the B3 catalyst afforded the product **66m** in 50% yield and 29% *ee* when molecular sieves were added. In the absence of molecular sieves, no product was formed. But compared to the zirconium complex, B3 catalysts gave the lower enantioselectivity (29% Vs 35%, scheme 2.3) and yield (50% Vs 89%, table 2.1) of the product. Therefore, zirconium complexes were selected to complete further optimization.

2.2.4 Study on phosphites

Various phosphites **65b-e** and diphenyl phosphine **65f** oxide were tested in the reaction (Table 2.3). With increasing the size of ethyl group on the phosphite to *iso*propyl, *tert*butyl and phenyl, yields dropped accordingly from 74% to 0 with VANOL zirconium catalyst, but without increases in enantioselectivity. No product was generated when diphenyl phosphine oxide was used instead of a phosphite. Di-*iso*-propyl phosphite was also examined with the VAPOL zirconium, catalyst giving 80% yield, but there was no increase in the asymmetric induction.

Table 2.3 Phosphites screen[a]



	R	% Yield[b]	% *ee*[c]
1[d]	OEt (**65b**)	74	-6
2	O*i*Pr (**65c**)	44	11
3	O*t*Bu (**65e**)	0	-
4	OPh (**65f**)	0	-
5	Ph (**65g**)	0	-
6[d,e]	O*i*Pr (**65c**)	80	-10

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(OiPr)_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-VANOL in dry toluene for 30 minutes at room temperature under the air; 100 wt% 4Å molecular sieves were added relative to the mass of **64a**; [b]Isolated yield; [c]*ee* was determined by HPLC; [d](R)-isomer was obsevered; [e]Ligand is (*S*)-VAPOL.

2.2.5 Solvent studies

Solvents such as dichloromethane, benzene, acetonitrile and THF were examined for the reaction, but none gave a significant improvement in the enantioselectivity. The best solvent was acetonitrile which delivered the product in 81% yield and 21% *ee*. However, toluene was still selected to be the solvent for the optimization as the procedure for preparing zirconium catalyst is easier in toluene (Table 2.4).

Table 2.4 Solvent screen[a]

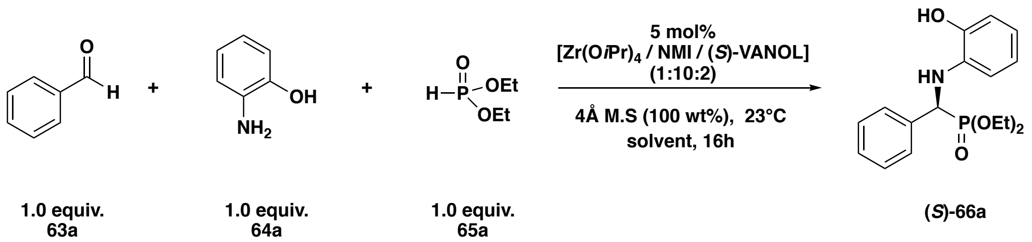


Table 2.4 (continued)

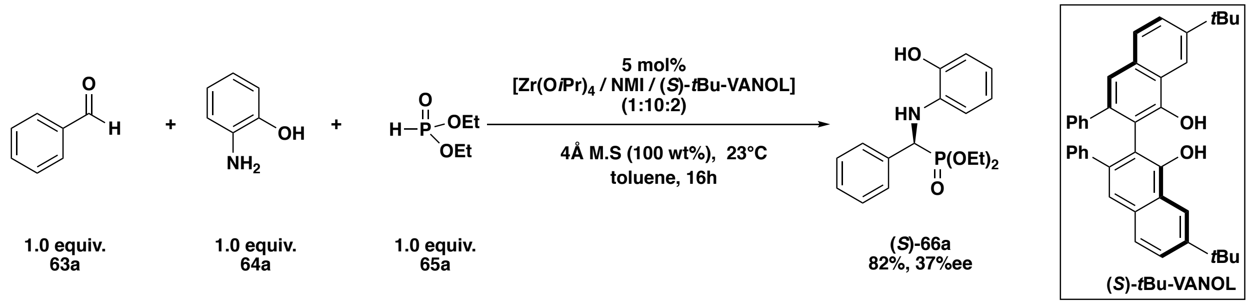
	Solvent	% Yield[b]	% *ee*[c]
1	Toluene	74	-6
2	DCM	95	-5
3	Benzene	88	-6
4	Acetonitrile	81	-21
5	THF	64	-7

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(OiPr)_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-VANOL in dry toluene for 30 minutes at room temperature under the air; 100 wt% 4Å molecular sieves were added relative to the mass of **64a**; [b]Isolated yield; [c]*ee* was determined by HPLC.

2.2.6 The first breakthrough with *t*Bu-VANOL and dimethyl hydroxylaniline

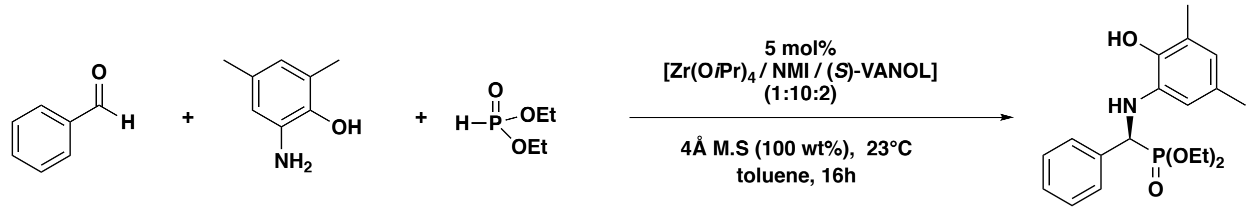
Having done screens of phosphites, solvents, and temperatures with zirconium catalysts from VANOL and VAPOL, attention was turned to optimization of the reaction to other ligands and other hydroxyl anilines. It was a delight to observe that the enantioselectivity of the desired product **66a** was increased to 37% *ee* when (*S*)-*t*Bu-VANOL was employed as the ligand (Equation 2.1) compared to 6% *ee* with the (*S*)-VANOL ligand under the same conditions (Table 2.1).

Equation 2.1 The first breakthrought by employing *t*Bu-VANOL



Furthermore, after replacing the unsubstituted 2-hydroxyaniline **64a** with 2-hydroxy-3,5-dimethylaniline **64b**, the yield and the enantioselectivity increased to 85% and 57% *ee*, respectively with (*S*)-VANOL catalyst (Equation 2.2). Those two experiments indicated the steric effect of substituents on the aniline and in the 7,7' positions of the VANOL have a great impact on the asymmetric induction.

Equation 2.2 The first breakthrough by empolying 2-hydroxy-3,5-dimethylaniline



1.0 equiv.
63a

1.0 equiv.
64b

1.0 equiv.
65a

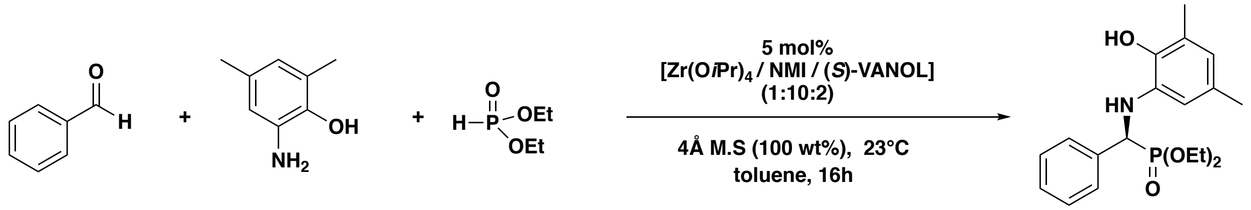
66b
85%, 57%ee

2.3 Further optimizations of the Kabachnik-Fields reaction

2.3.1 Ligand screen with 3,5-dimethyl-2-hydroxylaniline

A set of eleven different 7,7’-substituted VANOL derivative (**L1-L12**) were examined in the model reaction with benzaldehyde **63a**, 3,5-dimethyl-2-hydroxylaniline **64b** and diethyl phosphite **65a** (Scheme 2.6). Upon changing the substituents on the 7,7’ positions on the VANOL ligand, it was found that bulky alkyl substituted VANOL gave better result than other functional groups, such as halogen, aryl or heterocyclic groups. Among all of the alkyl substituted VANOLs, *n*Bu and cyclohexyl-VANOL (**L4** and **L12**) gave around 68% - 73% *ee* and 80% yields. Slightly lower yields and *ee* (55%, -67% *ee*) was obtained with *t*Bu-VANOL (**L5**). In terms of the previous solvent screen, acetonitrile showed good results to some extent in the model reaction and was tested with (*S*)-*t*Bu-VANOL (**L5**), but both yield and enantioselectivity was not better compared to toluene. The silyl substituted VANOL (**L3**) also gave 71% *ee* for the product, however the yield was only 47%.

Scheme 2.6 Ligand screen with 3,5-dimethyl-2-hydroxylaniline

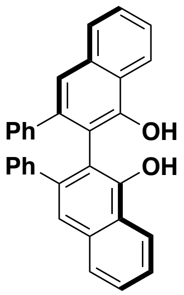


1.0 equiv. 63a

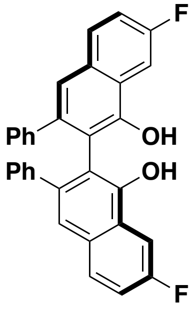
1.0 equiv. 64b

1.0 equiv. 65a

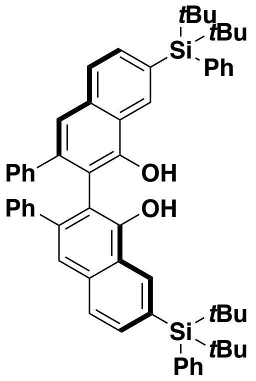
66b
85%, 57%ee



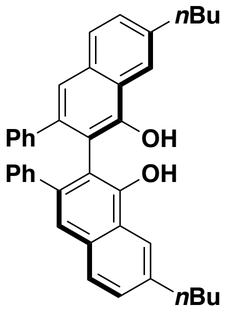
(*S*)-L1
85%, 57%ee



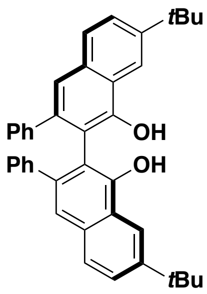
(*S*)-L2
62%, 7%ee



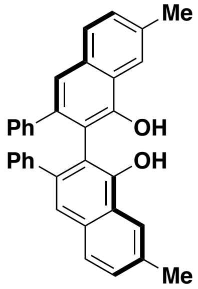
(*S*)-L3
47%, 71%ee



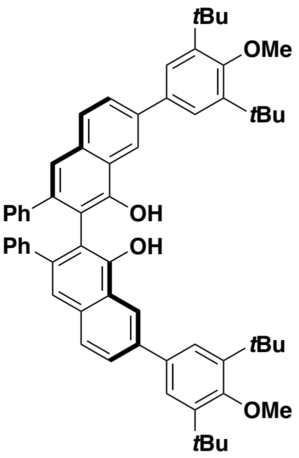
(*R*)-L4
82%, -68%ee[a]



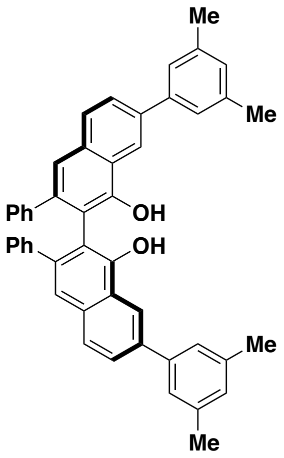
(*S*)-L5
55%, 67%ee
45%, 48% (in acetonitrile)[b]



(*S*)-L6
58%, 15%ee

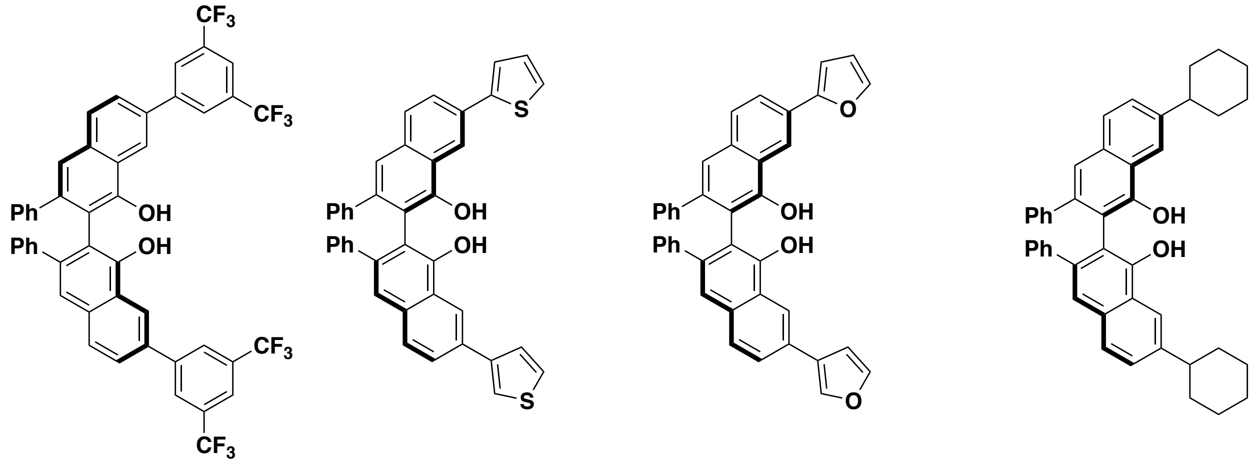


(*S*)-L7
10%, 6%ee



(*S*)-L8
77%, 50%ee

Scheme 2.6 (continued)



(*S*)-L9
70%, 7%ee

(*R*)-L10
43%, -56%ee[a]

(*R*)-L11
38%, -59%ee[a]

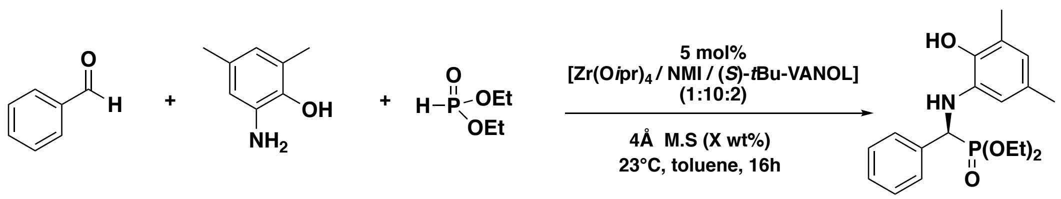
(*R*)-L12
81%, -73%ee[a]
(200 wt% M.S)[c]

[a](*R*)-isomer of the product was obtained; [b]the solvent is acetonitrile; [c]200 wt% of M.S was used.

2.3.2 Impact of the amount of 4Å molecular sieves

Molecular sieves can promote the *in-situ* generation of imine in the three-component Kabachnik-Fields reaction (table 2.2). From the ligand screen, it was found that the addition of 2.0 equivalents of 4Å molecular sieves (mass equivalent to 2-hydroxylaniline) with Cy$_2$VANOL (**L12**) gave a higher yield and enantioselectivity than 1.0 equivalent. Therefore, different amounts of 4Å molecular sieves were examined in the optimization process (Table 2.5).

Table 2.5 Screen of equivalent of 4Å molecular sieves[a]



1.0 equiv.
63a

1.0 equiv.
64b

1.0 equiv.
65a

(*S*)-66b

Table 2.5 (continued)

	X wt% (mass equiv. to **64b**)	% Yield[b]	% *ee*[c]
1	1	55	67
2	2	87	82
3	4	88	79
4	6	74	47

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(O\textit{i}Pr)_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; [b]Isolated yield; [c]*ee* was determined by HPLC.

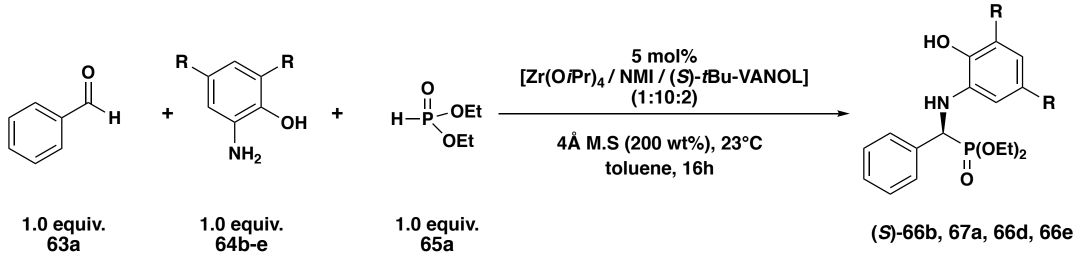
Form these experiments, it was found that when 200 wt% of 4Å molecular sieves was induced into the reaction, the yield of the product reached 87% and the *ee* was 82%. Although 400 wt% of 4Å molecular sieves gave similar results, the reaction became very sticky and it was hard to stir. 3Å and 5Å molecular sieves (not shown here) were also examined in previous studies with benzaldehyde (**63a**), 2-hydroxyaniline (**64a**) and diethyl phosphites (**65a**), they did not make much difference on the reaction outcome.

2.3.3 Screen of dialkyl-2-hydroxyanilines

As is described above in our first breakthrough came when it was found both the structure of the ligands and of the anilines have the strong impact on yields and enantioselectivity on the reaction (Equation 2.1 and 2.2), thus, additional dialkyl-2-hydroxyanilines were synthesized and examined in their reactions with the benzaldehyde (**63a**) (Table 2.6). It was delightful to see that after switching from a methyl to *iso*-propyl group on the aniline, the enantioselectivity increased to 90% *ee* with 76% yield (Table 2.6, entry 2). The reaction with *n*Butyl hydroxyanline (**64d**) gave a slight decrease in the yield and *ee* (73% and 82% ee). Bulkier *tert*-butyl group, boosted the enantioselectivity to 92% *ee* at the room temperature but with only 12% yield (entry 4). Increasing the temperature to 40°C and 60°C did help to improve the yield, but *ee* dropped back to 89% (entry 5 and

6). Therefore 3,5-diisopropyl-2-hydroxylaniline (**64c**) was selected as the standard aniline instead of 3,5-dimethyl-2-hydroxylaniline (**64b**).

Table 2.6 Screen of different dialkyl-substituted hydroxylanlines[a]



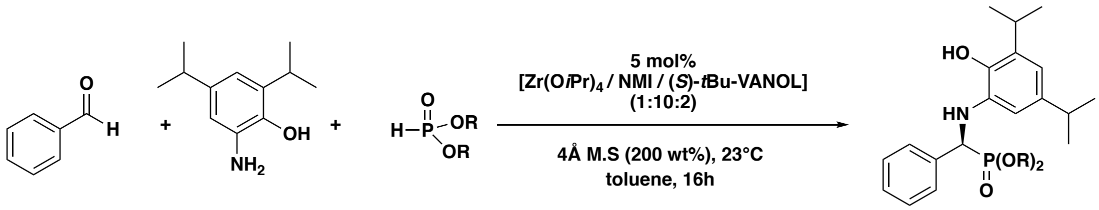
	R	Temperature(°C)	% Yield[b]	% *ee*[c]
1	Me (**64b**)	23	87	82
2	*i*Pr (**64c**)	23	76	90
3[d]	*n*Bu (**64d**)	23	73	-82
4	*t*Bu (**64e**)	23	12	95
5	*t*Bu (**64e**)	40	41	92
6[d]	*t*Bu (**64e**)	60	52	-89

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of the aniline were added; [b]Isolated yield; [c]*ee* was determined by HPLC; [d](*R*)-*t*Bu-VANOL was used in the reaction.

2.3.4 Screen of dialkyl phosphites

From the previous screen of dialkyl phosphites, diethyl phosphites (**65a**) gave the best result for delivering the desired product with 2-hydroxyaniline (Table 2.3). However, after 3,5-diisopropyl-2-hydroxylanilne (**64c**) was identified as the superior substrate, it was decided to examine different dialkyl phosphites again under the standard condition to see if a better combination of reagents could be found to improve the yield and enantioselectivity (Table 2.7).

Table 2.7 Screen of dialkyl phosphites with 3,5-di*iso*propyl-2-hydroxyaniline[a]



1.0 equiv. 63a

1.0 equiv. 64c

1.0 equiv. 65a-e

(*S*)-67pa-pe

	R	% Yield[b]	% *ee*[c]
1	Et (**65a**)	76	90
2	Me (**65b**)	71	79
3	*i*Pr (**65c**)	45	-91
4[d]	*n*Bu (**65d**)	65	-90
5[d]	*t*Bu (**65e**)	0	-

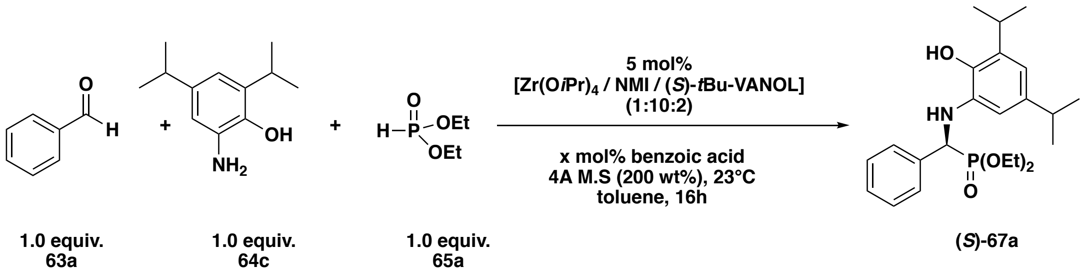
[a] Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b] Isolated yield; [c] *ee* was determined by HPLC; [d] (*R*)-*t*Bu-VANOL was used in the reaction.

With increasing the size of the alkyl group of the phosphites from methyl to *tert*-butyl group, the yield dropped from 71% to 0. However, except for dimethyl phosphite (**65b**), the enantioselectivity remained around 90% *ee* for diethyl, di*iso*propyl and di*n*butyl phosphites. No product could be detected when di*tert*-butyl phosphite was employed in the reaction. This could be the result of the steric effect of the *tert*-butyl group.

2.3.5 Benzoic acid as additive

An unusual observation was made when freshly distilled benzaldehyde was employed in the reaction. The yield of the reaction decreased to 60% from 76%. Considering that benzaldehyde is very easily oxidized to benzoic acid during storage, extra amounts of benzoic acid were added to the reaction to see if they help to increase the yield (Table 2.8).

Table 2.8 Different amounts of benzoic acid in the reaction[a]



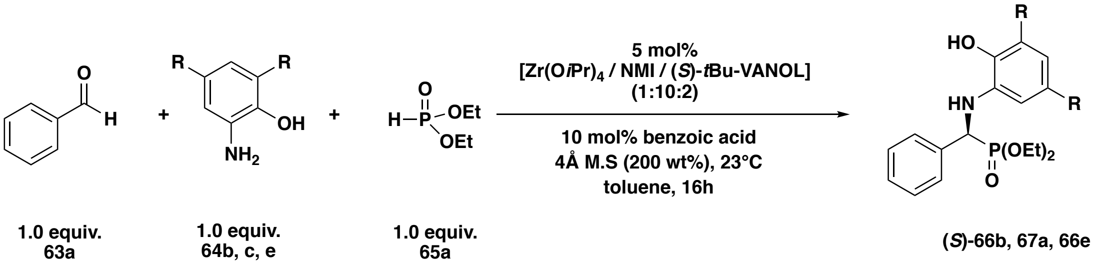
	X mol%	% Yield[b]	% *ee*[c]
1	0	60	89
2	5	86	92
3	10	83 (76)[d]	94 (94)
4	100	82	77
5[e]	5	59	88

[a] Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b] Isolated yield; [c] *ee* was determined by HPLC; [d] The yield in parentheses was the second time of running the same reaction; [e] 100 wt% of 4Å molecular relative to the mass of **64c** was added to the reaction.

From table 2.8, it can be noticed that the addition of 5 or 10 mol% of benzoic acid promoted the yield of the model reaction to around 80% and gave a slight increase in the *ee* to -94% when 10 mol% of benzoic acid was used (entry 3). Further raising the amount of benzoic acid to 100 mol% resulted in a drop in both yield and *ee* to 82% and 88%, respectively. The last experiment was carried out with 1.0 equivalent of molecular sieves and 5 mol% of benzoic acid to see if the amount of molecular sieves could be reduced. However, the result indicated that 200 wt% of 4Å molecular sieve relative to aniline was still necessary.

To further confirm the effect of benzoic acid, three dialkyl-2-hydroxy (**64b-e**) anilines were tested in the presence of benzoic acid (Table 2.9). The yields for all three of the dialkyl-2-hydroxylaniline slightly increased, but the *ee* stayed almost the same. This indicates that the effect of benzoic acid is mainly on the yield of the reaction, not enantioselectivity.

Table 2.9 Three dialkyl hydroxylanlines with 10 mol% of benzoic acid[a]

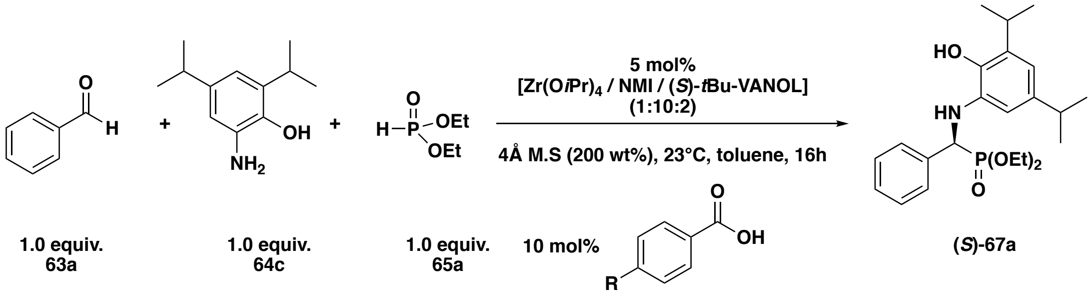


	R	% Yield[b,c]	% *ee*[c,d]
1	Me **(64b)**	87(87)	80(82)
2	*i*Pr **(64c)**	83(76)	94(90)
3	*t*Bu **(64e)**	17(12)	95(95)

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of the aniline were added; [b]Isolated yield; [c]The yield and *ee* in parentheses were from a reaction without 10 mol% of benzoic acid; [d]*ee* was determined by HPLC.

The benzoic acid effect was extended to 4-nitrobenzoic acid and 4-methoxylbenzoic acid, which were also tested in the reaction to discover the impact of the electronic status of the benzoic acid (Table 2.10). The enantioselectivity of the reactions with all of the benzoic acid derivatives are similar (94% *ee*), however, the yield increased from 72% with the electron-rich 4-methoxylbenzoic acid to 100% with the electron-poor 4-nitrobenzoic acid. This discovery could be of value in optimization of aliphatic aldehydes in Kabachnik-Fields reaction and will be discussed in the chapter 3.

Table 2.10 Screen of benzoic acids[a]



	R	% Yield[b]	% *ee*[c]
1	H	83	94
2	OMe	72	95
3	NO_2	100	94

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(OiPr)_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]Isolated yield; [c]*ee* was determined by HPLC.

2.3.6 Screen of reaction concentration

The standard concentration in studies to this point was 0.5 M and increasing the concentration to 1M, the reaction gave the similar results (83%, 94% *ee*, table 2.11, entry 1). Upon dropping the concentration to 0.05 M and 0.01 M, the yield decreased to 31% and 16%, respectively, but the enantioselectivity dropped only slightly to 85% *ee* (Table 2.11).

Table 2.11 Screen of reaction concentration[a]

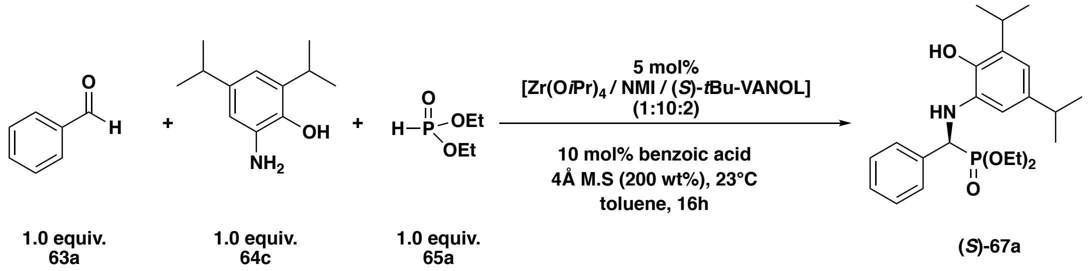


Table 2.11 (continued)

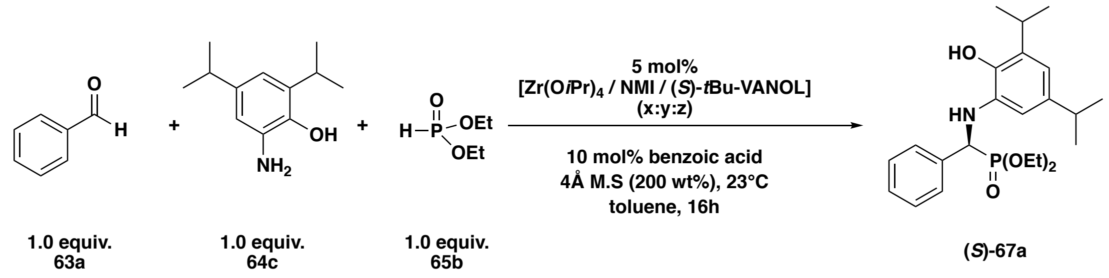
	Concentration	% Yield[b]	% *ee*[c]
1	1M	83	94
2	0.5M	83	95
3	0.05M	31	87
4	0.01M	16	83

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 10.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]Isolated yield; [c]*ee* was determined by HPLC.

2.3.7 Ratio of catalyst components

In all the previous studies, the zirconium catalyst for the reaction was prepared from 1.0 equivalent of zirconium(IV) *iso*propoxide *iso*propanol complex, 10.0 equivalents of *N*-methyl imidazole and 2.0 equivalents of ligands in toluene. However, in Xin's catalyst protocol for the α-iminol rearrangement[38], the ratio of zirconium, *N*-methyl imidazole and the ligands is 1:1:3. Therefore, several experiments were performed with different ratios of the catalyst components to see how the results would be impacted (Table 2.12).

Table 2.12 Screen of catalyst component ratio[a]



	Catalyst component ratio (x:y:z)[b]	% Yield[c]	% *ee*[d]
1	1:1:2	83	93
2	1:1:3	90	93
3	1:10:2	83	95

[a]Zirconium catalysts were prepared by stirring a mixture of x equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, y equivalents of N-methyl imidazole (NMI) and x equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]x is zirconium(IV) *iso*propoxide *iso*propanol; y is *N*-methyl imidazole and z is (*S*)-*t*Bu-VANOL; [c]Isolated yield; [d]*ee* was determined by HPLC.

Upon decreasing the loading of the *N*-methyl imidazole, the reaction is only slightly effected. When 3.0 equivalents of *t*Bu-VANOL was used in the preparation of the catalyst, the yield increased slightly to 90% but the *ee* remained the same (entry 2). It is quite surprising that 10.0 equivalent of *N*-methyl imidazole didn't kill the reaction, as in Xin's paper[38], since in Xin's study on the α-iminol rearrangement, 10.0 equivalents of NMI resulted in no product formed. This could imply that the catalyst in asymmetric Kabachnik-Fields reaction is not same as in α-iminol rearrangement, but this has yet to be determined.

2.3.8 Reaction time

In the end, reactions for different time from 4 hours to 24 hours were performed. After 4 hours, the *ee* reached 92% and after 8 hours, the yield of the reaction was similar (83% and 85%, respectively, Table 2.13, entry 2 and 3) and *ee* was 94% for both of them. The best result was achieved after 16 hours, which the yield was 90% and the *ee* was 94% (Table 2.13, entry 4). Continuously increasing the reaction time to 24 hours, the yield remained the same as 16 hours.

Table 2.13 Reaction time[a]

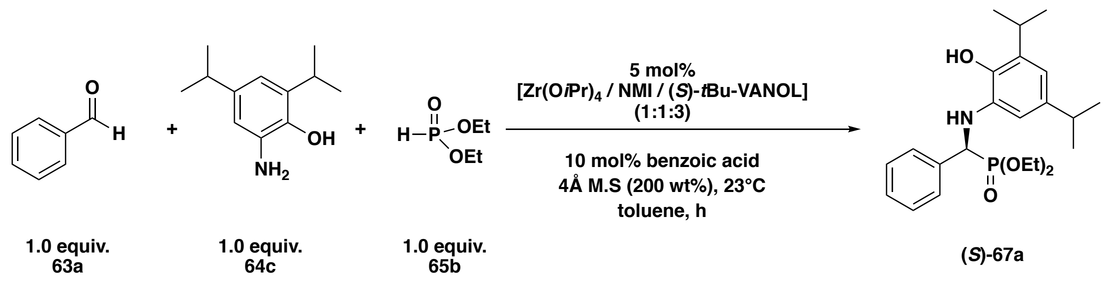


Table 2.13 (continued)

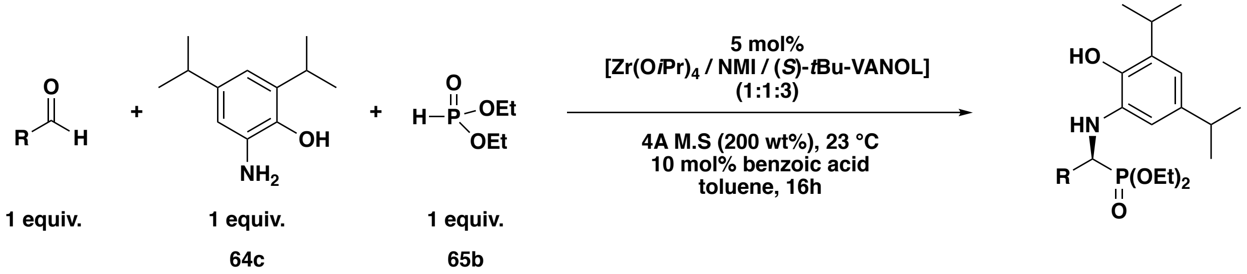
	Time (h)	% Yield[b]	% *ee*[c]
1	4	44	92
2	8	83	94
3	10	85	94
4	16	90	94
5	24	90	94

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(OiPr)_4$•HO*i*Pr, 1.0 equivalents of N-methyl imidazole (NMI) and 3.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]Isolated yield; [c]*ee* was determined by HPLC.

2.3.9 The optimal conditions for aromatic aldehydes

Finally, the optimal standard reaction conditions for asymmetric Kabachnik-Fields reaction with aromatic aldehydes were identified as those indicated in Scheme 2.7. The zirconium catalyst (5 mol%) was prepared from 1.0 equivalent of zirconium(IV) *iso*propoxide *iso*propanol, 1.0 equivalent of *N*-methyl imidazole and 3.0 equivalents of (*S*)-*t*Bu-VANOL in toluene, 10 mol% benzoic acid and 2 mass equivalents of 4Å molecular sieves were added to the reaction with 1.0 equivalent each of the aromatic aldehyde, 3,5-di*iso*propyl aniline and diethyl phosphite. The mixture was stirred 16 hours at room temperature under nitrogen and gave the desired aryl substituted α-amino phosphonates.

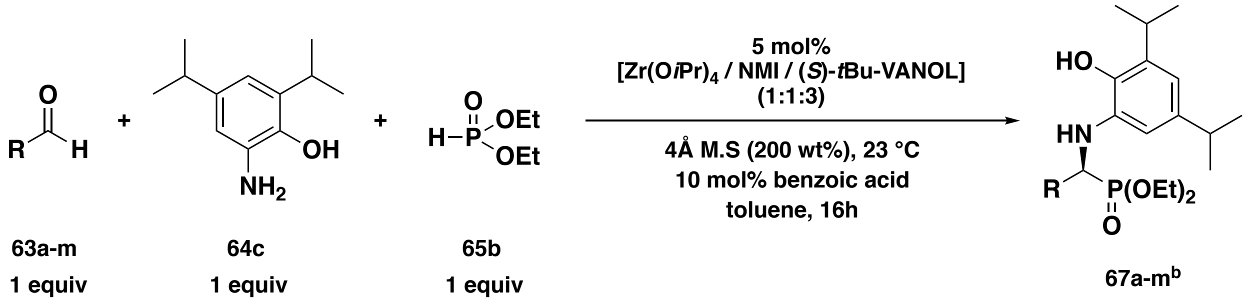
Scheme 2.7 Optimal reaction condition



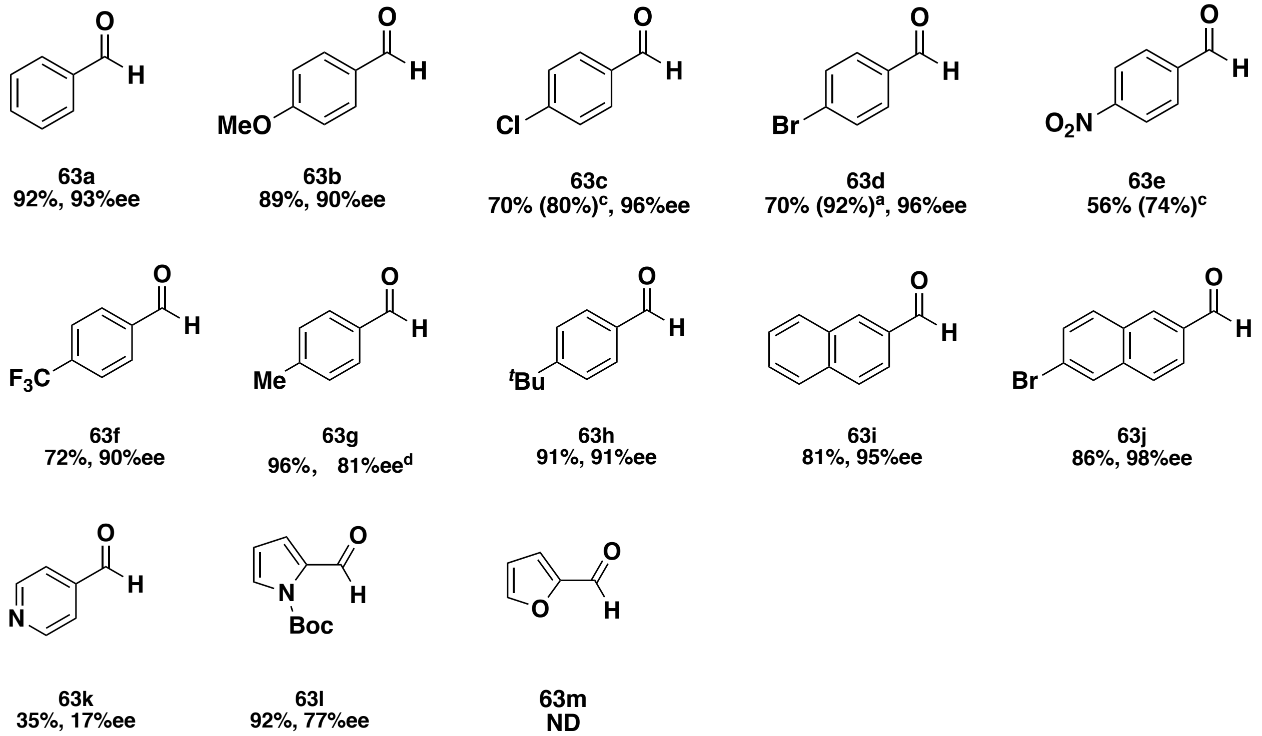
2.4 Substrate scope of aromatic aldehydes

Thirteen examples of different aromatic aldehydes have been examined under the optimal conditions (Scheme 2.8). Both electron-rich and electron-poor substituents on the *para* position of the benzaldehyde (**63b**, **63c**, **63d**, **63f**) are tolerated to give the corresponding α-amino phosphonates with excellent yield and *ee*. An exception is the 4-methylbenzaldehyde (**63g**), which could be converted to the product in 96% yield, but only 81% *ee*. Also 2-naphthaldehyde (**63i**) and its bromo-derivative (**63j**) could be converted in 93%, 86% yield and 95% *ee*, 98% *ee*, respectively. A few other heterocyclic aldehydes (**63k**, **63l**, **63m**) were also tested in the reaction. The desired product was only obtained with 35% yield and 17% *ee* with 4-pyridinecarboxylic aldehyde (**63k**). In the reaction with 2-furancarboxylic aldehyde, there was no product detected after 16 hours due to the instability of the starting material. When the 2-pyrrolcarboxylic aldehyde was employed in the reaction, the solution instantly went black which indicated the decomposition of the starting material and no product was generated. However, after protecting the nitrogen with a Boc group, a 92% yield and 77% *ee* of α-amino phosphonates **67l** was isolated.

Scheme 2.8 Scope of aromatic aldehydes[a]



Scheme 2.8 (continued)



63a
92%, 93%ee

63b
89%, 90%ee

63c
70% (80%)[c], 96%ee

63d
70% (92%)[a], 96%ee

63e
56% (74%)[c]

63f
72%, 90%ee

63g
96%, 81%ee[d]

63h
91%, 91%ee

63i
81%, 95%ee

63j
86%, 98%ee

63k
35%, 17%ee

63l
92%, 77%ee

63m
ND

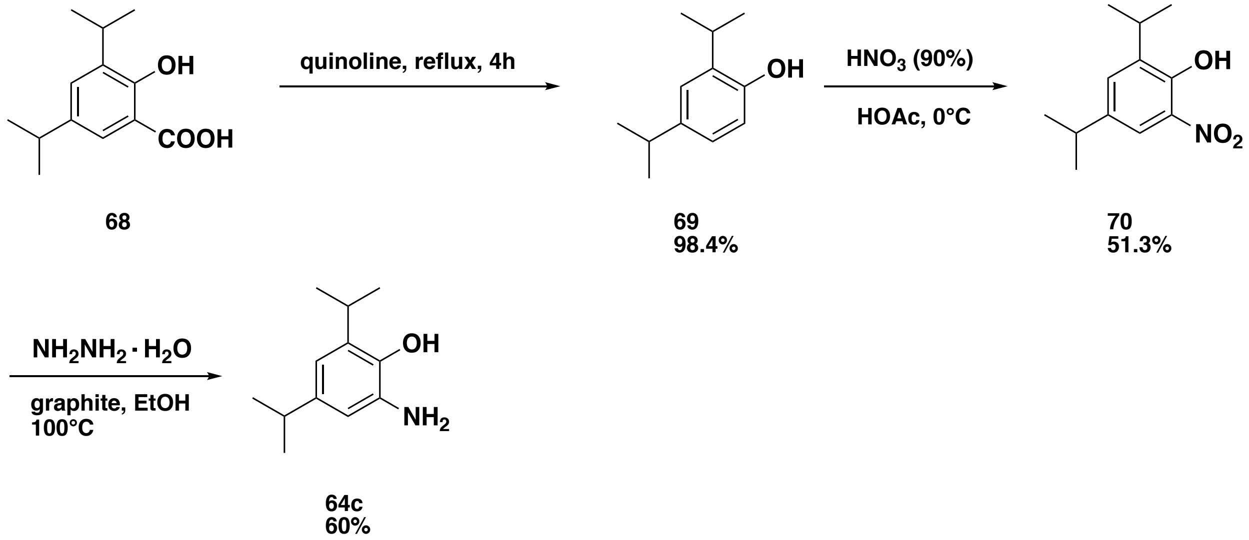
[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 1.0 equivalents of N-methyl imidazole (NMI) and 3.0 equivalents of (*S*)-*t*Bu-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]All yields are isolated yields and *ee* was determined by HPLC; [c]reaction time was 40h; [d]*ee* cannot be confirmed by HPLC for this substrate;[e]5 mol% benzoic acid was used.

2.5 Synthesis of starting materials

2.5.1 Synthesis of 2-hydroxy-3.5-di*iso*propylaniline (64c)

3,5-Di*iso*propyl-2-hydroxy (**64c**) aniline was synthesized from the commercial available 2-hydroxy-3,5-di*iso*propylbenzoic acid (**68**) (Scheme 2.9). 2-Hydroxy-3,5-di*iso*propylbenzoic acid (**68**) was refluxed in quinolone for 4 hours to furnish the decarboxylated product 2,4-diisopropyl phenol (**69**) in 94% yields[50]. The following nitration and reduction by hydrazine[51] produced the final 2-hydroxy-3.5-di*iso* propylaniline (**64c**) in moderate yield.

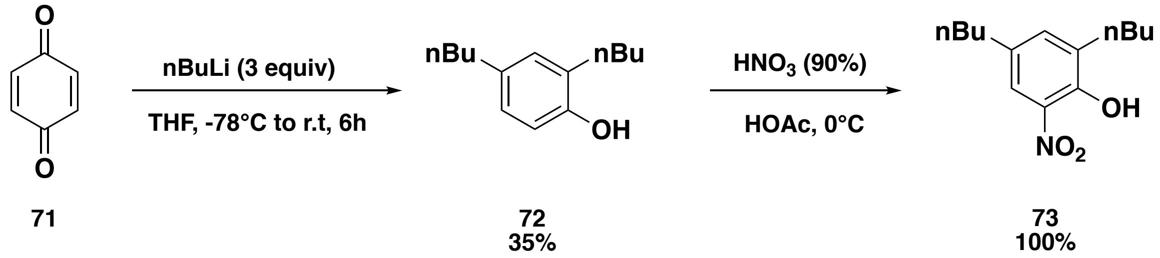
Scheme 2.9 Synthesis of 2-hydroxy-3.5-di*iso*propylaniline



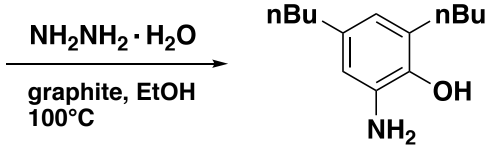
2.5.2 Synthesis of 3,5-di*n*butyl-2-hydroxyaniline (64d)

The synthesis of 2-hydroxy-3,5-di*n*butylaniline is a little different from above syntheses of **64c**. It starts from the reaction of benzoquinone (**71**) and 3.0 equivalents of *n*BuLi in THF at -78°C, which generated 2,4-di*n*butylphenol (**72**) in 35% yield[52]. The subsequent nitration (100%) and reduction[51] finally delivered the product **64d** in 49% yield (Scheme 2.10).

Scheme 2.10 Synthesis of 3,5-di*n*butyl-2-hydroxyaniline



Scheme 2.10 (continued)

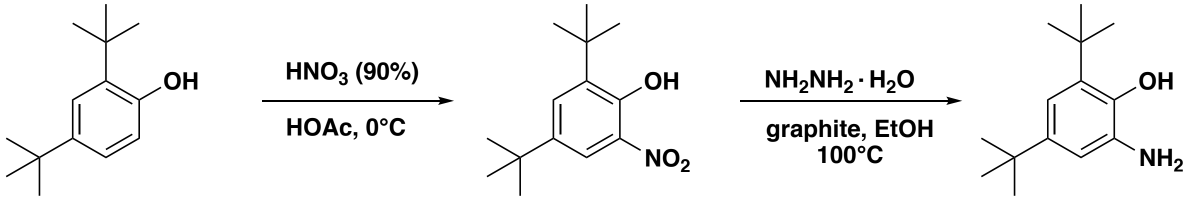


64d
49%

2.5.3 Synthesis of 3,5-di*t*butyl-2-hydroxyaniline (64e)

The synthesis of **64e** starts with the nitration of 2,4-di*t*butylphenol (**73**), which gave the 2,4-di*t*butyl-6-nitrophenol (**74**) in 56% yield[51]. Subsequent hydrazine reduction[51] completed the synthesis of the desired product **64e** in 94% yield (Scheme 2.11).

Scheme 2.11 Synthesis of 3,5-di*t*butyl-2-hydroxyaniline



73

74
56%

64e
94%

2.6 Conclusion

In this chapter, the asymmetric Kabachnik-Fields with aromatic aldehydes catalyzed by a *t*Bu-VANOL zirconium complex has been described in detail, including its initial development, optimization, substrate scope and the synthesis of necessary starting materials. In the finding of optimization process, two key effects were observed that greatly impacted the enantioselectivity. The first is the substituents on the 7 and 7'-positions of VANOL ligand. Switching the substituent from H to *t*butyl, *n*butyl and cyclohexyl groups, the enantioselectivity increased dramatically. The second has to do with the different sizes of the substituents on the 2-hydroxyanilines. With increasing the size of alkyl groups in the 3- and 5- positions of the 2-hydroxyanilines from H to *t*butyl group, the *ee* was boosted from 37% to 95%. These two key effects will also be of prime importance in directing the optimization on aliphatic aldehydes in the asymmetric Kabachnik-Fields reaction, which is more challenging because it is most undeveloped aspect of the reaction.

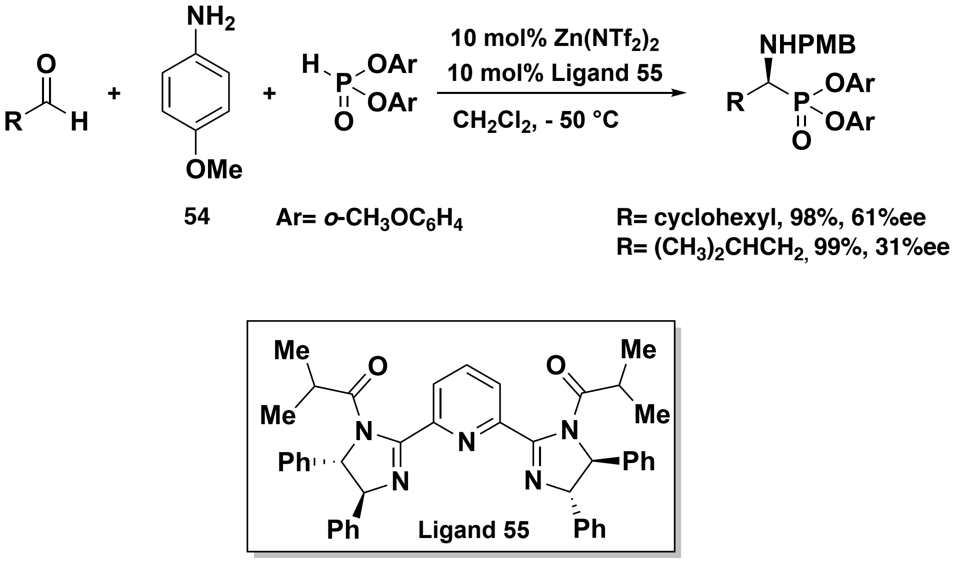
CHAPTER THREE

CATALYTIC ASYMMETRIC KABACHNIK-FIELDS REACTION WITH ALIPHATIC ALDEHYDES

3.1 Introduction

In this chapter, the discussion will be focused on the asymmetric Kabachnik-Fields reaction with aliphatic aldehydes. As mentioned in chapter one, there was only one paper that reported on the asymmetric three-component Kabachnik-Fields reaction with simple aliphatic aldehydes (only two examples) and the enantioselectivity was poor to moderate (Scheme 3.1).[35]

Scheme 3.1 Previous examples of asymmetric Kabachnik-Fields reaction with aliphatic aldehydes



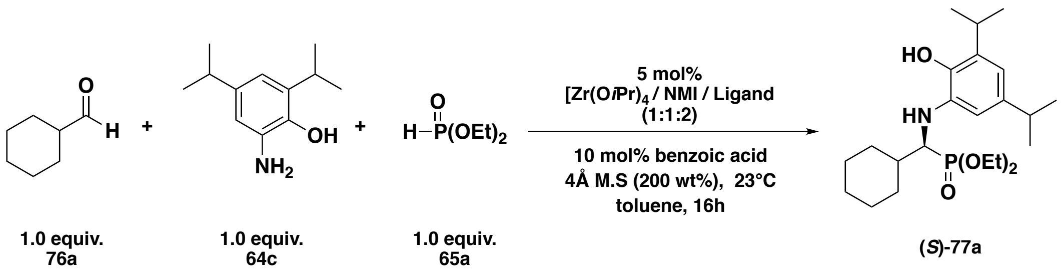
Therefore, achieving higher enantioselectivity and developing a broader reaction scope with milder reaction condition for aliphatic aldehydes would be compelling and important. Based on the experience of optimization with aromatic aldehydes, at the beginning study of the aliphatic substrates, the optimal reaction condition of aromatic aldehydes in the asymmetric Kabachnik-Fields reaction was applied to it.

3.2 Initial results

3.2.1 Ligand screen with 1:1:2 zirconium catalyst

Given the success with the optimized condition of aromatic aldehydes (Chapter 2, Table 2.12), the first experiment on an aliphatic aldehyde was carried out with cyclohexanecarboxylic aldehyde (**76a**), 2-hydroxy-3.5-di*iso*propylaniline (**64c**) and diethyl phosphite (**65a**) under catalysis by the *t*Bu-VANOL zirconium complex, which was prepared with 1.0 equivalent of Zirconium(IV) isopropoxide isopropanol, 1.0 equivalent of *N*-methyl imidazole and 2.0 equivalents of *t*Bu-VANOL. In addition, 5 mol% of benzoic acid and 200 wt% of 4Å molecular sieves (mass equivalents to aniline **64c**) were also added as additives into the reaction, after stirring 16 hours, a 45% yield and 11% *ee* of the desired α-amino phosphonates **77a** were obtained (Table 3.1, entry 1).

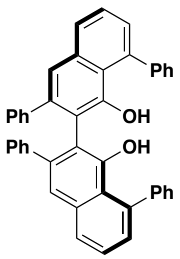
Table 3.1 Ligand screen with 1:1:2 zirconium complex[a]



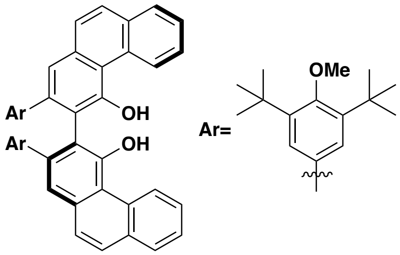
	Ligand	% Yield[b]	% *ee*[c]
1	(*S*)-*t*Butyl-VANOL	45	11
2	(*S*)-VAPOL	65	6
3	(*S*)-8,8'-Ph_2-VANOL	39	0
4	(*R*)-BUDAM-VAPOL	15	0
5	(*S*)-VANOL	63	28
6[d]	(*S*)-VANOL (1:2:3)	63	53

[a] Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 1.0 equivalents of N-methyl imidazole (NMI) and 2.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b] Isolated yield; [c] *ee* was determined by HPLC; [d] Catalyst component ratio is 1:2:3.

Table 3.1 (continued)



(*S*)-8,8'-Ph-VANOL

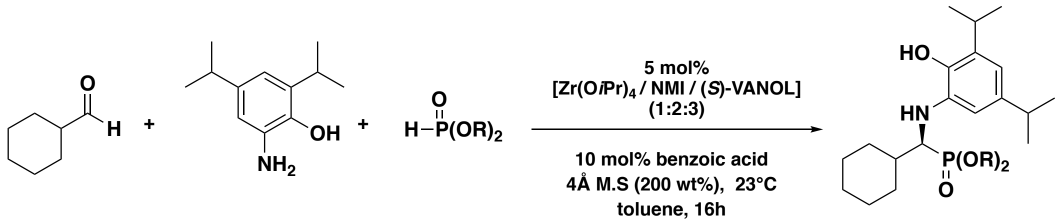


(*R*)-BUDAM-VAPOL

The best outcome was observed with a catalyst derived from VANOL (table 3.1, entry 5 and 6). Comparing with entry 5 with entry 6, the only difference is the ratio of the components in the catalyst. With 3.0 equivalents of VANOL, much high enantioselectivity can be achieved than with 2.0 equivalents (53% *ee* vs. 28% *ee*). This was not expected, since for the aromatic aldehydes the ratio of the components in the catalyst doesn't impact the enantioselectivity and the yield of the reaction. For other ligands, such as VAPOL and its derivatives, and 8,8'-diphenyl VANOL, both the yield and *ee* were low.

3.2.2 Phosphite screen

Table 3.2 Phosphite screen[a]



1.0 equiv.
76a

1.0 equiv.
64c

1.0 equiv.
65c, 65f

(*S*)-77a

	Phosphite	% Yield[b]	% *ee*[c]
1	Et (**65a**)	63	53
2	*i*pr **(65c)**	35	0
3	Ph **(65f)**	0	0

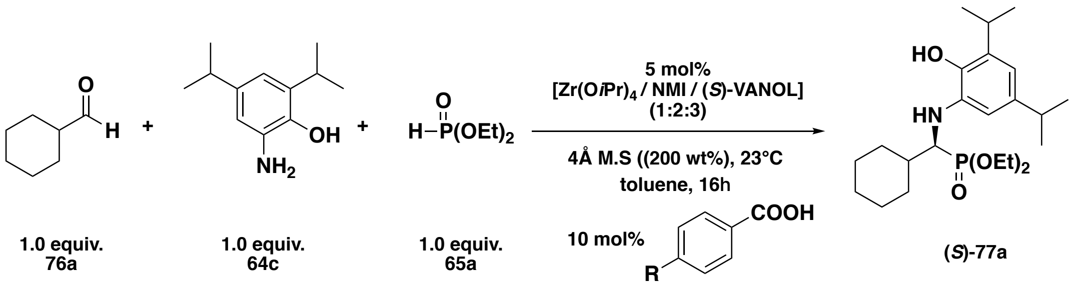
[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(OiPr)_4$•HO*i*Pr, 2.0 equivalents of N-methyl imidazole (NMI) and 3.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]Isolated yield; [c]*ee* was determined by HPLC.

Di*iso*propyl and diphenyl phosphites (**65c, 65f**) were examined after it was found that the VANOL-zirconium complex with 1:2:3 ratio works efficiently with the cyclohexanecarboxylic aldehyde (Table 3.2). By using di*iso*propyl phosphite, only a 35% of the product **77a** was observed with no enantiomeric excess. For diphenyl phosphites, no product was detected after a reaction of 16 hours.

3.2.3 Screen of benzoic acids

Previously it was discovered that 4-nitrobenzoic acid can improve the yield of the model reaction with benzaldehyde (Chapter 2, Table 2.10). A series of benzoic acids bearing different functional groups were examined here to see if they could also have some impact on the reaction with the aliphatic substrate **76a** (Table 3.3). For all of the 4-substituted benzoic acids, similar enantioselectivities were observed, which were around 55% *ee*. Benzoic acid (entry 1) and 4-nitrobenzoic (entry 4) acids gave 63% and 64%

Table 3.3 Screen of benzoic acids[a]



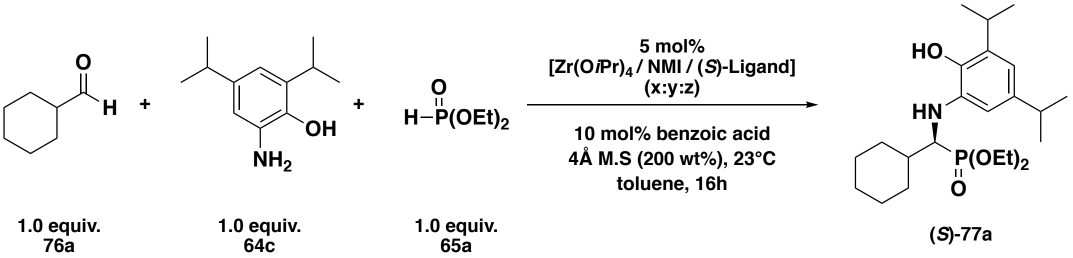
	R	% Yield[b]	% *ee*[c]
1	H	63(86)[d]	53(57)[d]
2	OMe	55	55
3	CF_3	40	53
4	NO_2	64	55
5	F	38	49
6	2,4,6-trimethyl	40	56
7	Phenyl acetic acid	76	33

[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 2.0 equivalents of N-methyl imidazole (NMI) and 3.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]Isolated yield; [c]*ee* was determined by HPLC;[d]10 mol% catalyst loading was used.

yields of desired products respectively. Electron-deficient 4-nitrobenzoic acid didn't show significant advantages compared with simple benzoic acid. The electronic status of the benzoic acids didn't have a major effect that can impact on the yield of the reaction. For example, 4-methoxybenzoic acid (entry 2) delivered the product in 55% yield, which was higher than 4-trifloromethylbenzoic acid (40%, entry 3). The highest yield (76%, entry 7) was achieved by employing phenyl acetic acid, but the enantioselectivity was only 33%.

3.2.4 Screen of catalyst component ratio

Table 3.4 Screen of catalyst component ratio with VANOL, *t*Bu-VANOL and VAPOL[a]

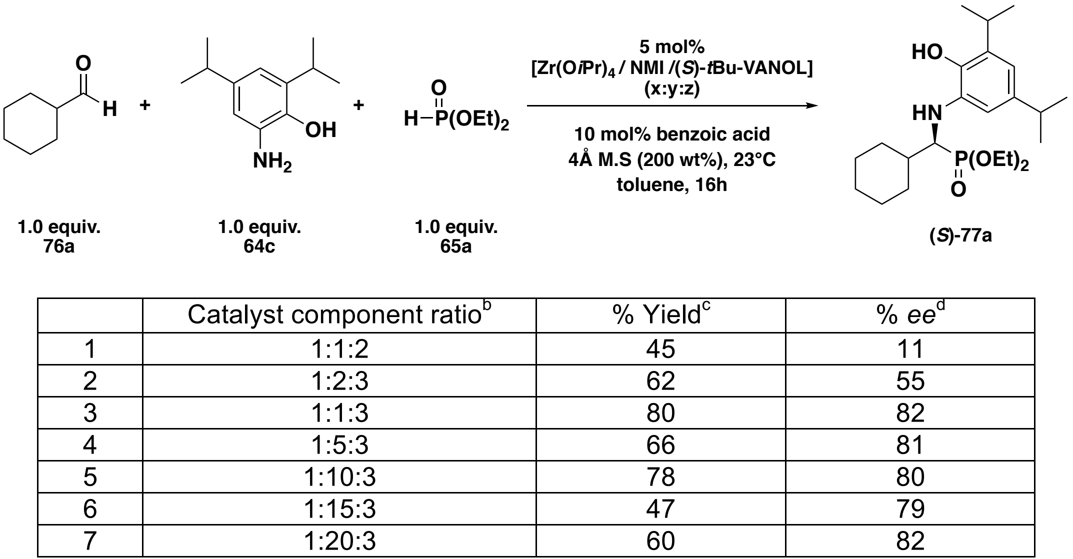


	Ligand	x:y:z[b]	% Yield[c]	% *ee*[d]
1	VANOL	1:1:2	63	28
2	VANOL	1:2:3	63	53
3	*t*Butyl-VANOL	1:1:2	45	11
4	*t*Butyl-VANOL	1:2:3	62	55
5	VAPOL	1:1:2	65	6
6	VAPOL	1:2:3	31	0

[a] Zirconium catalysts were prepared by stirring a mixture of x equivalents of Zr(O*i*Pr)$_4$•HO*i*Pr, y equivalents of N-methyl imidazole (NMI) and z equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b] x is zirconium(IV) *iso*propoxide *iso*propanol; y is *N*-methyl imidazole and z is ligand; [c] Isolated yield; [d] *ee* was determined by HPLC.

In the previous optimization process with aromatic aldehydes, experiments with variation in the ratio of component in the catalyst were conducted and the result showed that in comparing the ratio of 1:1:2 to 1:1:3 (zirconium *iso*propoxide: NMI: (*S*)-*t*bu-VANOL, Chapter 2, Table 2.12), the same enantioselectivities (93% *ee*) were obtained, but the latter only gave a 7% improvement in the yield. However, considering that aliphatic substrates may have different reactivities, more detailed screen of the catalyst component ratio with the ligands were examined (Table 3.4). In the initial optimization of the aliphatic aldehyde **76a**, zirconium-VANOL complex with a catalyst component ratio of 1:2:3 (zirconium *iso*propoxide: NMI: VANOL) gave the best result, which is 63% yield and 53% *ee* (entry 2). But when *t*Bu-VANOL was employed in the reaction, the enantioselectivity increased sightly to 55% *ee* (entry 4). There was almost no enantioselective induction for the VAPOL ligand with both ratios of 1:1:2 and 1:2:3 (entry 5 and 6).

Table 3.5 Screen of catalyst component ratio with *t*bu-VANOL[a]



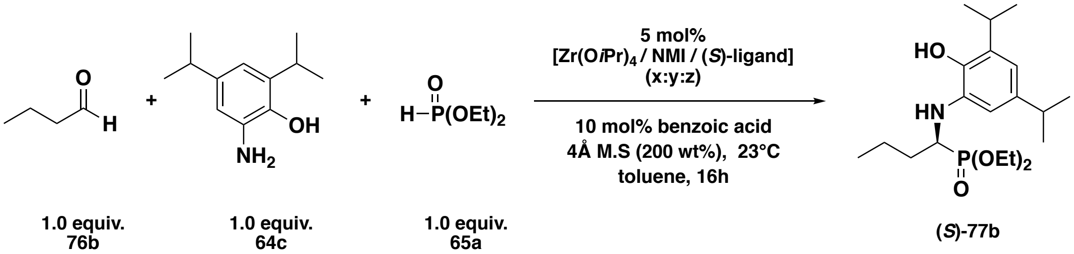
	Catalyst component ratio[b]	% Yield[c]	% *ee*[d]
1	1:1:2	45	11
2	1:2:3	62	55
3	1:1:3	80	82
4	1:5:3	66	81
5	1:10:3	78	80
6	1:15:3	47	79
7	1:20:3	60	82

[a]Zirconium catalysts were prepared by stirring a mixture of x equivalents of $Zr(OiPr)_4{\bullet}HOiPr$, y equivalents of N-methyl imidazole (NMI) and z equivalents of (*S*)- VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]x is zirconium(IV) *iso*propoxide *iso*propanol; y is *N*-methyl imidazole and z is (*S*)-*t*Bu-VANOL; [c]Isolated yield; [d]*ee* was determined by HPLC;

Since *t*Bu-VANOL is also the optimal ligand in the standard protocol for aromatic aldehydes, it was selected to be tested with additional variation in the catalyst component ratio (Table 3.5). When the catalyst was prepared from 1.0 equivalent of zirconium *iso*propoxide, 1.0 equivalent of *N*-methyl imidazole and 3.0 equivalents of (*S*)-*t*Bu-VANOL, the yield of **77a** was 80% with 82% ee (entry 3). It was quite surprising to find changing the catalyst composition ratio from 1:2:3 to 1:1:3 caused the enantioselectivity to increase 55% *ee* to 82% *ee*. (Table 3.4, entry 4 vs Table 3.5, entry 3). However, continuously increasing the equivalents of *N*-methyl imidazole from 5 to 20 (entry 4-7) did not result in increased yields and the enantioselectivity was unchanged around 80% *ee*. This is consistent with the results from the optimization of aromatic aldehydes where it was found that extra amounts of the base (NMI) did not kill the reaction (Chapter 2, Table 2.12).

The *n*-butanal was also examined with two catalysts with different ratios of catalyst components to confirm the impact of the catalyst component ratio (Table 3.6). From the results, *t*Bu-VANOL is superior to VANOL with a catalyst component ratio of 1:2:3. For a catalyst component ratio of 1:1:3, a 56% yield and 85% *ee* was obtained for (*S*)-**77b**, which is slightly higher than a ratio of 1:2:3.

Table 3.6 Screen of catalyst component ratio with *n*-butanal[a]



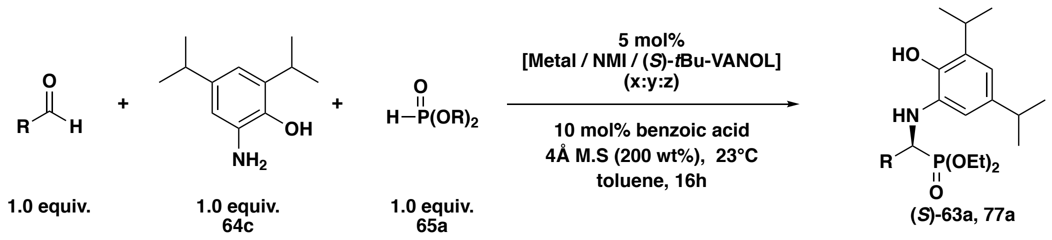
	Ligand	Catalyst component ratio (x:y:z)[b]	% Yield[c]	% *ee*[d]
1	VANOL	1:2:3	52	39
2	*t*Butyl-VANOL	1:2:3	51	81
3	*t*Butyl-VANOL	1:1:3	56	85

[a] Zirconium catalysts were prepared by stirring a mixture of x equivalents of Zr(O*i*Pr)$_4$•HO*i*Pr, y equivalents of N-methyl imidazole (NMI) and z equivalents of (*S*)-VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b] x is zirconium(IV) *iso*propoxide *iso*propanol; y is *N*-methyl imidazole and z is (*S*)-*t*Bu-VANOL; [c] Isolated yield; [d] *ee* was determined by HPLC.

3.2.5 Other metal catalysts

In addition to zirconium complexes, titanium and yttrium complexes, prepared from (*S*)-*t*Bu-VANOL and *N*-methyl imidazole, were also tested in reactions with cyclohexanecarboxylic aldehyde and benzaldehyde (Table 3.7). The titanium catalyst with a catalyst component ratio of 1:2:3 and 1:1:2 afforded the product with 30% and 10% yield and no asymmetric induction was detected. Applying the yttrium complex with a catalyst component ratio of 1:1:3 in the reaction, with cyclohexanecarboxylic aldehyde gave 73% yield and 30% *ee*. Reaction with benzaldehyde gave 25% yield and 43% *ee* with a catalyst component ratio of 1:10:3. In terms of the results, both titanium and yttrium catalysts are not as good as zirconium complex. For cyclohexanecarboxylic aldehyde, the yttrium complex showed higher yield and enantioselectivity compared to the titanium catalyst. In the future, further studies could be done on yttrium complexes, which may possibly be useful in the development of other new reactions.

Table 3.7 Screen of other metal catalysts[a]



	R	metal	x:y:z[b]	% Yield[c]	% *ee*[d]
1	Cyclohexyl **76a**	Titanium	1:2:3	30	0
2	Cyclohexyl **76a**	Titanium	1:1:2	10	-
3	Cyclohexyl **76a**	Yttrium	1:1:3	73	30
4	Phenyl **63a**	Yttrium	1:10:3	25	-3

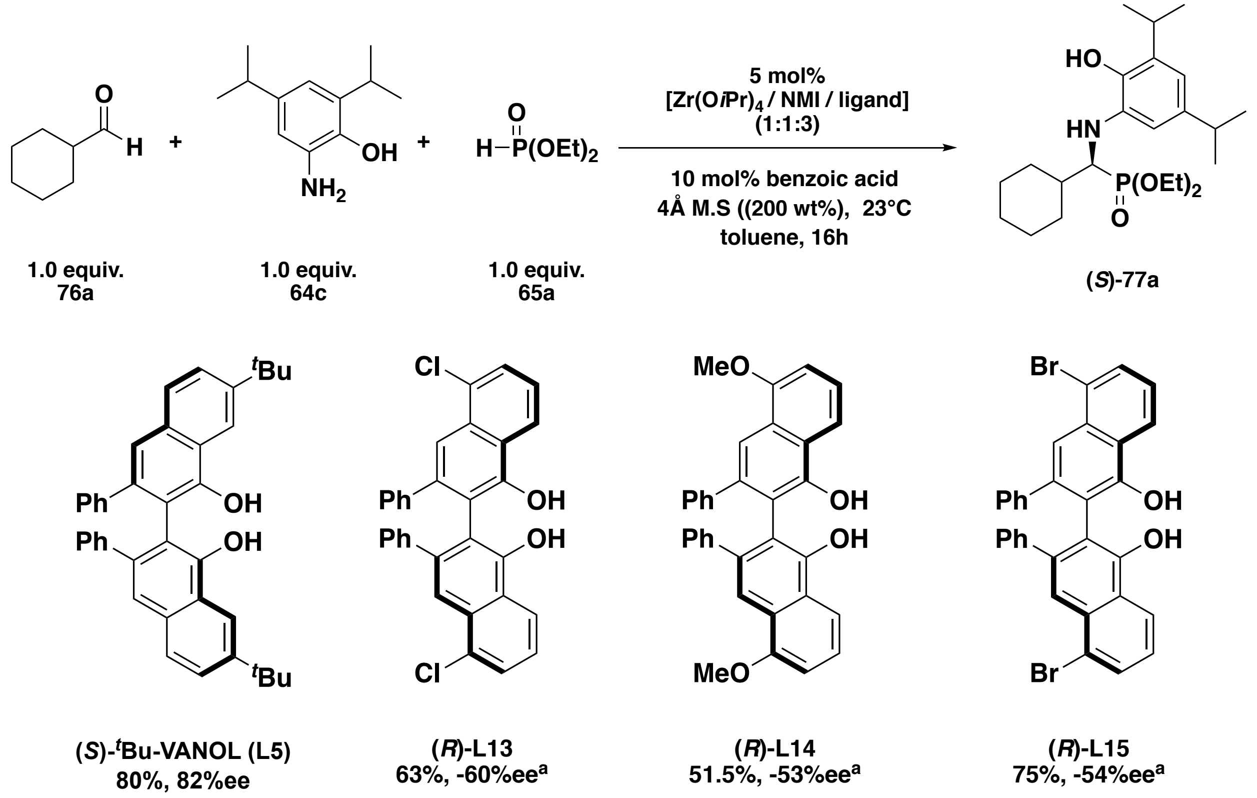
[a] Zirconium catalysts were prepared by stirring a mixture of x equivalents of Ti(O*i*Pr)$_4$ or Y(O*i*Pr)$_3$, y equivalents of N-methyl imidazole (NMI) and z equivalents of (*S*)- VANOL in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b] x is Ti(O*i*Pr)$_4$ or Y(O*i*Pr)$_3$, y is *N*-methyl imidazole and z is (*S*)-*t*Bu-VANOL; [c] Isolated yield; [d] *ee* was determined by HPLC.

3.3 Further studies on optimization

3.3.1 Ligand screen

From the initial optimization, with cyclohexanecarboxylic aldehyde **76a**, the zirconium catalyst with a catalyst component 1:1:3 ratio (1.0 equivalent of zirconium *iso*propyl oxide, 1.0 equivalent of *N*-methyl imidazole and 3.0 equivalents of *t*Bu-VANOL) and 10 mol% benzoic acid was found to be the optimal conditions. At this point, the highest enantioselectivity achieved was 82% with *t*Bu-VANOL. However, in our goal, for the model reaction with cyclohexanecarboxylic aldehyde **76a** is to achieve an enantioselectivity can reach over 90% *ee*. Therefore, a new series of VANOL/VAPOL derivatives were examined to the reaction (Scheme 3.2).

Scheme 3.2 Screen of more ligands



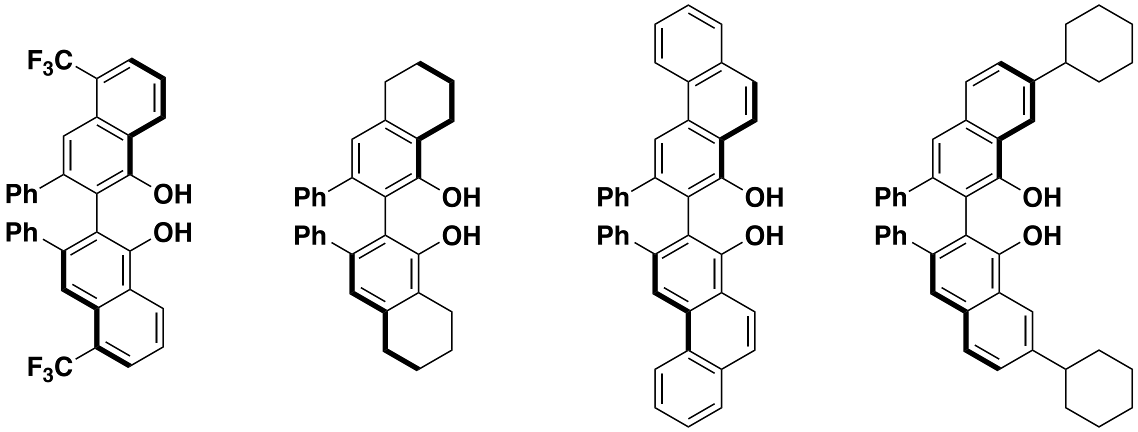
(*S*)-^{t}Bu-VANOL (L5)
80%, 82%ee

(*R*)-L13
63%, -60%ee[a]

(*R*)-L14
51.5%, -53%ee[a]

(*R*)-L15
75%, -54%ee[a]

Scheme 3.2 (continued)



(*R*)-L16
80%, -58%ee^a

(*R*)-L17
<5%

(*R*)-L18
78%, -69%ee^a

^{b}(*R*)-L19
60%, -56%ee^a

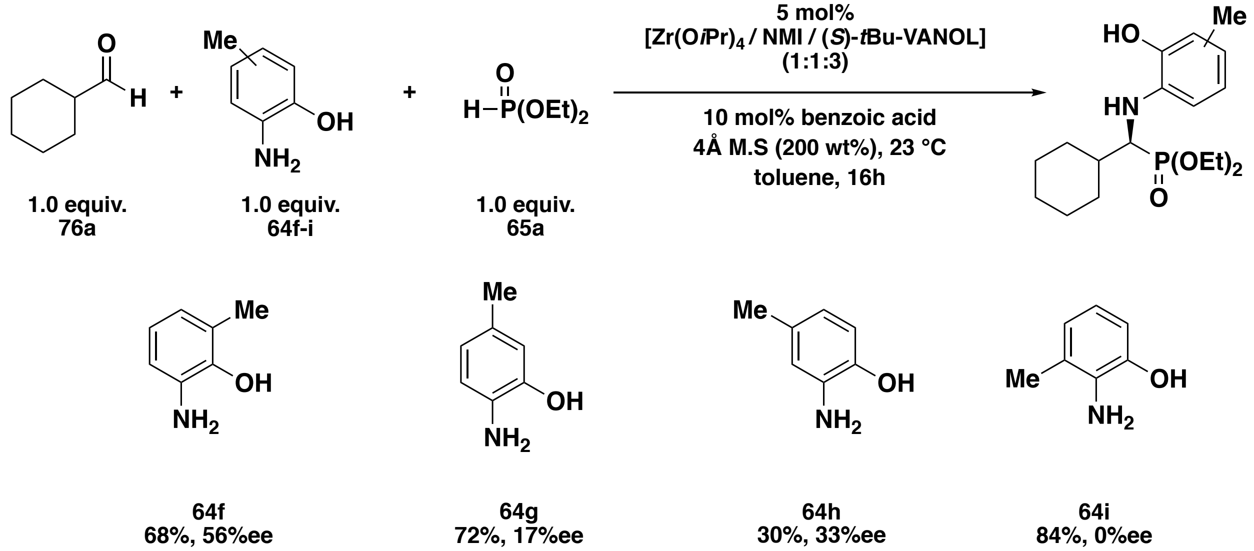
^{a}(*R*)-isomer of the product was obtained; ^{b}10 mol% of catalyst was used.

Upon examining four 5,5-substituted VANOL derivatives (**L13-L16**), it was found that the enantioselectivities of the model reaction were all around 60%. The highest yield was obtained by using 5,5'-ditrifluoromethyl VANOL (**L16**), which gave 80% yield and is close that for the *t*Bu-VANOL. Additionally, Iso-VAPOL (**L18**) gave 78% yield and 69% *ee*. Octahydro-VANOL (**L17**) afforded the product with in less than 5% yield. A new 7,7'-disubstituted VANOL derivative **L19** was also tested and gave 60% yield and 56% *ee*. Unfortunately, none of the above ligands works better than *t*Bu-VANOL.

3.3.2 Screen of 2-hydroxyanilines

After screening of ligands in Scheme 3.2, no improvement on the enantioselectivity was found for any of the ligands. Attention was next focused on the substitution pattern in the 2-hydroxyanilne. In the optimization process for aromatic substrates, big increases in the enantioselectivity were achieved when 2-hydroxy-3.5-dii*so*propylaniline (**64c**) was used in the reaction (Chapter 2, Table 2.6). Therefore, considering that by testing some other anilines with substituents in different positions of the phenyl ring, a relationship may be revealed between steric effect of anilines and the enantioselectivity of the reaction. A set of 2-hydroxyanilines with methyl groups in all four possible positions (**64f-i**) on the phenyl ring were first examined in the reaction (Scheme 3.3).

Scheme 3.3 Screen of methyl-2-hydroxyaniline with cyclohexanecarboxylic aldehyde



64f
68%, 56%ee

64g
72%, 17%ee

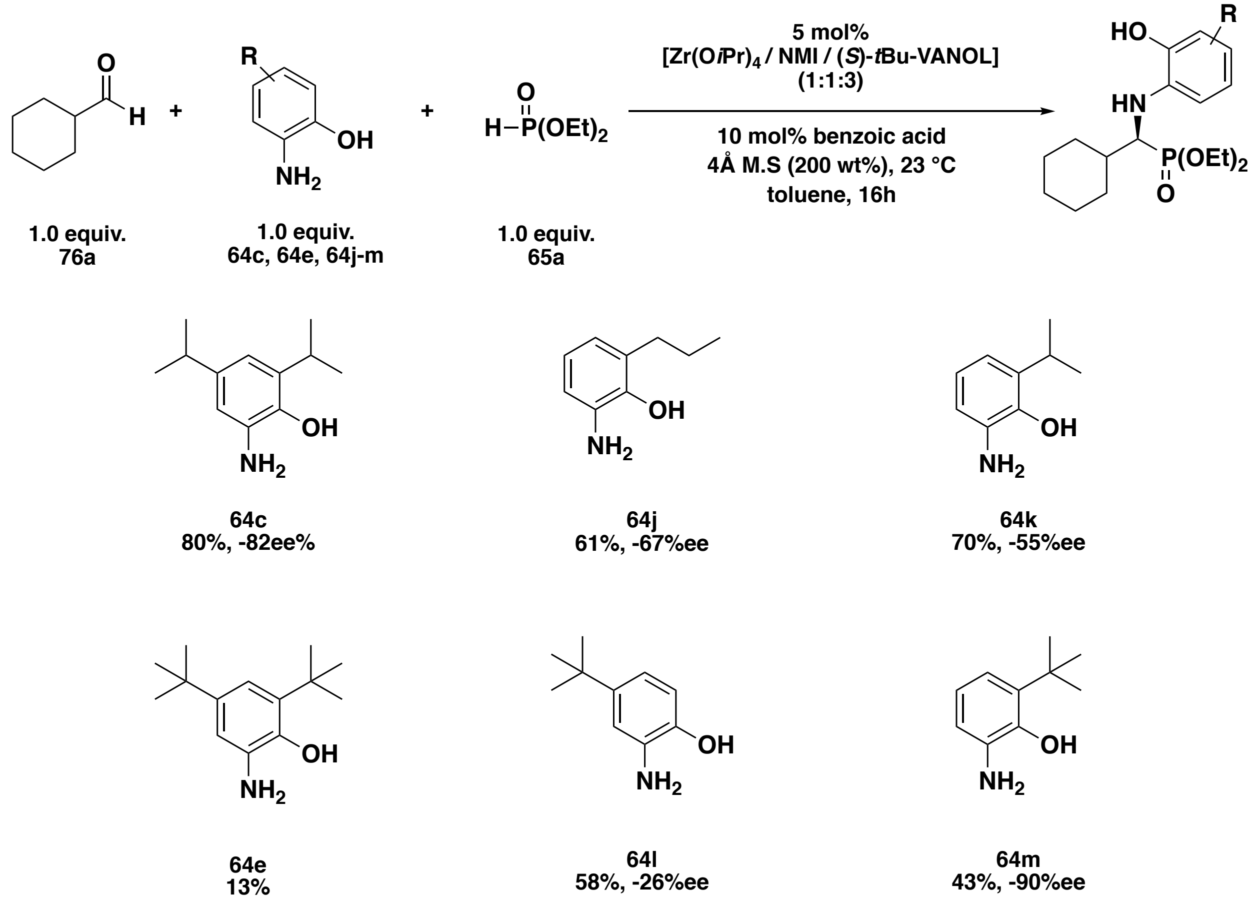
64h
30%, 33%ee

64i
84%, 0%ee

The best result was achieved with 3-methyl-2-hydroxyaniline (**64f**), which gave the product in 68% yield and 56% *ee*. The second best was found to be 5-methyl-2-hydroxyaniline (**64h**) and the corresponding product was obtained in 30% yield and 33% *ee*. For a methyl group on the 4 or 6 positions (**64g, 64i**), higher yields were observed, but with lower asymmetric inductions. Previously, in the reaction with aromatic substrates, 2-hydroxy-3,5-di*iso*propylaniline (**64c**) was found to be the best one, which can generate the products with *ee* up to 94% (Chapater 2, Table 2.9). This is consistent with the results above that a methyl on the 3 or 5 position can crucially effect the asymmetric induction. This provided a lead for further efforts to achieve higher enantioselectivity with aliphatic aldehydes in the asymmetric Kabachnik-Fields reaction.

Four new 3 or 5-substituted-2-hydroxyanilne were synthesized following a similar protocol for the synthesis of 3,5-di*iso*proyl-2-hydroxyaniline described in the chapter two. Namely, it includes 3-propyl-2-hydroxyaniline (**64j**), 3-*iso*propyl-2-hydroxyaniline (**64k**), 3-*t*butyl-2-hydroxyanilne (**64m**) and 5-*t*butyl-hydroxyaniline (**64l**) (Scheme 3.4).

Scheme 3.4 Screen of 2-hydroxyanilnes with cyclohexanecarboxylic aldehyde



64c
80%, -82ee%

64j
61%, -67%ee

64k
70%, -55%ee

64e
13%

64l
58%, -26%ee

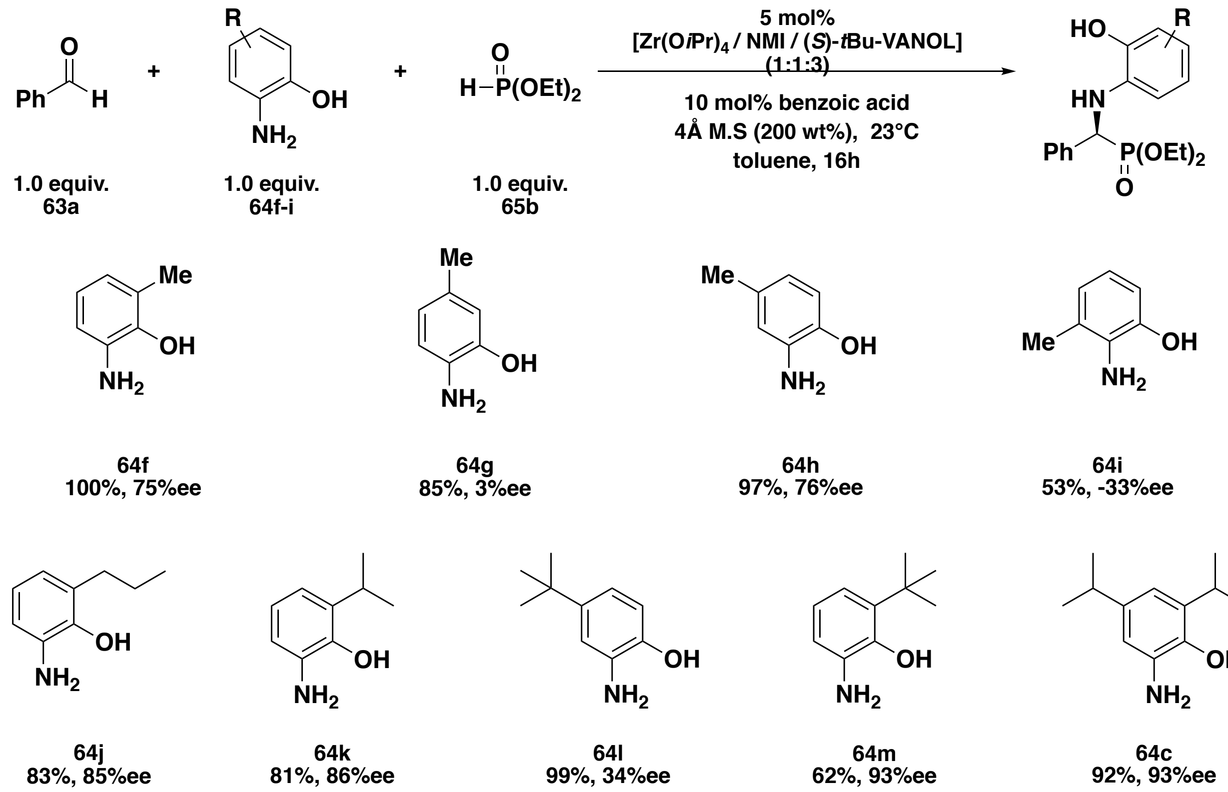
64m
43%, -90%ee

With the increasing in size of the alkyl group (*iso*propyl, *n*butyl, *t*butyl) on the 3-position of the phenyl ring, the enantioselectivity of the product rose from 55% to 90%. The 3,5-ditbutyl-2-hydroxyaniline (**64e**) was also tested, but afforded only a 13% yield of the desired product probably because of the steric bulky of two *t*butyl groups. The previous optimal aniline for this reaction was the 2-hydroxy-3,5-diisopropylaniline **64c**

(Table 3.5, entry 3). However, the present screen in Scheme 3.4 revealed that the 3-*t*Buyl-2-hydroxyaniline **64m** gives the product in 90% *ee* and 43% yield.

Similar threads for the substitution pattern in the 2-hydroxyanilines were also observed for the reaction with benzaldehyde (Scheme3.5). The 2-and 5-methyl-2-hydroxyanilines (**64f, 64h**) gave higher enantioselectivity (75% *ee* and 76% *ee*) than 4 and 6-positioned methyl derivatives (**64g, 64i**) (43% *ee* and 33% *ee*). For mono-substituted-2-hydroxyanilines, 2-hydroxy-3-*t*butylaniline (**64m**) gave 93% *ee*, which was the same as 3,5-di*iso*propyl-2-hydroxyanilne (**64c**). The 3-propyl-2-hydroxyaniline (**64j**), and the 3-*iso*propyl-2-hydroxyaniline (**64k**) provided slightly lower *ee* (85% *ee* and 86% *ee*), but higher yields (83% and 81%) than **64m**. Interestingly, with the 5-tbutyl-2-hydroxyaniline (**64l**), the product can be obtained in 99% yield, but with only 34% *ee*.

Scheme 3.5 Screen of 2-hydroxyanilines with benzaldehyde

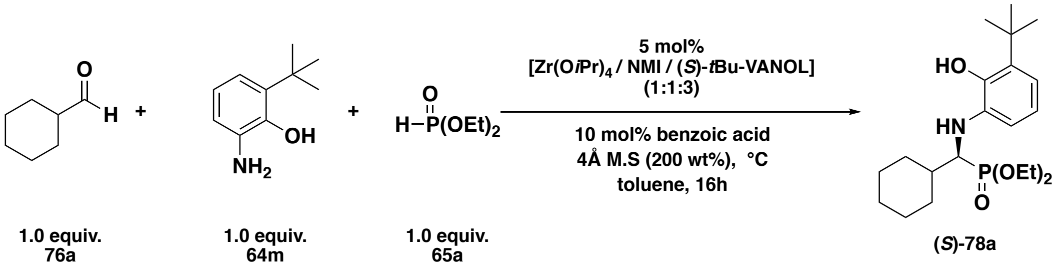


These results indicate that the substituent on the 3-position of the phenyl ring has the largest effect of the asymmetric induction. However, with increasing the size of the group on that position, the yield will decrease accordingly. Thus 2-hydroxy-3.5-di*iso*propylaniline (**64c**) still remains as the optimal starting material in the reactions of aromatic aldehyde due to its higher yield than **64m.**

3.3.3 Temperature screen

The enantioselectivity of the reaction with cyclohexanecarboxylic aldehyde reached 90% *ee* first time with 2-hydroxy-3-*t*buylaniline (Scheme 3.4). However, the yield was only 40% and therefore, more efforts are needed to improve the reaction yield. The first such effort involved examining the reaction temperature (Table 3.8). When the temperature was decreased to 0°C, the yield diminished to 23%, with a slight increase of the enantioselectivity to 92%. When the temperature was raised to 70°C, both the yield and enantioselectivity dropped (32%, 81% *ee*, entry 4). Notably, it was found that an

Table 3.8 Temperature screen[a]



	Temperature	% Yield[b]	% *ee*[c]
1	0	23	92
2	23	40	89
3[d]	40	48	89
4	70	32	81
5[d]	23	53	90

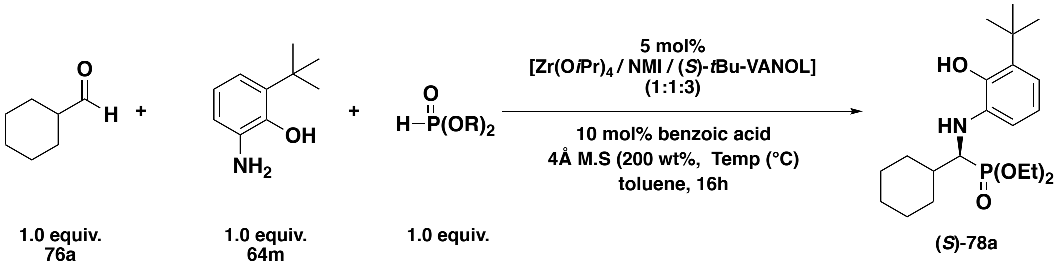
[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(OiPr)_4{\bullet}HOiPr$, 1.0 equivalents of N-methyl imidazole (NMI) and 3.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]Isolated yield; [c]*ee* was determined by HPLC;[d]10 mol% of the catalyst loading.

increase in the loading of the more zirconium catalyst to 10 mol% in the room temperature, boosted the yield to 53% without any change in the enantioselectivity (entry 5).

3.3.4 Phosphite screen

Considering that the much bulkier 2-hydroxy-3-*t*butylaniline (**64m**) was now used in the reaction instead of 2-hydroxy-3.5-di*iso*propylaniline (**64c**), different alkyl groups on phosphite were tested to see if the yield could be improved (Table 3.9). Upon changing diethyl phosphite **65b** to dimethyl phosphite **65a**, the yield slightly increased to 45%, but the *ee* dropped to 79% with 5 mol% catalyst loading. For the diisopropyl phosphite (**65c**), less than 10% of the product was observed. Thus, diethyl phosphite is still the optimal one in the reaction with aliphatic aldehydes.

Table 3.9 Screen of the reaction with aniline 64m with phosphites[a]



	R	% Yield	% *ee*
1	Et **(65a)**	50	90
2	Me **(65b)**	45	79
3	*Iso*propyl **(65c)**	<10	-

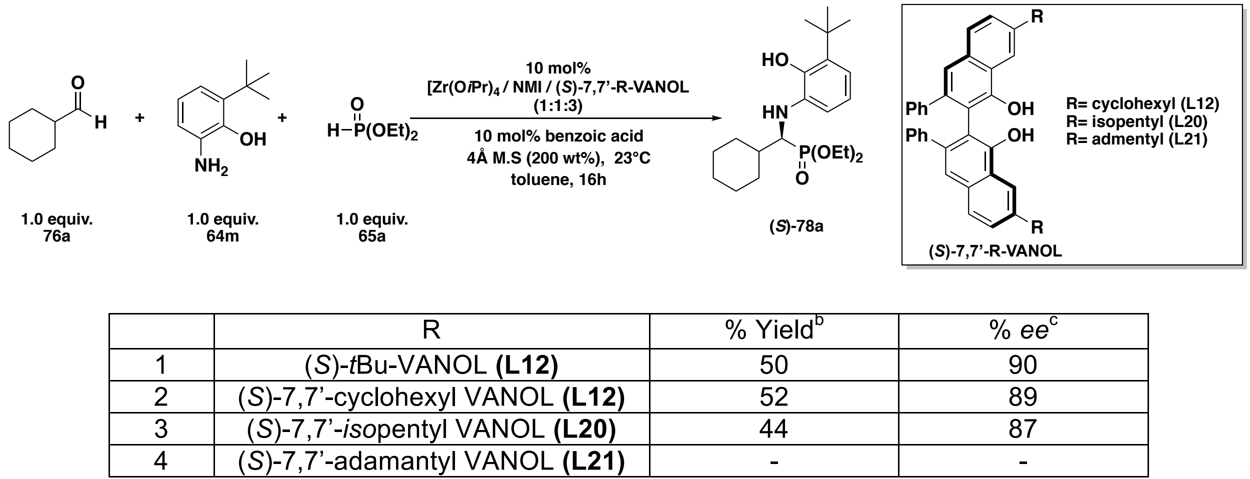
[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 1.0 equivalents of N-methyl imidazole (NMI) and 3.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b]Isolated yield; [c]*ee* was determined by HPLC.

3.3.4 Further attempts at optimization with additional VANOL ligands

Finally, another three 7,7-substituted VANOL ligands were examined under the new conditions with 2-hydroxy-3-*t*butylaniline (Table 3.10). Both the (*S*)-7,7'-cyclohexyl

VANOL (**L12**) and the (*S*)-7,7'-*iso*pentyl VANOL (**L20**) delivered the product **78a** with similar yields and *ee's* as the (*S*)-*t*Bu-VANOL. For the 7,7'-adamantyl VANOL (**L21**), no product was formed, probably due to its much bulkier size. There appears to be a relationship between the effectiveness of the reaction with the size of the substituent in the 7,7'-positions on the VANOL ligand. Present group members are now making other 7,7'-alkyl substituted VANOL derivatives, including methyl, ethyl, *iso*propyl etc. In future studies, these ligands could be tested in the reaction to find if there is a correlation with the steric size of the substituent.

Table 3.10 Other two ligands screen[a]



	R	% Yield[b]	% *ee*[c]
1	(*S*)-*t*Bu-VANOL **(L12)**	50	90
2	(*S*)-7,7'-cyclohexyl VANOL **(L12)**	52	89
3	(*S*)-7,7'-*iso*pentyl VANOL **(L20)**	44	87
4	(*S*)-7,7'-adamantyl VANOL **(L21)**	-	-

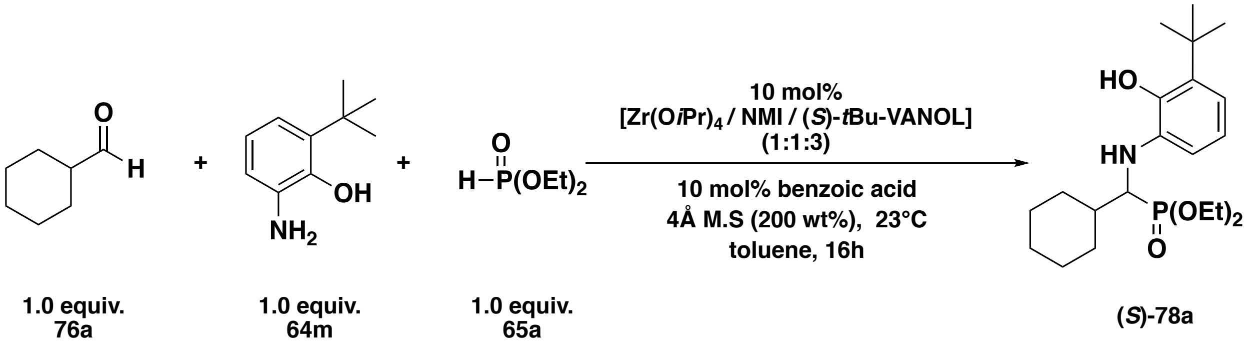
[a]Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of Zr(O*i*Pr)$_4$•HO*i*Pr, 1.0 equivalent of N-methyl imidazole (NMI) and 3.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64m** were added; [b]Isolated yield; [c]*ee* was determined by HPLC.

3.3.5 The optimal condition for aliphatic aldehydes

After all efforts having been made for the optimization of aliphatic aldehydes, the optimal reaction conditions for aliphatic aldehydes in the asymmetric Kabachnik-Fields reaction is shown in Scheme 3.6. The protocol involves 10 mol% of the zirconium catalyst prepared from 1.0 equivalent of zirconium(IV) *iso*propoxide *iso*propanol, 1.0 equivalent of

N-methyl imidazole and 3.0 equivalents of (*S*)-*t*Bu-VANOL in toluene. To the catalyst was added 10 mol% benzoic acid and 2.0 mass equivalents of 4Å molecular sieves along with 1.0 equivalent each the of aliphatic aldehyde, 2-hydroxy-3-*t*butylaniline (**64m**) and diethyl phosphite (**65a**). The mixture stirred for 16-48 hours at room temperature and produced the desired aliphatic α-amino phosphonates.

Scheme 3.6 Optimal reaction condition

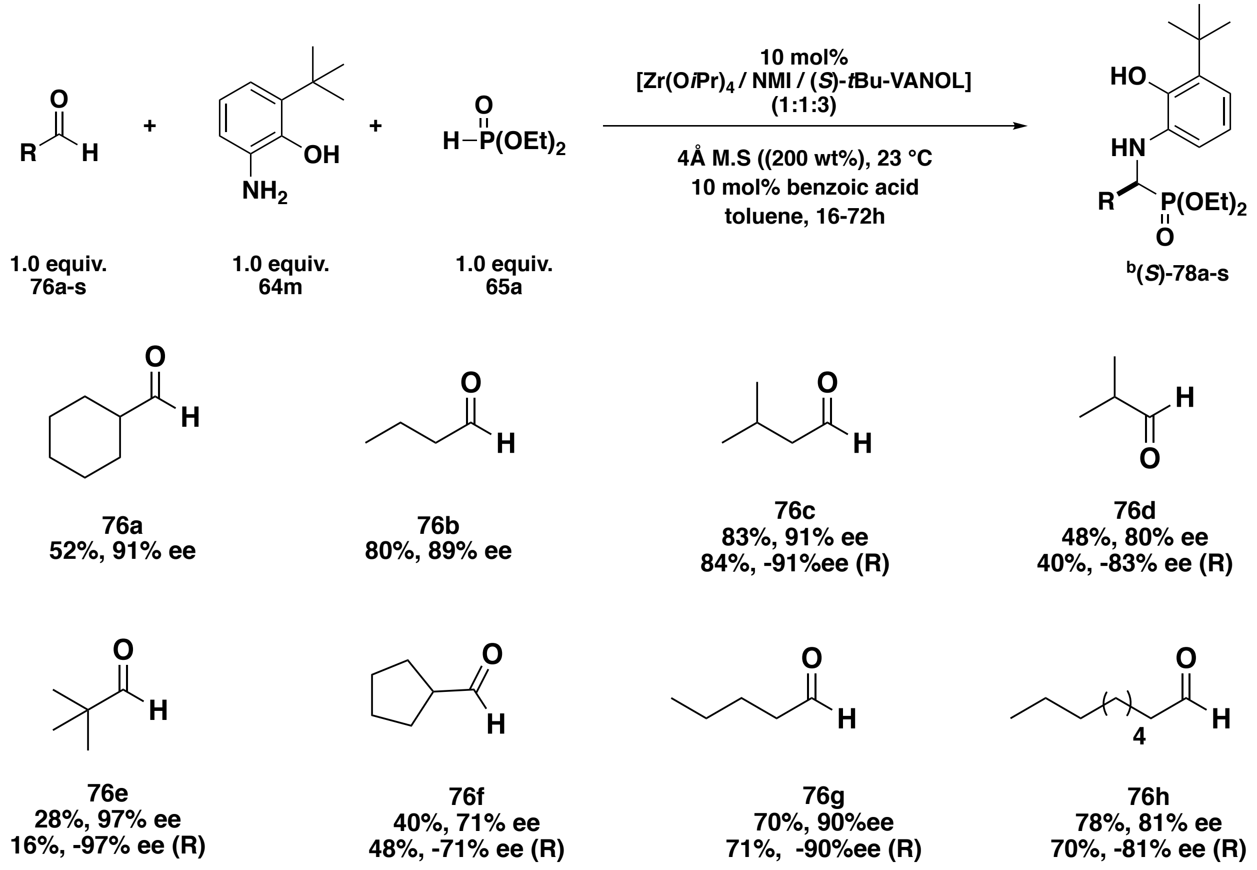


3.4 Substrate scope of aliphatic aldehydes

A set of 19 aliphatic aldehydes bearing various functional groups have been examined under the standard reaction conditions described in Scheme 3.6 and the results are given Scheme 3.7. In contrast with cyclohexanecarboxylic aldehyde, cyclopentanecarboxylic aldehyde (**76f**) gave both lower yield and enantioselectivity (40%, 71% *ee*). For branched aliphatic aldehydes, the bulkiest *t*butyl aldehyde (**76e**) afforded the product with highest enantioselectivity and lowest yield, which is 97% *ee* and 28% yield. The other simple linear aldehydes with different carbon numbers, such as butyraldehyde (**76b**) and pentanal (**76g**) gave 80% and 70% yield and 89% *ee* and 90% *ee*, respectively. For nonanal **76h** with a longer carbon chain, moderate yield (78% yield) and enantioselectivity (81% *ee*) was obtained. Many functioned aliphatic substrates were also tested in the reaction. It was delightful to see that silyl ether (**76i, j**), methyl ester

(**76k**), protected amines (**76l, p**), bromo aldehyde (**76m**) and azido aldehydes (**76q**) can all participate in the reaction to give the desired products with moderate to good yields and around 90% *ee*. Through later stage modifications, those α-amino phosphonates could potentially be transformed into valuable motifs in pharmaceutical and industrial fields. A higher yield was observed (24% vs. 53%) for the reaction with phthalimide substrate (**76p**), when increasing the reaction time from 16 hours to 72 hours. Hept-6-ynal (**76o**) and hex-5-enal (**76r**) were also examined in the reaction. The former gave 50% yield and 90% *ee* and the later gave 20% and 88% *ee*. However, for the cyclic alkene substrate (**76s**), the corresponding product was almost racemic in 25% yield.

Scheme 3.7 Scope of aliphatic aldehydes[a]



76a
52%, 91% ee

76b
80%, 89% ee

76c
83%, 91% ee
84%, -91%ee (R)

76d
48%, 80% ee
40%, -83% ee (R)

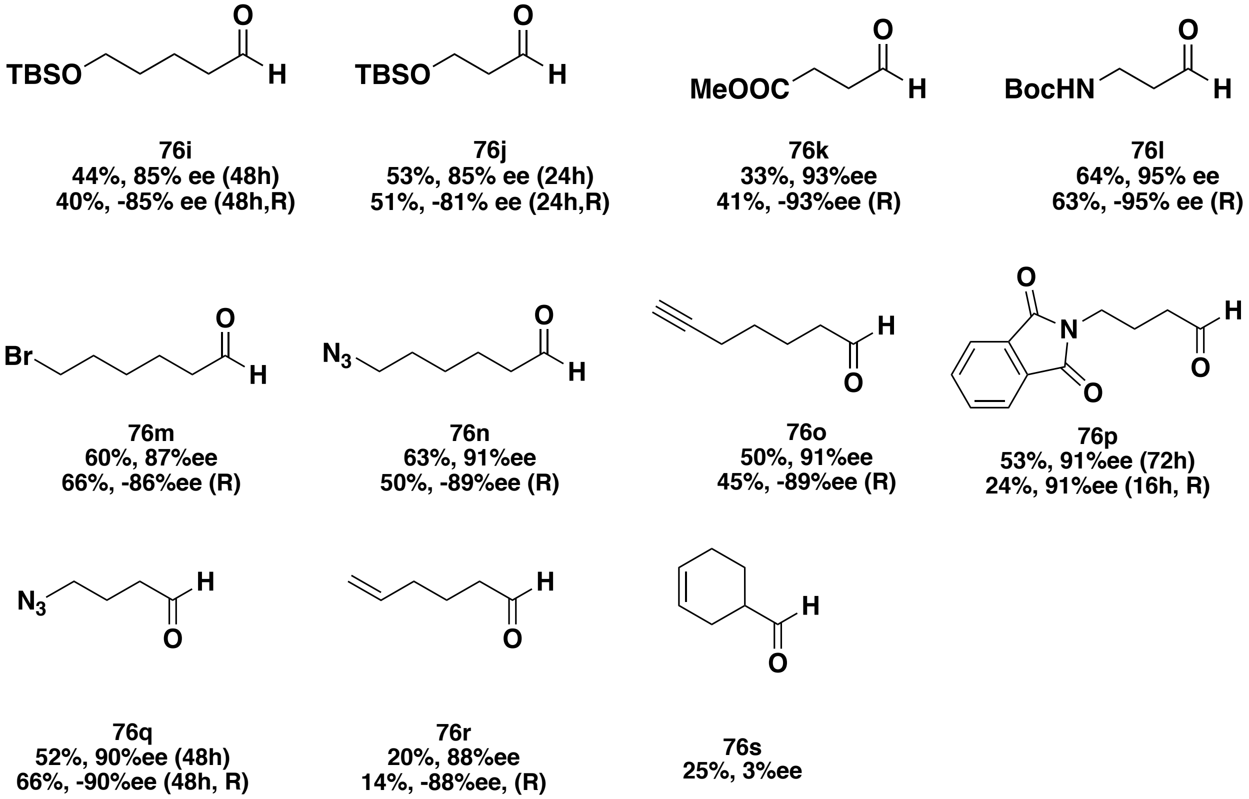
76e
28%, 97% ee
16%, -97% ee (R)

76f
40%, 71% ee
48%, -71% ee (R)

76g
70%, 90%ee
71%, -90%ee (R)

76h
78%, 81% ee
70%, -81% ee (R)

Scheme 3.7 (continued)



76i
44%, 85% ee (48h)
40%, -85% ee (48h,R)

76j
53%, 85% ee (24h)
51%, -81% ee (24h,R)

76k
33%, 93%ee
41%, -93%ee (R)

76l
64%, 95% ee
63%, -95% ee (R)

76m
60%, 87%ee
66%, -86%ee (R)

76n
63%, 91%ee
50%, -89%ee (R)

76o
50%, 91%ee
45%, -89%ee (R)

76p
53%, 91%ee (72h)
24%, 91%ee (16h, R)

76q
52%, 90%ee (48h)
66%, -90%ee (48h, R)

76r
20%, 88%ee
14%, -88%ee, (R)

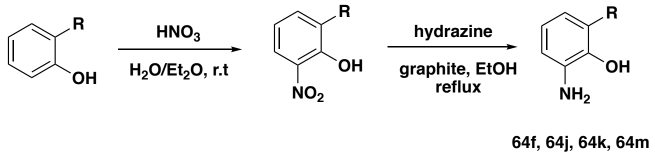
76s
25%, 3%ee

[a] Zirconium catalysts were prepared by stirring a mixture of 1.0 equivalent of $Zr(OiPr)_4$•HO*i*Pr, 1.0 equivalents of N-methyl imidazole (NMI) and 3.0 equivalents of ligand in dry toluene for 30 minutes at room temperature under the air; 200 wt% 4Å molecular sieves relative to the mass of **64c** were added; [b] All yields are isolated yields and *ee* was determined by HPLC; [c] (*R*)-isomer of the product was obtained when (*R*)-*t*Bu-VANOL was used in the reaction and *ee* was shown in minus.

3.5 Synthesis of mono-substituted-2-hydroxyanilines

The synthesis of the mono-substituted-2-hydroxyanilines all started from their corresponding phenols by nitration and their reduction to generate proper 2-hydroxyanilines. (Table 3.11).

Table 3.11 Synthetic route for mono-3-substituted-2-hydroxyanilines



	R	% Yield (nitration)	% Yield (reduction)
1[a]	Me **(64f)**	20[53]	70
2	*n*Propyl **(64j)**	17[54]	70
3	*iso*Propyl **(64k)**	25[55]	75
4	*t*Butyl **(64m)**	55[56]	70

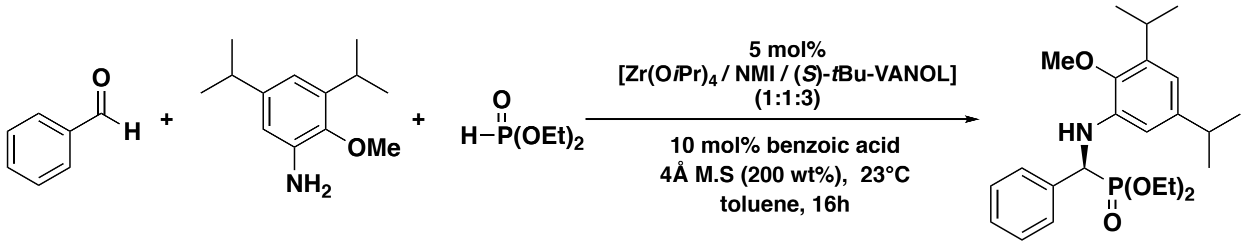
[a]The nitration was carried in the acetic acid with nitric acid at -15°C.

Low yields were typically achieved in the first nitration step. For the 2-hydroxy-3-*t*butylaniline (**64m**), reaction time was 3 days, which gave the desired product in 55% yield. The subsequent reduction with hydrazine usually gives around 70% yield for most of the anilines. Recrystallization needs to be carried out after purification by flash column chromatography.

3.6 Preliminary mechanism investigation

Several sets of experiments were conducted to investigate the mechanism of the reaction. Firstly, the 2-methoxy-3,5-di*iso*propylaniline (**64c'**) was synthesized and tested under the standard conditions for aromatic aldehydes (Equation 3.1). Only a 9% yield of racemic product was observed after the reaction. This implies that the hydroxyl group on the aniline is key to both the yield and asymmetric induction. As described in chapter two (Figure 2.1), in previous studies on the Mannich reaction[36], a zirconium complex intermediate was proposed with a covalent bond between the oxygen on the aniline and the zirconium metal. In the present reaction, the phenol hydroxyl is certainly important and may be involved in H-bonding with the catalyst or have a covalent bond with the catalyst.

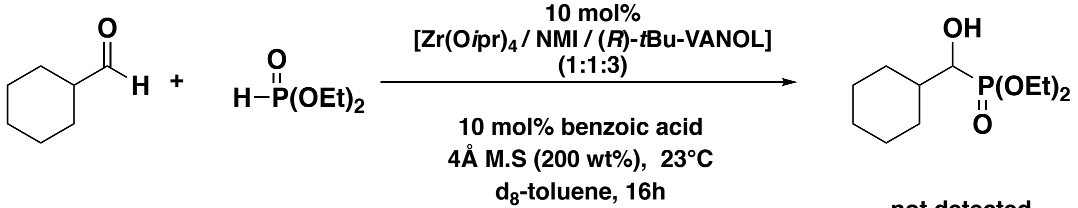
Equation 3.1 The standard reaction with 2-methoxy-3,5-di*iso*propylanline



1.0 equiv. **63a** 1.0 equiv. **64c'** 1.0 equiv. **65a** (*S*)-**79** 9% yield, 0 ee

It is known that various catalysts facilitate the reaction of phosphites with aldehydes to give α-hydroxyl phosphonates.[57] Thus a control experiment was carried out in the d_8-toluene to detect the existence of any background reactions (Equation 3.2-3.5). Cyclohexanecarboxylic aldehyde (**76a**) and diethyl phosphite (**65a**) were stirred under the standard reaction conditions for 16 hours. After comparing with the H^1NMR spectrum of pure diethyl phosphite and (S)-*t*bu-VANOL, it was concluded that no α-hydroxyl phosphonate was formed and only starting materials were observed.

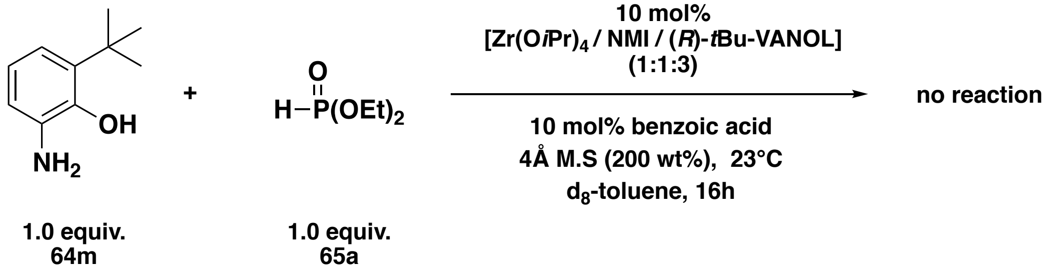
Equation 3.2 The reaction of cyclohexyl carboxylic aldehyde and diethyl phosphite



1.0 equiv. **76a** 1.0 equiv. **65a** not detected

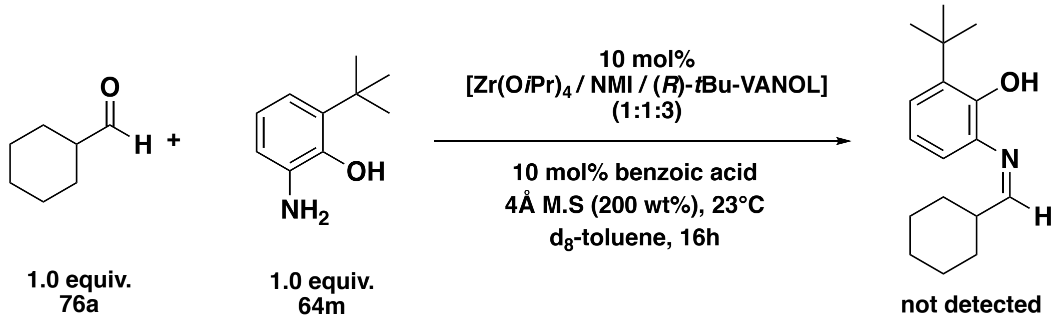
Then it was decided to check and see if any reaction between diethyl phosphite (**65a**) and 2-hydroxy-3-*t*butylaniline (**64c**) across under the standard reaction conditions but only starting materials were detected after 16 hours when the reaction was followed in d_8-toluene (Equation 3.3).

Equation 3.3 The reaction of 2-hydroxy-3-*t*butylaniline and diethylphosphite



In an additional experiment, 2-hydroxy-3-*t*butylaniline (**64m**) and cyclohexanecarboxylic aldehyde (**76a**) were reacted under the standard reaction conditions in d_8-toluene (Equation 3.4). Both starting materials were consumed and a number of products were observed by TLC and ^{1}H NMR. Thus, the imine may have formed, but reacted to give other compounds. Later attempts to synthesize this same imine by traditional imine generation methods failed.[58] Given that the multi-component Kabachnik-Fields reactions does work, it is thought likely once the imine is formed in the presence of the catalyst, it immediately reacts with the phosphite.

Equation 3.4 The reaction of cyclohexyl carboxylic aldehyde and 2-hydroxy-3-*t*butylaniline



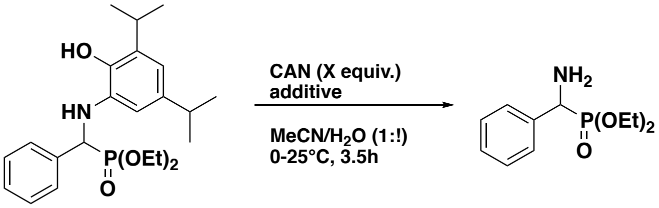
3.7 Deprotection of α-amino phosphonates

Now that the protected α-amino phosphonates are in hand, a proper method was needed to remove the 3,5-di*iso*porpyl-2-hydroxy-phenyl or 3-*t*butyl-2-hydroxy-phenyl protecting group on the nitrogen to access the unprotected forms of α-amino phosphonates.

3.7.1 Deprotection of the aromatic α-amino phosphonates by CAN and other oxidants

The most common way to remove the PMP (para-methoxylphenyl) group on nitrogen is by using CAN (ceric ammonium nitrate) in a co-solvent of water and acetonitrile.[32, 36] Since the protecting groups in α-amino phosphonates produced in this work are related to the PMP group, two different conditions with CAN were first examined (Table 3.12).

Table 3.12 Deprotection of 63a by CAN



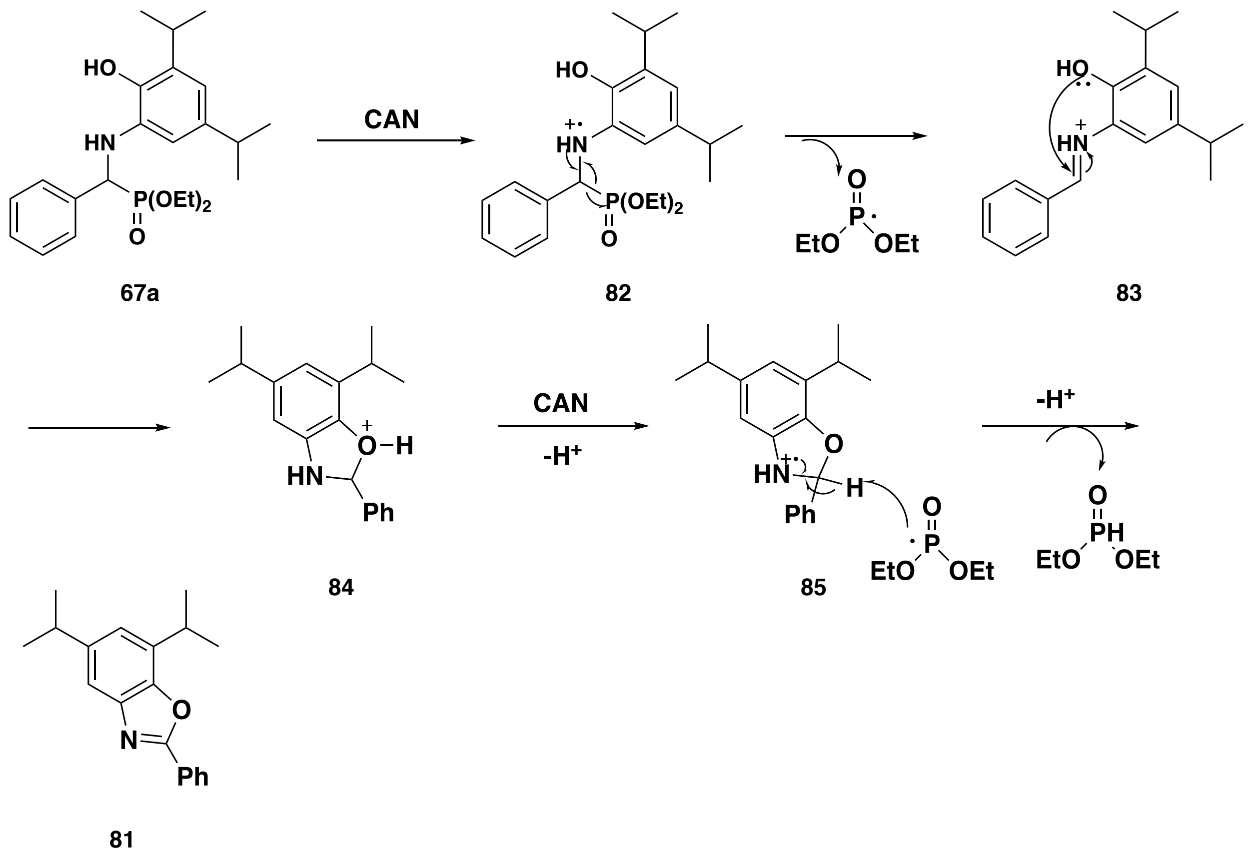
67a **80**

	X (equiv.)	additive	% Yield
1	4	1 N HNO_3	ND
2	5	none	ND

ND= not detected.

There was no desired deprotected product generated in either of the two reactions. Instead, a side product **81** of 33% yield was observed. The proposed mechanism for the formation of this side product is described in scheme 3.8.

Scheme 3.8 Proposed mechanism for the formation of 81

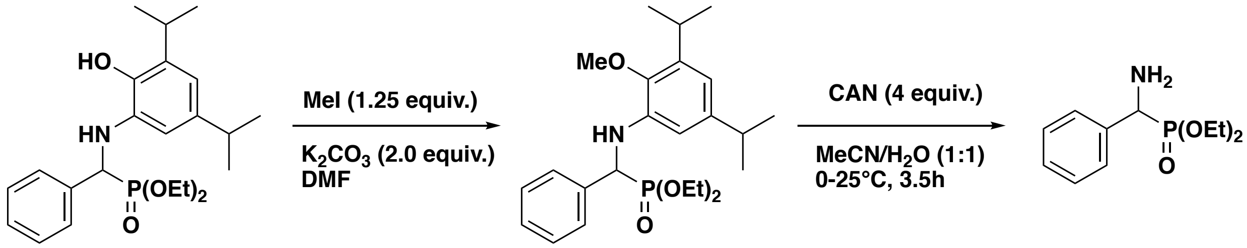


Instead of oxidizing the phenyl ring on the nitrogen, as would be expected in the normal PMP deprotection pathway, the nitrogen itself in **67a** was oxidized by CAN to generate a radical cation **82**. This is followed by cleavage of the C-P bond and then attack by oxygen onto the C-N double bond of the imminium cation **83** to gave the ring-closed intermediate **84.** After the second oxidation of the nitrogen by CAN and abstraction of hydrogen by the previously released phosphonate radical from the intermediate **85,** the final product **81** was obtained. This proposed mechanism indicates that the CAN oxidation prefers to take place on nitrogen rather than on the phenyl ring in **67a** and the subsequent cleavage of the C-P bond makes this step non-reversible. Therefore, to avoid the oxidation of the nitrogen, it was thought to add an electron withdrawing group, such as

Boc, on the nitrogen, which could possibly increase the difficulty of the oxidation of the nitrogen. Alternatively, the phenol could be methylated and this may cause a change in the oxidation.

After treating **67a** with methyl iodide and potassium carbonate in DMF, **79** was produced in 75% yield. Then it was treated with 4 equivalents of CAN. A mixture of several unknown compounds were produced, no desired product **80** but the same side product **81** was detected (20% yield) (Equation.3.5).

Equation 3.5 Deprotection of the methylated product 79 by CAN



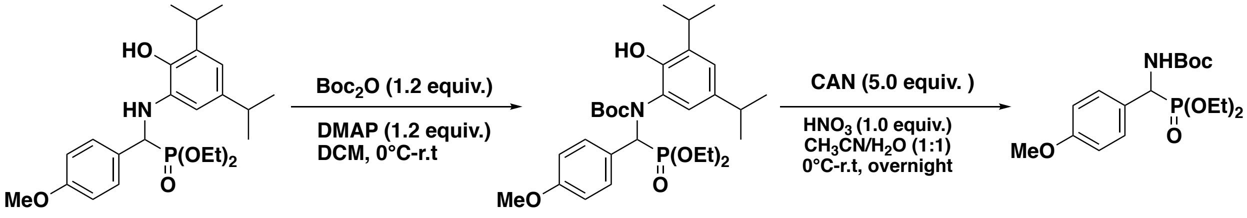
67a

79
75%

80
not detected

The Boc-amide **67b**, which synthesized by Boc anhydride and DMAP in 74% yield. It reacted with 5.0 equivalents of CAN as indicated in Equation 3.6. After 12 hours of stirring, all starting material was consumed but none of the desired product **Boc-80** was formed (Equation.3.6).

Equation 3.6 Deprotection of the boc protected 67b by CAN



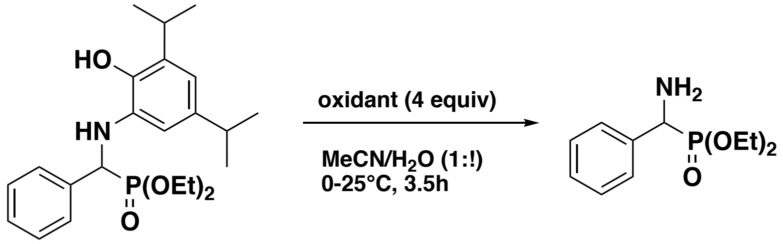
67b

Boc-67b

Boc-80
not detected

Since cleavage of N-protecting group with CAN didn't work on either Boc protected or methoxylated Kabachnik-Fields adducts, other oxidants [59] were tested in the reaction. Trichloroisocyanuric acid (TCCA), pyridinium bromide-perbromide (PBB), (Diacetoxyiodo)benzene, Dess-Martin reagent and periodic acid were examined with the same deprotection condition of CAN (Table 3.13) and for the Dess-Martin reagent and periodic acid, they had been also tested with Boc protected **67b** as the starting material (not listed). However, from all these reactions, no desired amine product was observed and reaction usually gave the nitrogen oxidized products with a mixture of other unknown compounds.

Table 3.13 Deprotection of 63a by other oxidants



67a **80**

	oxidant	% Yield
1	TCCA	ND
2	PBB	ND
3	$PhI(OAc)_2$	ND
4	Dess-Martin reagent	ND
5	H_5IO_6	ND

ND= not detected

3.7.2 Deprotection of the aromatic α-amino phosphonates by N-halosuccinimide

In the work of Shibata and co-workers, N-bromosuccinimide (NBS) was used to cleave the PMP group on their Kabachnik-Fields products (Scheme 3.9).[35] According to their protocol, 1.0 equivalent of NBS in a co-solvent of water and acetonitrile was added to (*S*)-**86** and the mixture was warmed from 0 °C to room temperature. The deprotected α-amino phosphonates (*S*)-**87** was obtained in 55% yield with no loss in the optical purity. These same conditions were applied to **67a**. A mixture of the starting material and other unknown compounds was obtained, but no desired product (**80b**) was found (Table 3.13, entry 1).

Scheme 3.9 Shibata's deprotection protocol with NBS

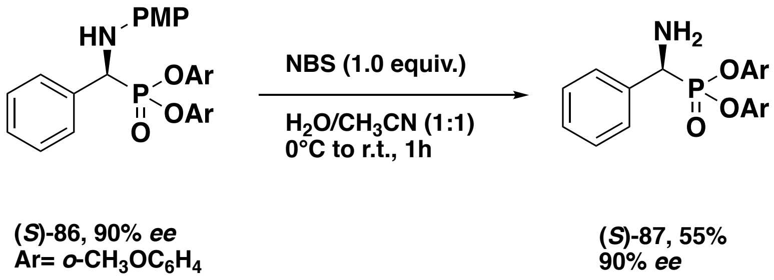
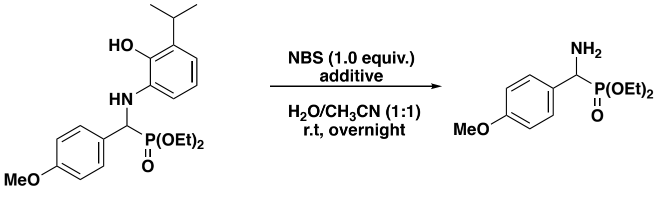


Table 3.14 Deprotection by NBS



67ka

80b

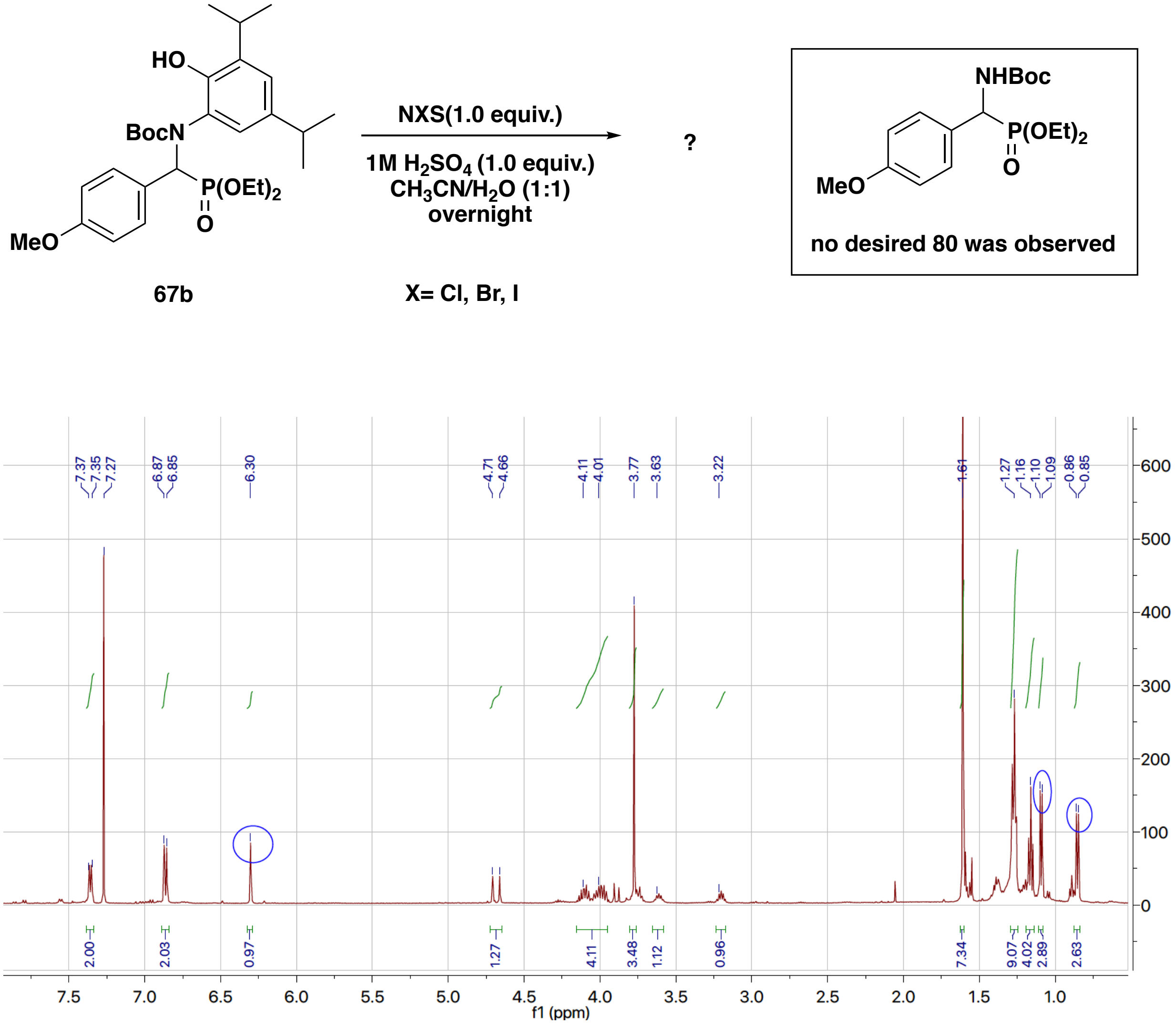
	Additive	% Yield
1	None	ND
2	1M H_2SO_4 (1.0 equiv.)	ND
3	1M H_2SO_4 (10.0 equiv.)	ND

ND= not detected.

Another procedure that was reported by Rutjes[59] included the addition of 1.0 equivalent of 1M sulfuric acid along with the NBS. This procedure was also tested with 1.0 equivalent and 10.0 equivalents of H_2SO_4 (Table 3.11, entry 2 and 3), however no desired product was detected and the ^{1}H NMR was messy.

The Boc protected **67b** was reacted with NBS, NCS (N-chlorosuccinimide) and NIS (N-iodosuccinimide) and there was a major side product (~ 30% yield) formed after the reactions (Figure 3.1).

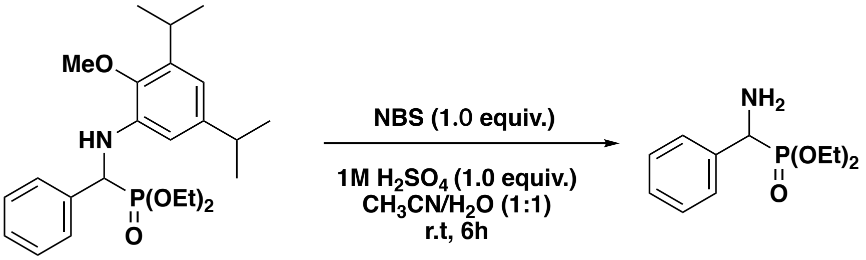
Figure 3.1 ^{1}H NMR spectrum of a major side product of deprotection by NXS with 67b



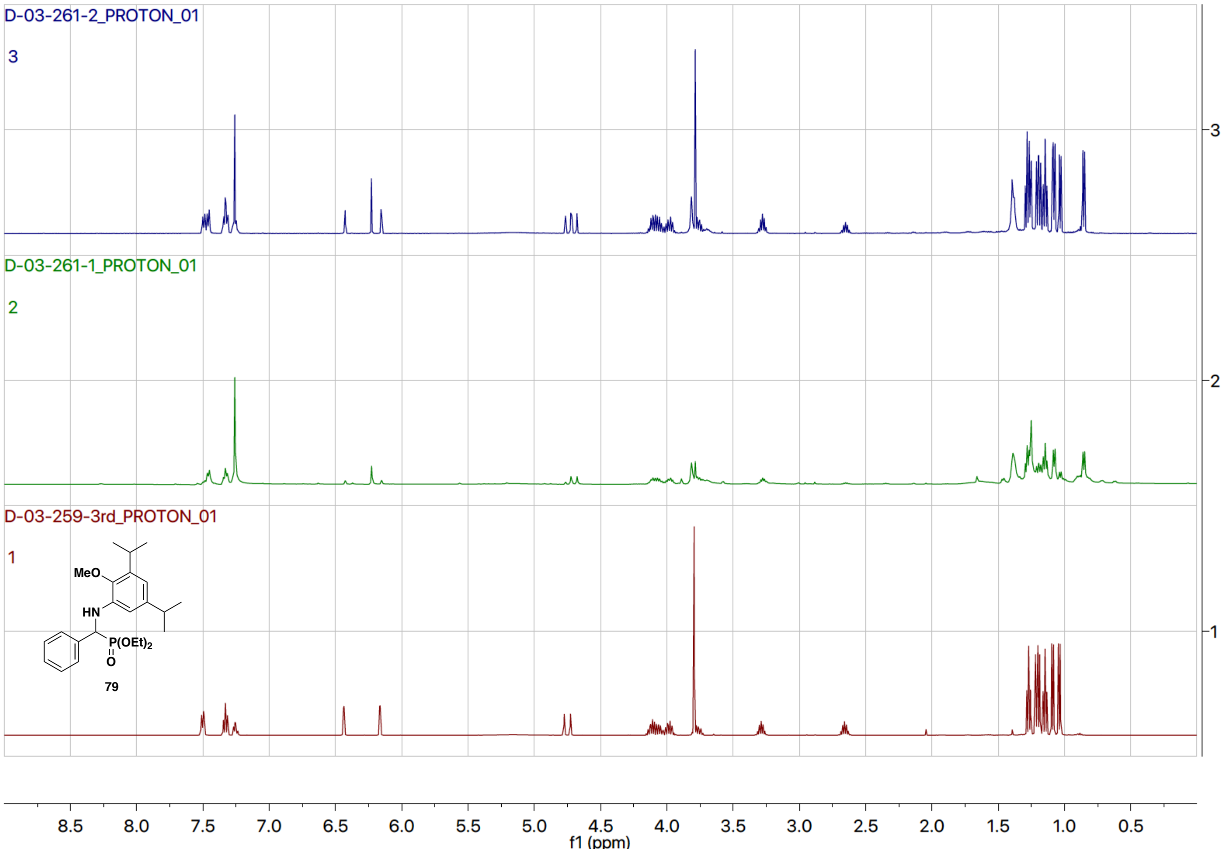
At first, the mixture was thought to be a combination of the desired product **80** and another impurity. If the singlet at 6.3 ppm (in blue circle) and the two doublets at 1.09 ppm and 0.85 ppm (in blue circle) were excluded, the other peaks seem to match well with the desired product **80**. Thus, this sample was subjected high resolution mass analysis (HRMS), but no exact mass of the desired **80** was found.

Since deprotection of the Boc protected **67b** were failed under different deprotection conditions (Eq. 3.6), the deprotection of **67a** was then attempted in the form of its methyl ether **79** (Figure 3.2).

Figure 3.2 ^{1}H NMR spectrum of the deprotection of 79 with NBS and sulfuric acid

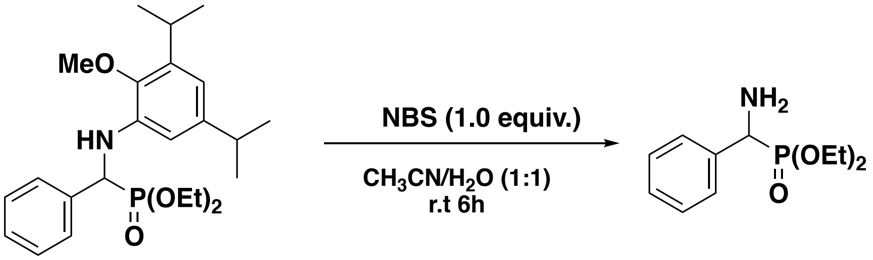


79 **80**

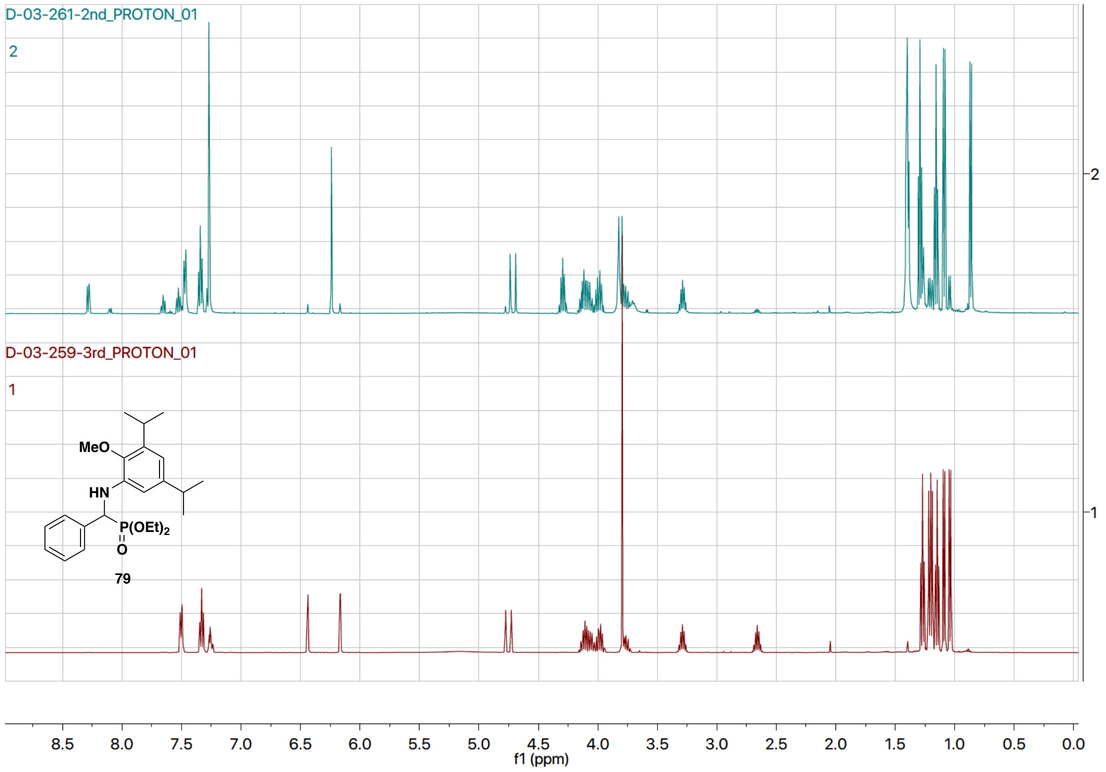


The reaction mixture for **79** and NBS on a silica gel column to give two major portions which were collected and examined by ^{1}H NMR. By comparison with the ^{1}H NMR spectrum of the starting material **79** (at the bottom, Figure 3.2), the top spectrum was of a mixture of starting material **79** and an unknown side product, which was a similar side product seen in Figure 3.1, and the second spectrum was that of the pure side product. The same reaction was repeated without sulfuric acid and the ^{1}H NMR spectrum is shown in Figure 3.3.

Figure 3.3 ^{1}H NMR spectrum of the deprotection reaction of 79 with NBS



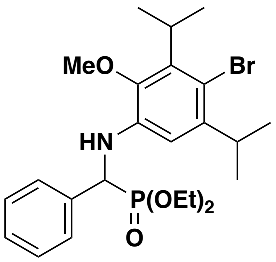
79 **80**



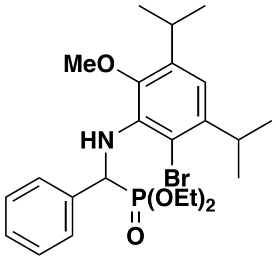
Despite the presence of the same side product, there was no starting material **79** left and a doublet showed up around 8.2 ppm, which would be expected for a proton on an imine carbon. From those two reactions, it is indicated that in one aspect, sulfuric acid is considered to be more likely to prevent the formation of imine byproducts. On the other hand, the possible structure of that unknown side product needs to be proposed.

In the ^{1}H NMR spectrum of starting material **79**, there are two singlet peaks in the range of 6.0-6.5 ppm (Figure 3.2, the bottom spectrum) and those are the two protons on the phenyl ring on the nitrogen. However, in the ^{1}H NMR spectrum of the unknown, only one singlet appears at 6.2 ppm (Figure 3.2, the middle spectrum). In our hypothesis, one of the proton in the aromatic range is supposed to be replaced by bromine. Two possible structures were listed in the Figure 3.4.

Figure 3.4 Two possible structures of the unknown side product 88 and 89



88

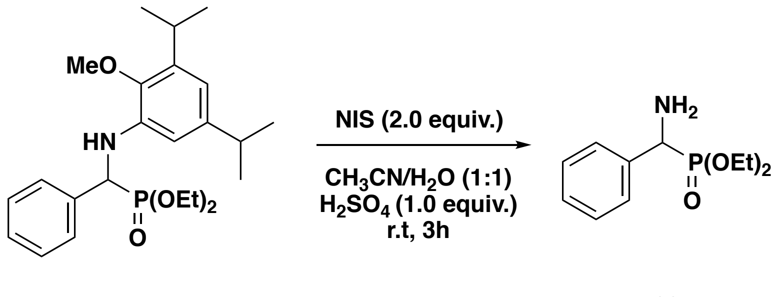


89

The exact mass (plus Na^+) of the unknown compound is 534.1385, which is identical to the calculated mass of either **88** or **89**. Now it is known that NBS reacted with **79** through the electrophilic aromatic substitution, but the subsequently the deprotection did not occur. If more equivalents NBS was added to the reaction, only the hydrolysis product of the **88** or **89** will be obtained.

In the contrast to NBS, NIS has different electronic and steric status and it is much harder for adding the iodine to the phenyl ring than bromine, which possibly could prevent the formation of the side product and promote the deprotection. By employing 2.0 equivalents of the NIS and 1.0 equivalent of 1M sulfuric acid, 75% yield of the deprotected product **80** was finally achieved (Equation.3.7).

Equation 3.7 Deprotection of the aromatic product 79 by NIS

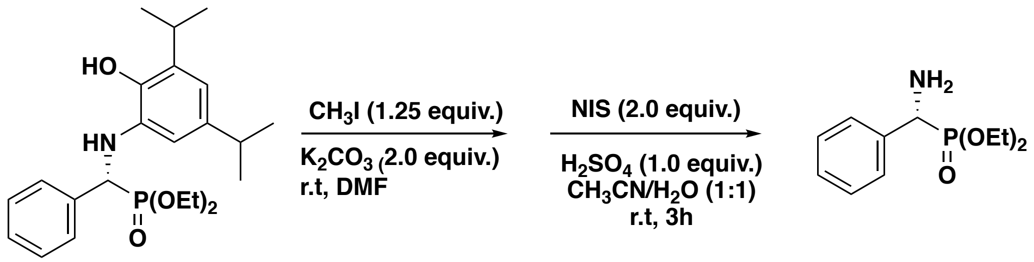


79

80
75%

NIS oxidation was also tested directly on the Kabachik-Fields product **67a**, but the reaction afforded the desired deprotected α-amino phosphonate **80** in only 10% yield. Thus, it is clear that the deprotection of **67a** will require two steps. Specifically the standard protocol for deprotection of aromatic α-amino phosphonates involves first methylation with methyl iodide and then oxidation with NIS to give **80** in overall 65% yield. (Scheme 3.10). The absolute configuration of **80** was confirmed by comparing the the sign of its optical rotation with that reported in the literature[60] and ECCD also gave the identical result based on the method developed by Babak Bohan's group (see details in chapter 6).[61]

Scheme 3.10 Standard procedure for deprotection of aromatic α-amino phosphonates



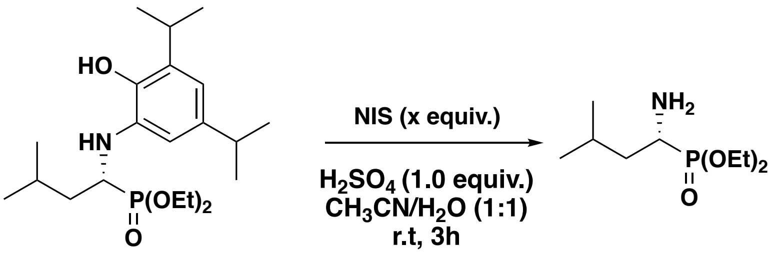
(*R*)-67a
90% *ee*

80
65% (two steps)
$[a]_D^{20} = +17.2$ (c= 1.0)[7]
$[a]_D^{20} = +10.2$ (c= 0.8)

3.7.3 Deprotection of the aliphatic α-amino phosphonates by N-iodosuccinimide

Following the standard protocol of deprotection of aromatic α-amino phosphonates, it was found that the methoxylation of the aliphatic α-amino phosphonates produced some unknown side products and the yield of the desired methoxylated product was low (~30%). Thus the deprotection was examined directly without methoxylation. **76c** was selected to perform the deprotection, as its α-amino phosphonic acid, (*R*)-phospholeucine[14-16], is a potent inhibitor of the metalloenzyme leucine aminopeptidase in biochemistry (Table 3.14).

Table 3.15 Deprotection of 76c with NIS



76c

90
$[a]_D^{20} = -20.6$ (c= 1.0)[12]
$[a]_D^{20} = -36.7$ (c= 0.72)

Table 3.15 (continued)

	NIS (x equiv.)	% Yield
1	1.0	27
2	3.0	60
3	5.0	50

With adding of 1.0 equivalent of NIS, the reaction only afforded the deprotected product **90** in 27% yield. Increasing the equivalents of NIS to 3.0, the yield reached to 60%. However, when 5.0 equivalents of NIS was added to the reaction, the yield dropped to 50% along with some unknown solid side products. NBS and CAN were also examined in the deprotection of **76c**, neither of them gave the desired product **90**. The absolute configuration of the **90** was confirmed by comparing the the sign of its optical rotation with that reported in the literature[62] and ECCD method[61].

3.8 Conclusion

In this chapter, a new method for the asymmetric Kabachnik-Fields reaction with aliphatic aldehydes was developed. By utilizing 2-hydroxy-3-*t*butylaniline as the amine source, the asymmetric induction of direct three-component hydrophosphonylation reaction of aliphatic aldehydes reaches over 90% *ee* for the first time. The protecting group on the product could be cleaved by a new NIS deprotection protocol. Multi-functional aliphatic aldehydes were tolerated under the mild reaction conditions and afford desired products with good yields and enantioselectivities. From mechanism investigations, it was found that the hydroxyl group on the aniline plays an important role in asymmetric induction. Based on other control experiments, it was found there was no background reaction between the aldehyde and the phosphite. In the future studies, more experiments will be focused on getting a crystal structure of the zirconium catalyst and to applying this catalyst to other asymmetric reactions involving an imine.

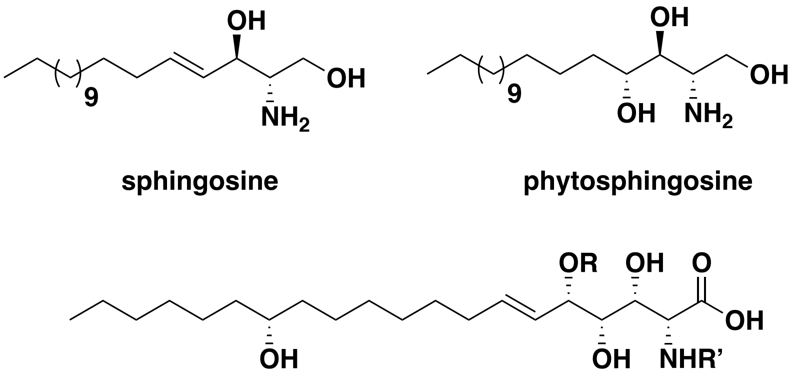
CHAPTER FOUR

TOTAL SYNTHESIS OF SPHINGOID BASES

4.1 Introduction

Sphingolipids are an important class of lipids containing the backbone of sphingoid bases. They can be found in both plants and animals, and play various structural and regulatory roles inside the body.[63-65] Some highly modified sphingolipids, such as the sphingofungins and sphingosine (Figure 4.1), which exist in lower invertebrates and microbes can function as inhibitors in the pathway of mammalian sphingolipid biosynthesis[66].

Figure 4.1 Structures of sphingofungins and sphingosines



sphingosine

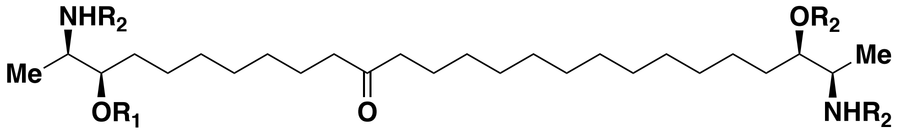
phytosphingosine

sphingofungin A (R = H; R' = C(NH)NH$_2$)
sphingofungin B (R = H; R' = H)
sphingofungin C(R = Ac; R' = H)
sphingofungin D (R = H; R' = Ac)

In contrast to most all sphingionoid molecular, two-headed sphingolipids from marine sponges have an unique tail-to-tail dimeric (bipolar) structures compared to normal sphingosine, which are composed of a α,ω-bis-aminoalkanol or aminoalkanediols motif. For example, rhizochalin (**100**), which was first discovered near the north-west shore of Madagascar island (-15m) in 1989 by Stonik group (Figure 4.2)[67], contains a

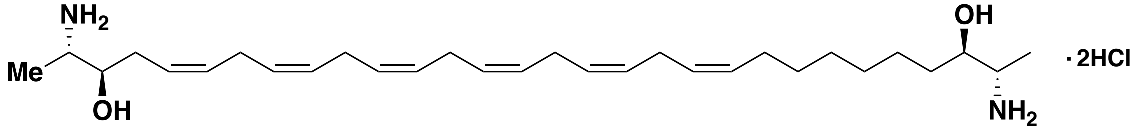
C28 lipid chain with both ends terminated by a vicinal amino alcohol (one of them is the glycosidic amino alcohol). Leucettamols A (**101**) and B (**102**), isolated in 1992 by Faulkner and his coworkers, also have a similar structure (Figure 4.2)[68]. Those two-headed sphingolipids exhibit varied potent biological effects including antifungal activity against the pathogenic Fluconazoleresistant yeast *Candida glabrata*[69-70], antibacterial activity against *Staphylococcus aureus*[67], anticarcinogenic properties[71], induction of apoptosis in cultured leukemic cells[72], selective DNA damaging activity[73], inhibition of protein kinase C[74] and UBc13-Uev1A interaction[75].

Figure 4.2 Structures of rhizochalin (100) and leucettamols (101, 102)



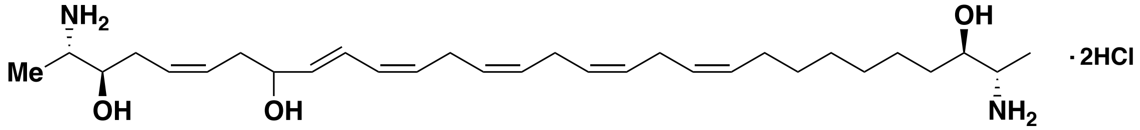
100

Rhizochalin, R$_1$= β-D-galactopyransyl, R$_2$= H



101

leucettamols A

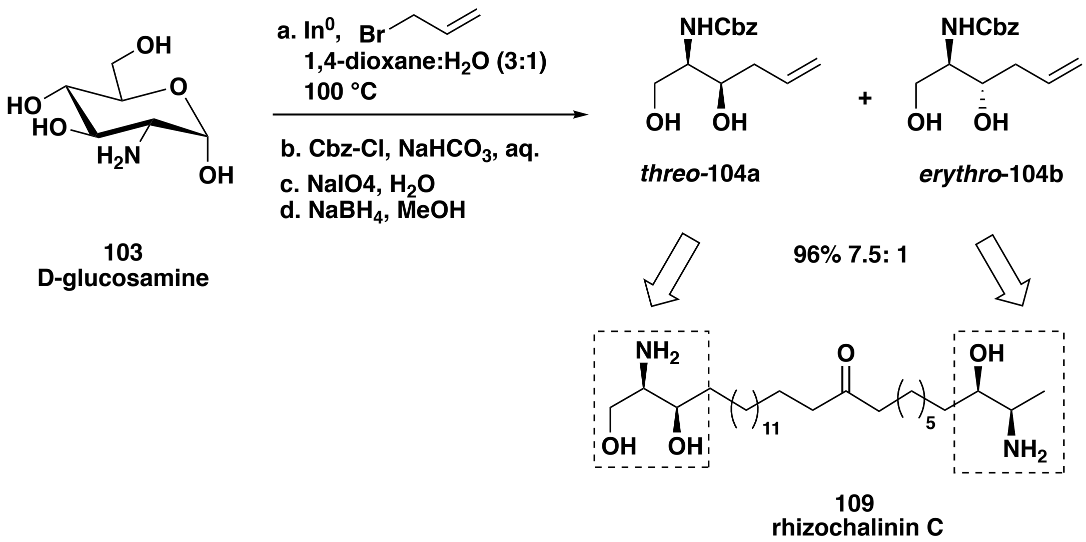


102

leucettamols B

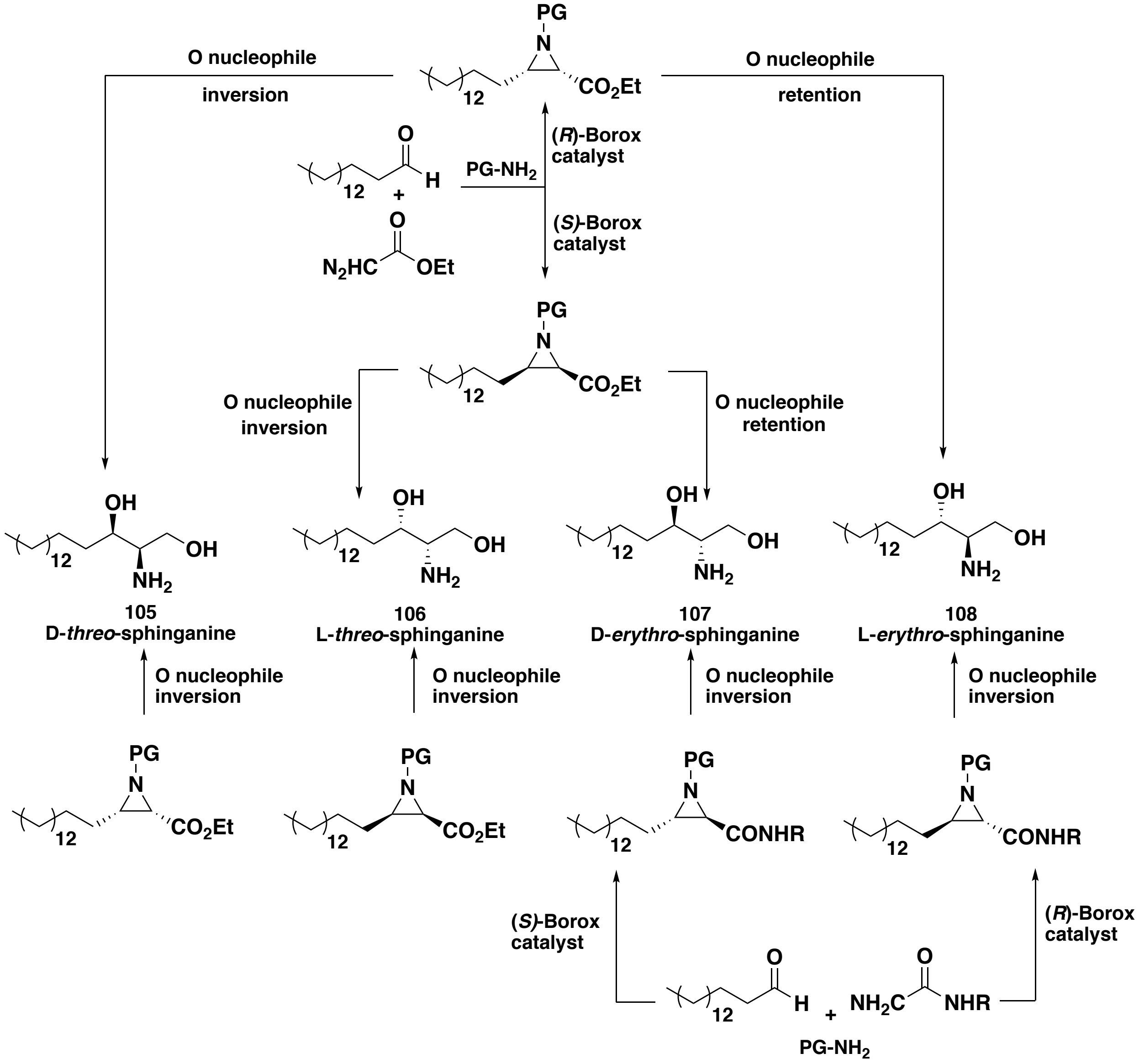
However, up to now there is only one report described total synthesis of rhizochalinin C (**109**) in by Molinski's group in 2013[76]. By employing an unprotected D-glucosamine (**103**), they disclosed an optimized procedure based on an In-mediated allylation for rapid diastereoselective access to protected L-threo-sphingoid base synthons (**104a**) and (**104b**) in a five-step, one-pot conversion. This protocol was chosen as an alternative to employing expensive D-amino acids. Subsequent chain elongation of both heads and final Horner-Emmons-Wadsworth coupling reaction followed by deprotection provided the free base rhizochalinin C (**109**) as a single stereoisomer (Scheme 4.1). This synthesis is non-asymmetric since it starts with D-glucosamine from the chiral pool.

Scheme 4.1 Total synthesis of rhizochalinin C (109) from D-glucosamine



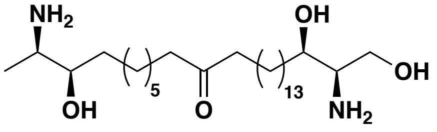
In the two past decades, the catalytic asymmetric synthesis of *cis*- and *trans*-aziridination has been developed in our group.[43, 45, 47, 77-80] Both methodologies were applied to the synthesis of all four diasteroisomers of sphinganines (**105**, **106**, **107**, **108**, Scheme 4.2).[81-82] The first approach involved the stereo-controlled opening of each enantiomer of cis-aziridine a with an oxygen nucleophile with either retention or inversion of configuration to achieve all four diasteroisomers.[81] In a second approach, a previous group member Yubai Zhou published another method affording all four diastereomers directly via either a *cis*- or *trans*-aziridination (Scheme 4.2).[82]

Scheme 4.2 Synthesis of all four diasteroisomers of sphinganine by catalytic asymmetric aziridination

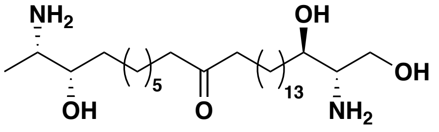


Based on these promising results, attention was turned to the synthesis of the more complicated two-headed sphingoid bases, rhizochalinin C (**109**) and D (**111**)[83-84], calyxinin (**110**)[73] and oceanin (**112**)[69-70, 85] (Figure 4.3). They all have either a C28 or C29 chain but with different chirality in the aminoalkanol or glycosidic aminoalkanol motifs at both termini. It was thought that these compounds could be achieved via a catalytic asymmetric aziridination in high diastereoselectivity without relying on the chiral pool. This chapter will mainly focus on the synthesis of rhizochalinin C (**109**) and D (**111**).

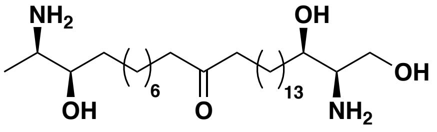
Figure 4.3 Structures of the two-headed sphingoid bases rhizochalinin C (109) and D (111), calyxinin (110) and oceanin (112)



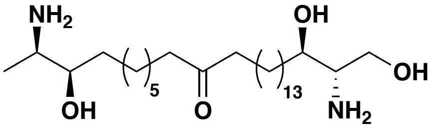
109
rhizochalinin C



110
calyxinin



111
rhizochalinin D

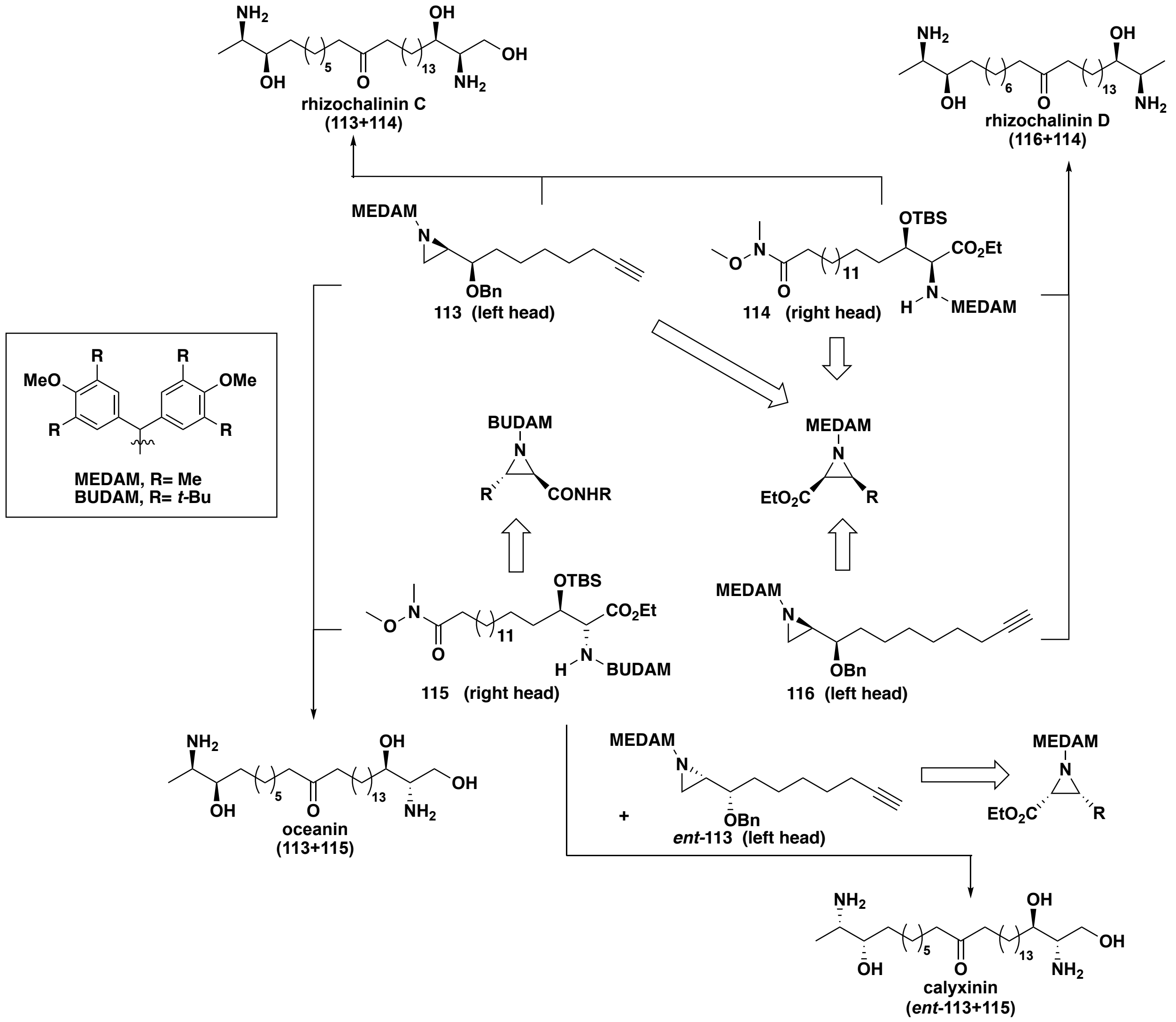


112
oceanin

4.2 General synthetic route to the four two-headed sphingoid bases 109-112

The general synthetic design is outlined in Scheme 4.3. It was envisioned that the synthesis of the four two-headed sphingoid bases could be accomplished by a coupling reaction of left head and right head fragments, which in turn could be obtained from either the catalytic asymmetric cis- or trans-aziridination followed by the ring-opening reaction.

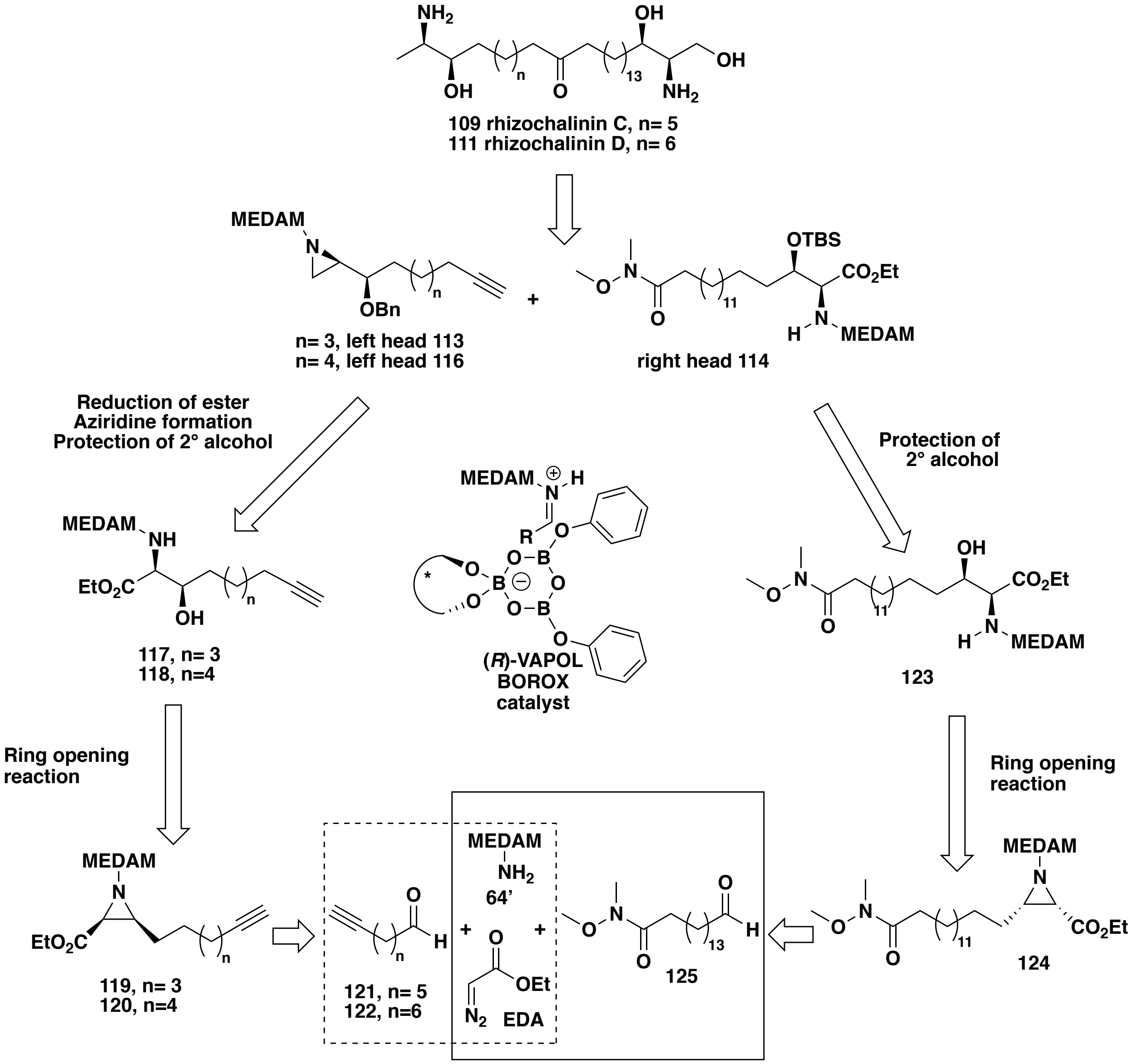
Scheme 4.3 General synthetic design of four two-headed sphingoid bases



4.2.1 Retro-synthetic analysis of rhizochalinin C (109) and D (111)

Rhizochalinin C (**109**) and D (**111**) have the identical configuration of the four stereo centers in the structure, the only difference being that the carbon chain in rhizochalinin D (**111**) is one carbon longer than C (**109**). Both molecules should be achievable via a nucleophilic addition to the right head amide **114** with either the left head acetylene **113** or **116**. The construction of right head **114** is envisioned from the *cis*-aziridine **124**, which is to be synthesized through *cis*-aziridination of the aldehyde **125**, with ethyl diazoaectate (EDA) and MEDAM amine **64’** catalyzed by a chiral borox complex followed by ring-opening reaction. Moreover, the left heads **113** and **116** are to be accessed by aziridine formation from **117** and **118**, whose chiral amino alcohol scaffolds can be installed from the *cis*-aziridination from aldehyde **121** and **122** bearing a terminal acetylene and the subsequent ring-opening reaction (Scheme 4.4).

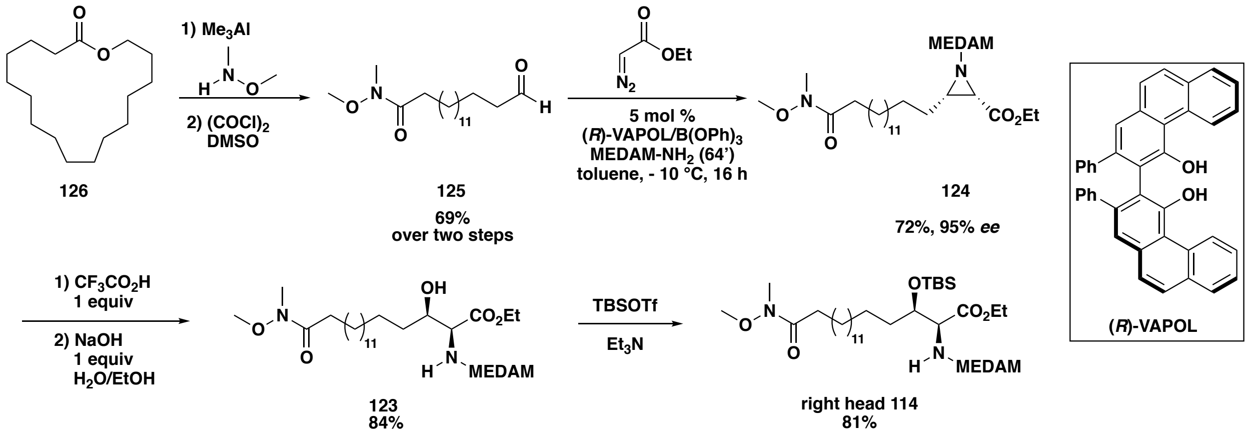
Scheme 4.4 Retrosynthetic route of rhizochalinin C



4.3 Synthesis of right head 114

The synthesis route for the right head **114** was developed by our former group member Xin Zhang[51], which commenced with commercially available 16-hexadecanolide **126** (Scheme 4.5). Ring-opening of **126** with Weinreb's amine and then Swern oxidation produced the corresponding aldehyde **125** in 69% yield over two steps. The subsequent *cis*-aziridination catalyzed by (*R*)-VAPOL-borox complex with ethyl diazoaectate and MEDAM amine (**64'**) at -10°C gave the *cis*-aziridine **124** in 72% yield and 95% *ee*. Ring-opening with TFA followed by hydrolysis delivered the compound (**123**) in overall 84% yield in 10:1 ratio of regioisomers, which were separated. The final 2° hydroxyl group protection with TBSOTf afforded the right head (**114**) in 81% yield.

Scheme 4.5 Synthesis of right head 114

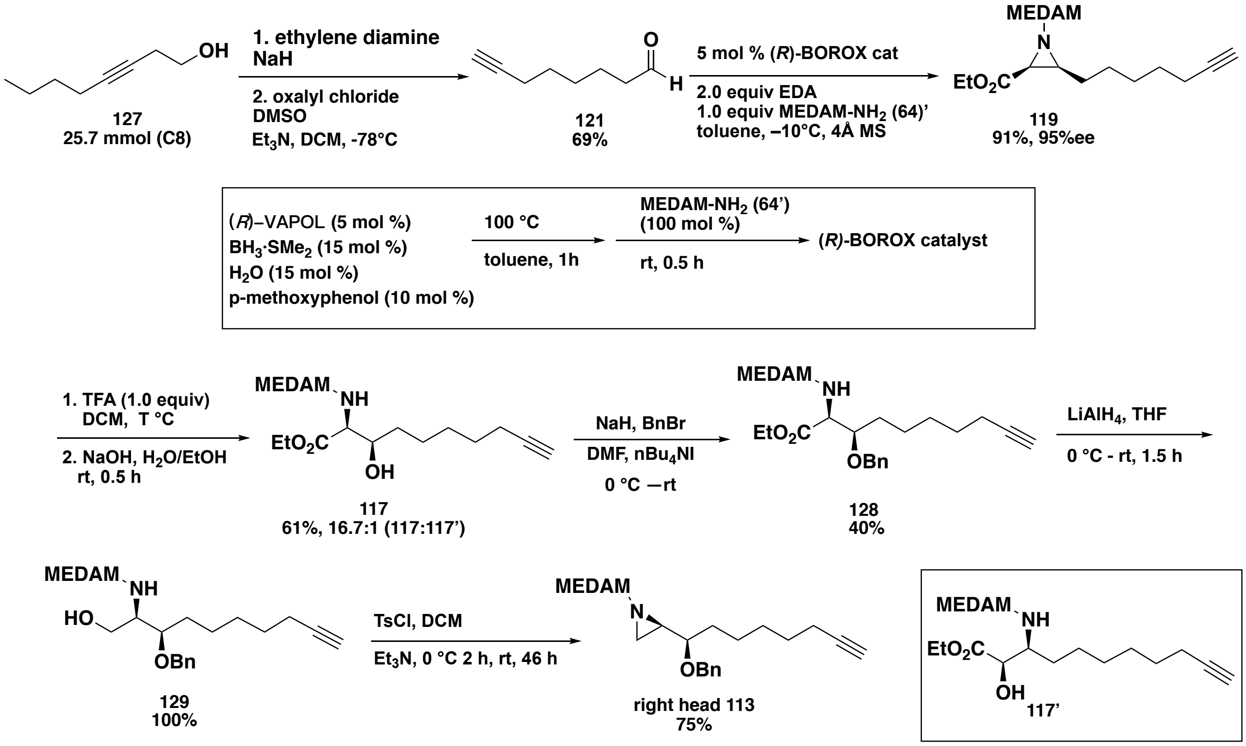


4.4 Synthesis of left head 113

The synthesis of left head **113** was carried out according to the procedure developed a former group member Wenjun Zhao (Scheme 4.6).[86] Commercially available oct-3-yn-1-ol (**127**) was transferred to its corresponding aldehyde **121** and then subjected to (*R*)-VAPOL-borox complex catalyzed *cis*-aziridination with ethyl diazoaectate and MEDAM amine (**64'**) at -10°C, which generated the aziridine (**119**) in

92% yield and 95% *ee.* This procedure involves generation of the BOROX catalyst with ρ-methoxyphenol. The BOROX catalyst incorporating phenol is equally effective but separation of the product from phenol is difficult. The subsequent ring-opening reaction with TFA and hydrolysis by aqueous NaOH at room temperature afforded the desired product **117** in 61% yield with a regioselectivity of 16.7:1, and both of isomers can be separated from column chromatography. The 2° hydroxyl group in **117** was protected with BnBr, followed by the reduction of the ester to the primary alcohol **129** in overall 40% yield. Finally, the left head **113** was accomplished in 75% yield by activation of the primary alcohol with TsCl in dichloromethane and the formation of aziridine.

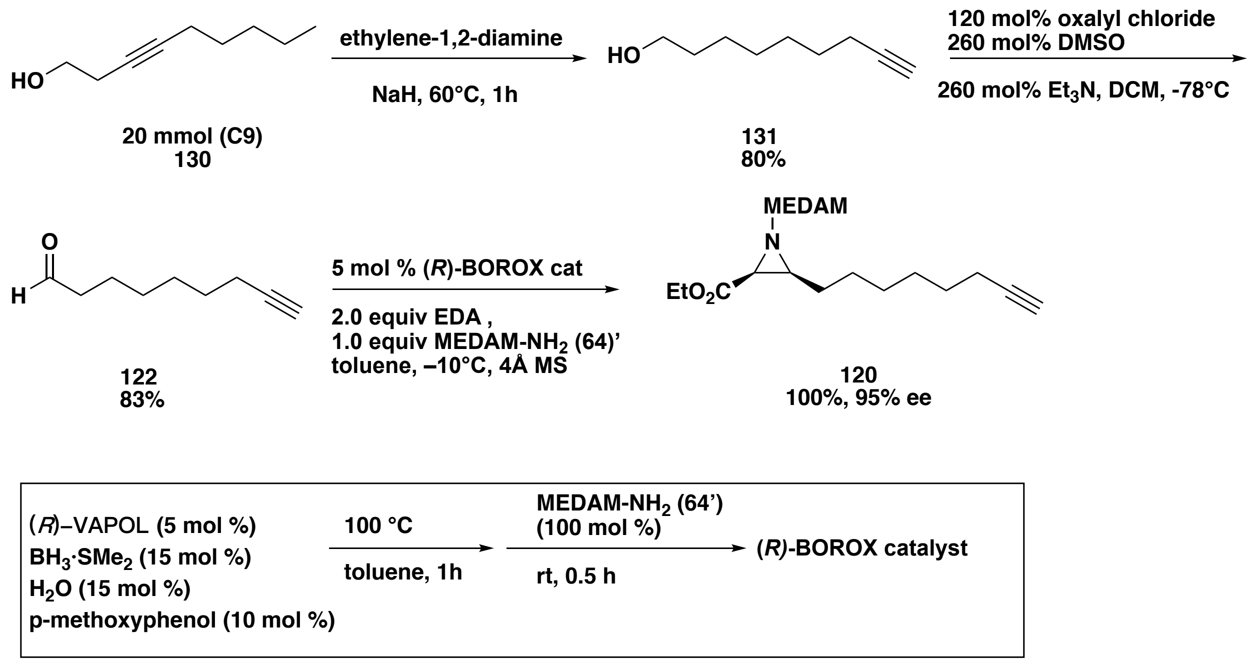
Scheme 4.6 Synthesis of left head 113



4.5 Synthesis of left head 116

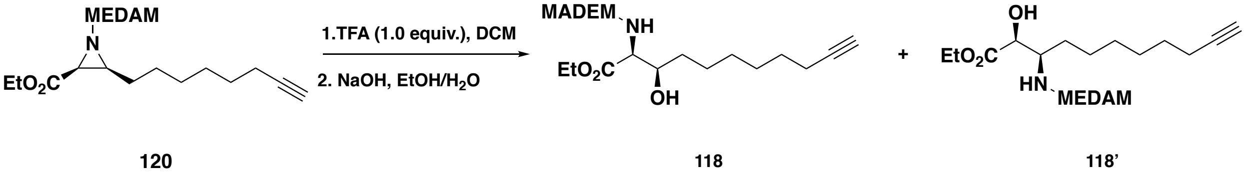
Left head **116** of rhizochalinin C is only one more carbon longer than left head **113**, whose synthesis is shown in Scheme 4.7. The synthetic route to **116** is almost identical to that for **113**, and only minor modifications were made to several certain steps. The synthesis starts with isomerization of non-3-yn-1-ol **130** to terminal acetylene **131**, and the following Swern oxidation provided the corresponding aldehyde **122** in 83% yield. Aziridine **120** was achieved by applying the multi-component *cis-* aziridination with ethyl diazoaectate (EDA) and MEDAM amine (**64'**) catalyzed by (*R*)-VAPOL-borox complex at room temperature in quantitate yield and 95% *ee*.

Scheme 4.7 Synthesis of aziridine 120



The regioselectivity in ring-opening of **119** in Scheme 4.6 is 16.7:1. Applying the same ring-opening conditions to aziridine **120**, it was surprisingly found that both the yield and regioselectivity were lower despite the fact that compound **120** only has a carbon chain that is one carbon longer than **119**. Therefore, different reaction concentrations and reaction times were examined (Table 4.1). The conversion reached 100% with increasing the reaction time, and no starting material was observed after 42 hours. Reducing the reaction concentration from 0.1 M to 0.05 M resulted in a slight increase in both of the yield and regioselectivity to 68% yield and 11:1 ratio of **118** to **118**’ (entry 3). A Large scale reaction was also carried out twice at the lower concentration of 0.05 M to give a 75% yield and a 9:1 regioselectivity after 48 hours (entry 4) and both of isomers can be separated on column chromatography.

Table 4.1 Ring-opening reaction of aziridine 120

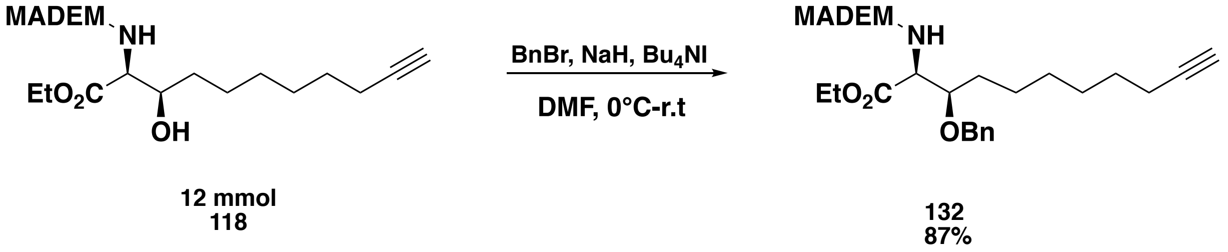


	Reaction scale	Conc. (M)	Temp (°C)	Time (h)	**118/118’**	Yield (%) of **118**[a]
1	0.34	0.10	r.t	22	10/1	58[b]
2	0.25	0.10	r.t	42	10/1	63
3	0.26	0.05	r.t	45	11/1	68
4	7.92	0.05	r.t	48	9/1	75[c]

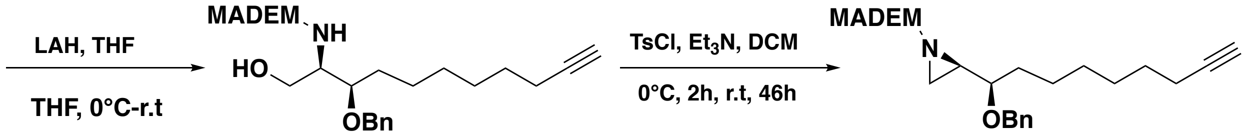
a] Isolated yield. [b] 18% of starting materials was recovered after the reaction. [c] Average result of two runs.

Furthermore, following 2° alcohol protection with BnBr and then reduction of the ester to a primary alcohol by $LiAlH_4$, compound **133** was obtained in 87% yield over two steps. Finally, aziridine formation with TsCl and triethylamine afforded the left head (**116**) in 88% yield (Scheme 4.8).

Scheme 4.8 Synthesis of left head 116



Scheme 4.8 (continued)



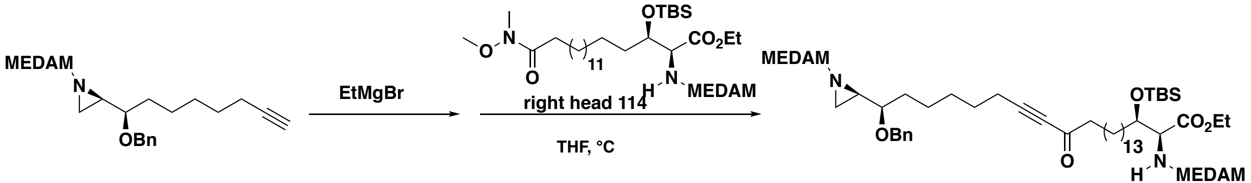
133
100%

left head 116
88%

4.6 Coupling reaction with right head 114 and left head 116

Once the right head **114** and the left head **116** were in hand, the next step is to couple them by a nucleophilic addition of the alkyne with the Weinreb amide. Based on Wenjun's method[86], EtMgBr was first added to a THF solution of left head **113** as a base at 0°C followed by the addition of right amide head **116** and then increasing reaction temperature to 65°C. After the mixture was stirred for 6 hours, the desired product **135** can be achieved in 82% yield (Scheme 4.9).

Scheme 4.9 Coupling of right head 114 and left head 113 by Wenjun's protocol

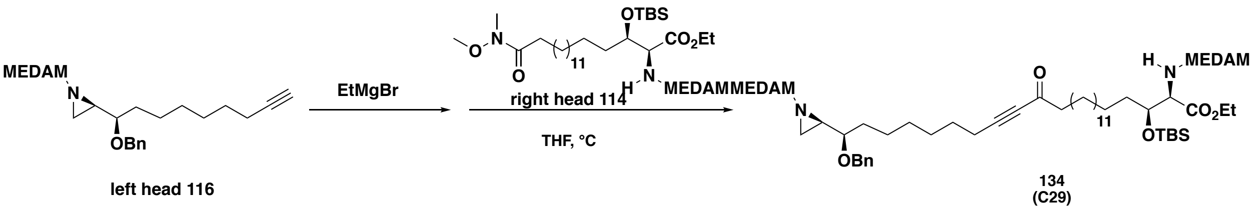


left head 113

135 (C28)
82%

However, when left head **116** was employed to react with right head **114**, under the same conditions, only starting material was recovered. With the concerning the concentration of the EtMgBr (2.5 M in ether solution), different equivalents of EtMgBr was tested in the coupling reaction (Table 4.2).

Table 4.2 Coupling of right head 114 and left head 116.



	Reaction scale	Equivalent of EtMgBr	Yield (%) of **134**[a]
1[b]	0.1	1.0	0[d]
2[b]	0.1	1.5	0[d]
3[b]	0.1	2.0	24[e]
4[b]	0.1	3.0	30[f]
5[b]	0.1	3.5	41[f]
6[b]	0.1	5.0	62
7[c]	0.5	1.0	0[g]
8[c]	0.4	2.0	25
9[c]	0.4	3.0	40
10[h]	0.4	3.0	35[i]

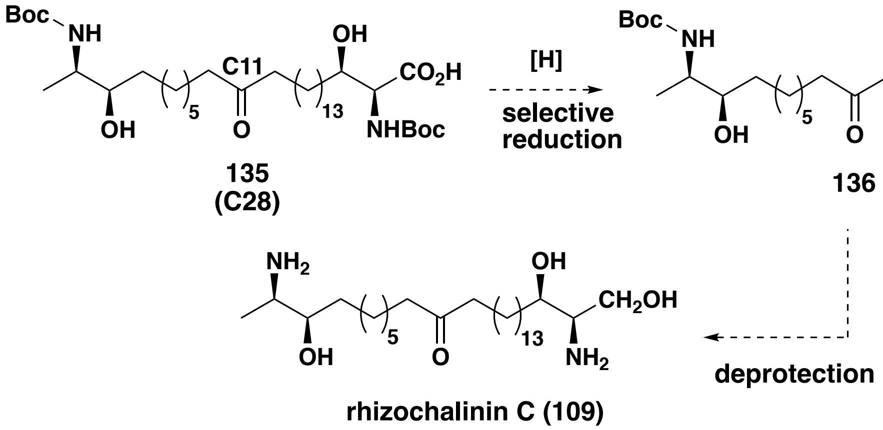
[a] Isolated yield. [b] An old bottle of EtMgBr (2.5 M in ether) was used in the reaction. [c] EtMgBr was titrated. [d] All starting material **114** was recovered. [e] Some unknown product was observed. [f] NMR yield. [g] All unknown products. [h] New bottle of EtMgBr from Sigma-Aldrich company. [i] Average yields based on 5 runs of reaction.

Although a 62% yield of **134** was obtained when 5.0 equivalents of EtMgBr (old bottle without titration) were added to the reaction, this result was not reproducible (entry 6). Later, after the EtMgBr solution was titrated and 3.0 equivalents was used in the reaction (which was equivalent to the 5.0 equivalents in the old bottle), but the reaction only afforded a 40% yield (entry 9). A new bottle of EtMgBr (2.5 M in ether) was purchased from Sigma-Aldrich, and this reagent gave an average 35% yield in 5 runs (entry 10). Other bases such as *n*BuLi and NaH were also examined in the reaction, but no desired product was detected. When the reaction of right head **114** and left head **113** was carried out with the new bottle of EtMgBr following the procedure reported by Wenjun Zhao, only 30% yield of the product **135** was obtained (same reaction as shown in Scheme 4.9).

4.7 Later stage selective oxidation

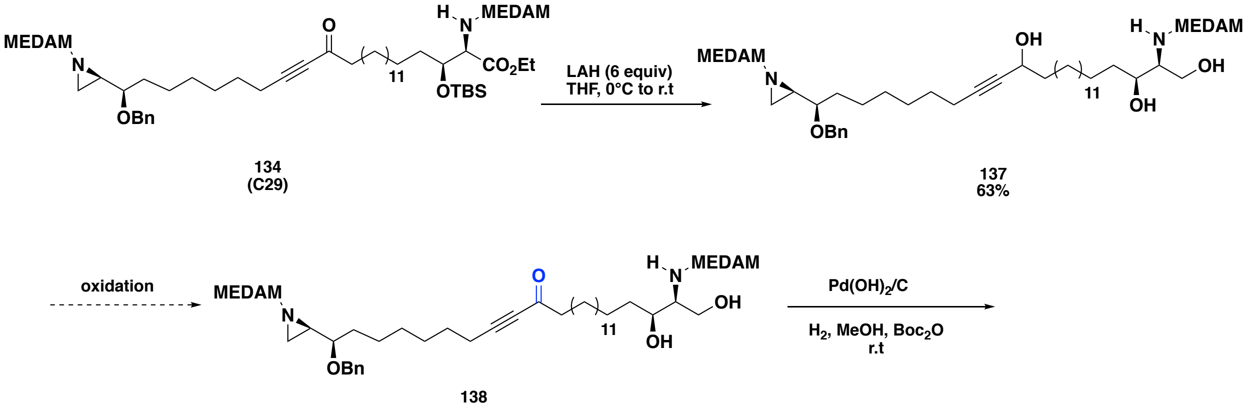
In Wenjun's synthetic route[86], after all protecting groups were removed, the final step was to be a selective reduction of the acid in the presence of ketone on the carbon 11. Several attempts had been made, but none were successful (Scheme 4.10).

Scheme 4.10 Wenjun's later stage selective reduction

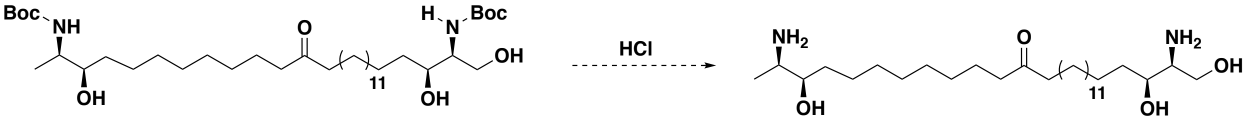


Therefore, in consideration of the difficulties in selective reduction of the acid over the ketone, a strategy was attempted in which both ester and ketone were reduced to give the diol **137**. This is to be followed by selective oxidization of the 2° hydroxyl group (propargylic alcohol) back to the ketone to furnish the target molecule **138** (Scheme 4.11).

Scheme 4.11 Synthetic route involving a later stage selective oxidation



Scheme 4.11 (continued)



139

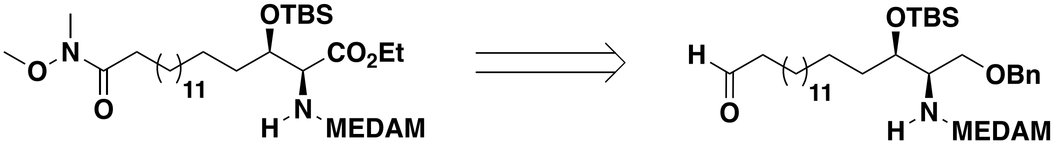
rhizochalinin D (111)

Reduction of both the ketone and carboxylic ester by $LiAlH_4$ provided the compound **137** in 63% yield in which the TBS group was also removed. The subsequent selective oxidation of the propargyl alcohol in the the presence of a primary alcohol was attempted under MnO_2 and $Vo(acac)_3$[87]in several different conditions, however no desired product was successfully observed. Moreover, as the yield of previous coupling reaction was low, a new synthetic route was designed for the approach to rhizochalinin C (**109**) and D (**111**).

4.8 New design of right head 140

An alternative way to avoid the late stage selective oxidation or reduction is to employ a reduced from of the carboxylic ester in the right head **114** prior to coupling with the left head **116**. Furthermore, in this new strategy, the amide is to be replaced with the more reactive aldehyde in the right head and this should promote a more efficient coupling reaction to achieve in intact carbon skeleton. Therefore, the final molecules could be accomplished by oxidation of 2° alcohol and the subsequent deprotection (Scheme 4.12).

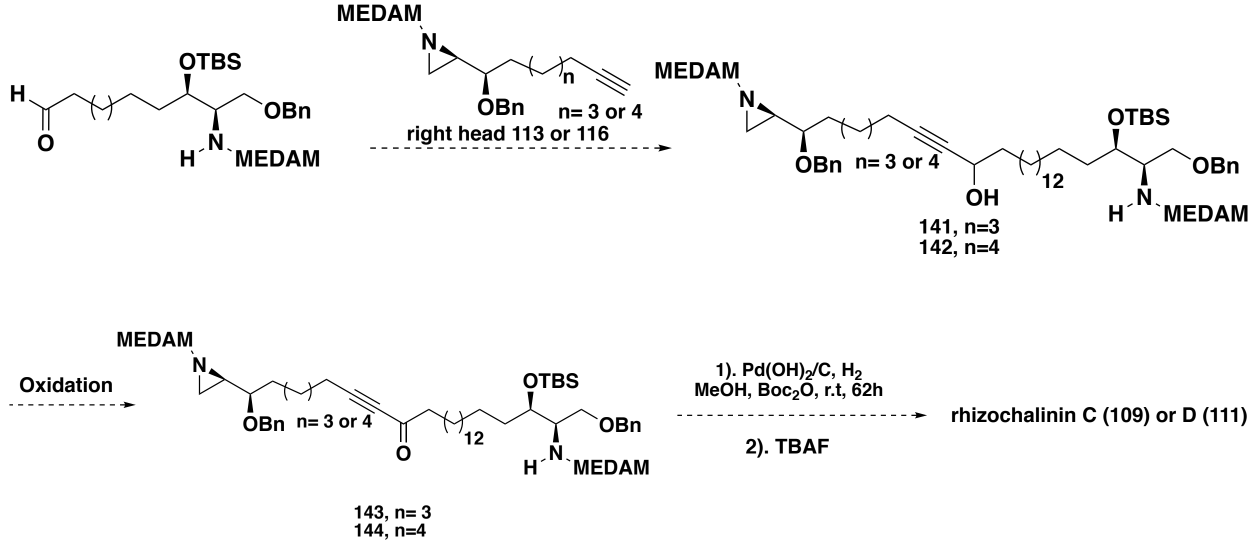
Scheme 4.12 New design of right head 140 towards the synthesis of rhizochalinin C (109) and D (111)



right head 114

new right head 140

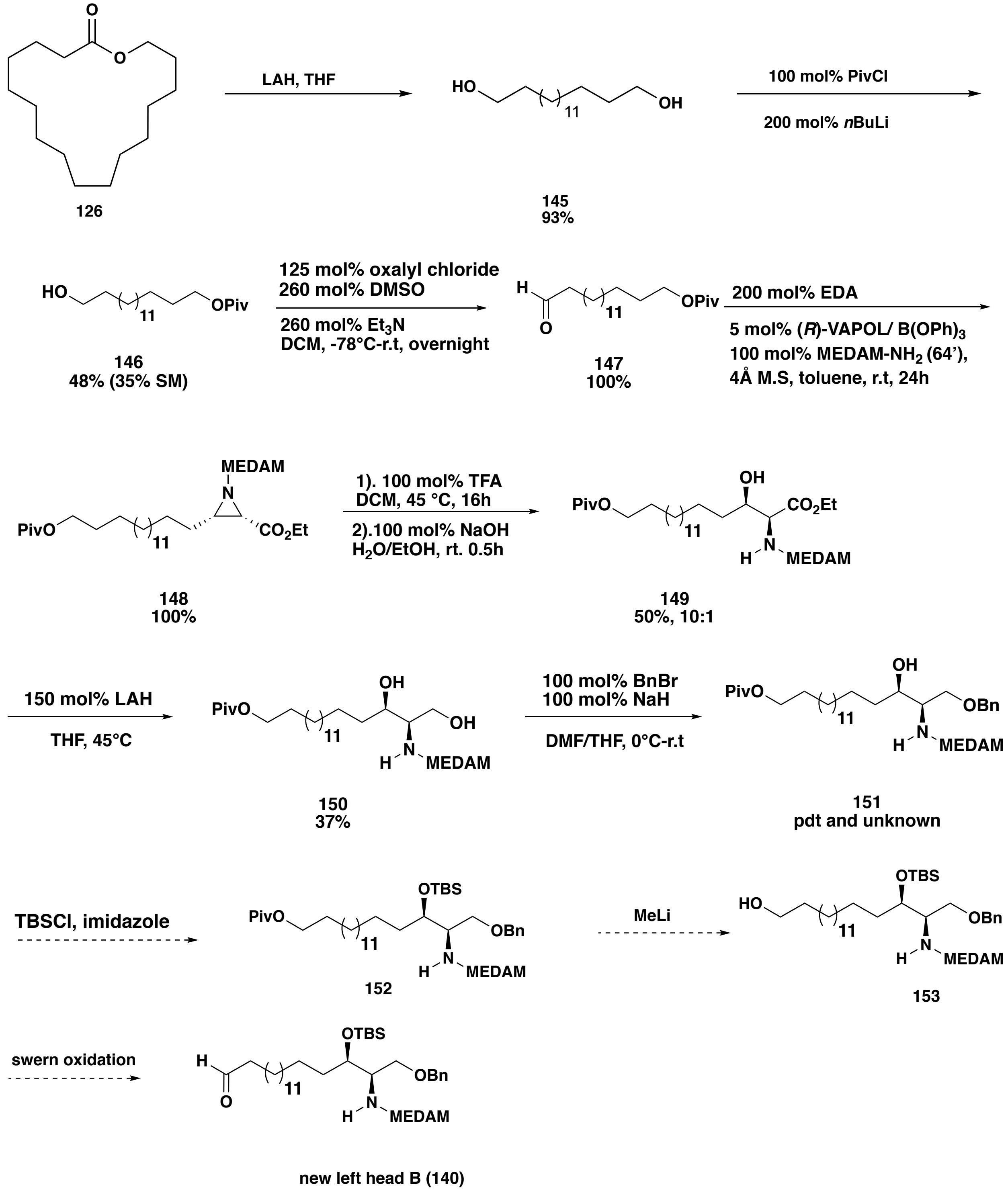
Scheme 4.12 (continued)



4.9 Synthesis of new right head 140

The synthetic route for the new right head **140** is described in the Scheme 4.13. It commences with the reduction of the commercially available 16-hexadecanolide **126** to the diol **145** with $LiAlH_4$ in 93% yield. Mono-protected diol **146** was produced by reaction with pivaloyl chloride and nBuLi in 50% yield (35% of the starting diol was recovered). Subsequent Swern oxidation and *cis*-aziridination with (*R*)-VAPOL-borox catalyst afforded the aziridine **148** in 100% yield and 95% *ee* over two steps. Ring-opening on the the aziridine **148** with TFA and subsequent hydrolysis gave the alcohol **149** 50% yield and with a 10:1 regioselectivity (isomers were not separated). The ester reduction of the ethyl ester in the presence of the pivaloyl ester by $LiAlH_4$ provided the diol **150** in 37% yield. The following protection of the primary hydroxyl group in the presence of the 2° alcohol afforded an unknown byproduct along with the desired product **151** in low yield, which were not separated. At this point, three additional steps will be developed in the future to access the new right head **140**.

Scheme 4.13 Synthesis of new right head 140



4.10 Conclusion

In this chapter, two synthetic routes to rhizochalinins C (**109**) and D (**111**) were explored. In the first approach, right head **114** and left head **113**, **116** were accomplished and in the later stage transformation to the target rhizzochalinins D (**111**), unsuccessful attempts were made to selectively oxidize the 2° alcohol in the presence of primary alcohol. Another alternative approach was then explored to avoid in an effort either a selective oxidation or reduction in a late stage intermediate. In this new approach, right head **140** was designed and considerable progress was made in its synthesis. Future work will be focused on finishing the synthesis of the new right head **140** and in additional, it would be important to optimize several of the steps with low yields.

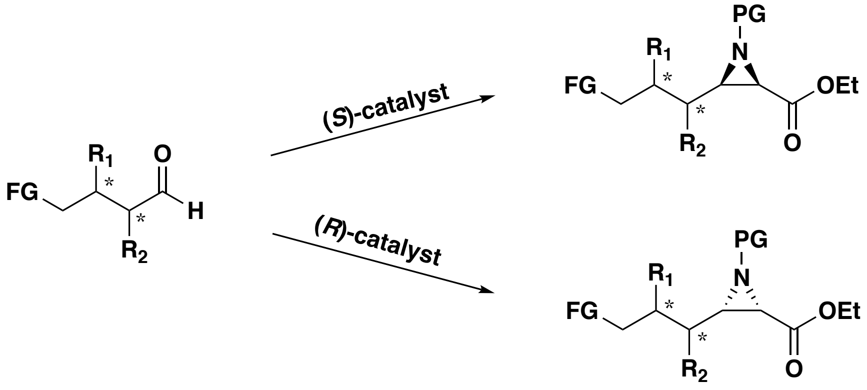
CHAPTER FIVE

CATALYST-CONTROLLED MULTICOMPONENT AZIRIDINATION OF CHIRAL ALDEHYDES

5.1 Introduction

Asymmetric catalysis has been well developed over a range of diverse reactions in the over past twenty years and its wide applications in the pharmaceutical and industrial areas simplifies the synthetic routes for the construction of chiral molecules in a more environmental and economic way[88]. However, methodologies involving of real catalyst control in setting the stereochemistry of new chiral centers in the presence of another chiral center that already exists in a molecule is not common.[89] In the case of catalyst controlling reactions, finding matched and mis-matched pairs between the catalyst and the optical substrates which selectively generates one of the possible diastereomers is the key[90]. Based on the previous experience of asymmetric aziridination in our lab[43, 45, 47, 77-82], the first example of a catalyst-controlled multicomponent asymmetric aziridination of chiral aldehyde was identified (Scheme 5.1)[91]. The absolute stereochemistry of the newly formed aziridine is a function of the catalyst, not the chiral center in the aldehyde present at either the α- or β-positions.

Scheme 5.1 Catalyst-controlled multicomponent aziridination

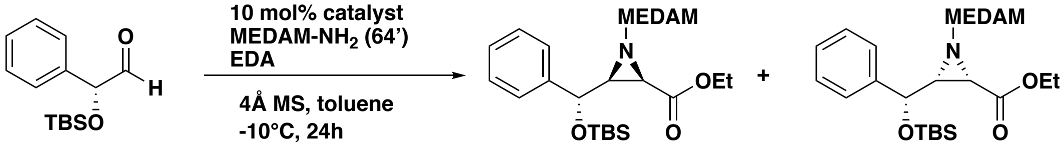


Since our previous group member Munmun Mukherjee[92] finished the primary study of this reaction and Yubai Zhou[93]did much of optimization work and the investigation of the substrate scope, in this chapter two other chiral aldehyde substrates will be examined and also a synthetic application of this methodology for the synthesis of β^3-homo-D-allosisoleucine and β^3-L-isoleucine will be described.

5.2 Two chiral aldehyde substrates of the catalyst-controlled aziridination

The optimized reaction conditions were only developed after considerable effort had been made by Munmun and Yubai (Table 5.1). For the model reaction, the (*R*)-α-silyloxyphenylacetaldehyde (**154a**), MEDAM amine (**64'**) and ethyl diazoacetate accomplished a 98:2 selectivity for the *anti*-aziridine (**155a**) over the *syn*-aziridine (**155a'**) with the catalyst derived from (*S*)-VAPOL. The aziridination with non-chiral aldehydes catalyzed by (*S*)-ligand catalyst gave addition to the *Si*-face of the imine and thus formed the corresponding aziridine with a (2*R*)-configuration[44-45]. When the (*R*)-VAPOL catalyst was employed into the reaction, a 99:1 ratio of aziridine in favor of *syn*-isomer (**155a'**) was obtained. From those results, a very high level of catalyst control can be confirmed in the reaction by Yubai and Munmun.

Table 5.1 Optimized reaction condition for the model reaction



(*R*)-154a **(2*R*, 4*R*)-155a** **(2*S*, 4*R*)-155a'**

Table 5.1 (continued)

Entry	Ligand	% Total yield[a]	(2*R*)/(2*S*)
1	(*S*)-VAPOL	90	98:2
2	(*R*)-VAPOL	90	1:99

Unless otherwise specified, all reactions were performed with amine **64’** (0.2 mmol, 1.0 equiv.), with EDA (1.2 equiv.), and aldehyde (*R*)-**154a** (1.05 equiv.) at 0.4 M in toluene for 24 h at -10°C in the presence of powdered 4Å molecular sieves, and reached 100% completion. The BOROX catalyst was assembled by heating a solution of **64’** (100 mol%), ligand (10 mol%), and $B(OPh)_3$ (30 mol%) in toluene at 80°C for 0.5 h. After cooling to -10°C, (*R*)-**154a** and 4Å molecular sieves were added, followed directly by EDA. [a]Yield of (2*R*,4*R*)-**155a** a and (2*S*,4*R*)-**155a’** isolated together after silica gel chromatography.

As part of this thesis work the aziridination of the aldehyde (*S*)-**154b** with similar size groups at the 2-chiral center was examined. A number of chiral aldehydes react with high catalyst control under the standard condition, but for the α-branched aliphatic aldehyde **154b**, the reaction didn’t give a higher degree of catalyst control with the VAPOL catalyst (75:25 and 33:67). Later it was discovered that using *t*Bu-VANOL instead of VAPOL and decreasing the reaction temperature to -40°C, perfect catalyst control could be achieved in 96:4 and 4:96 respectively (Table 5.2).

Table 5.2 Catalyst-controlled multicomponent aziridination with aldehyde (154b)

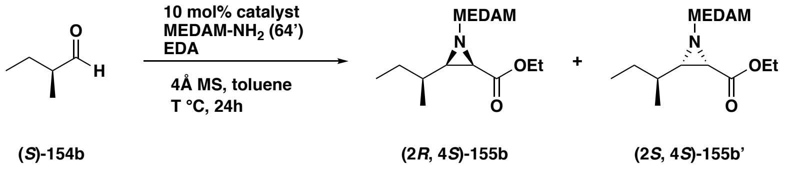


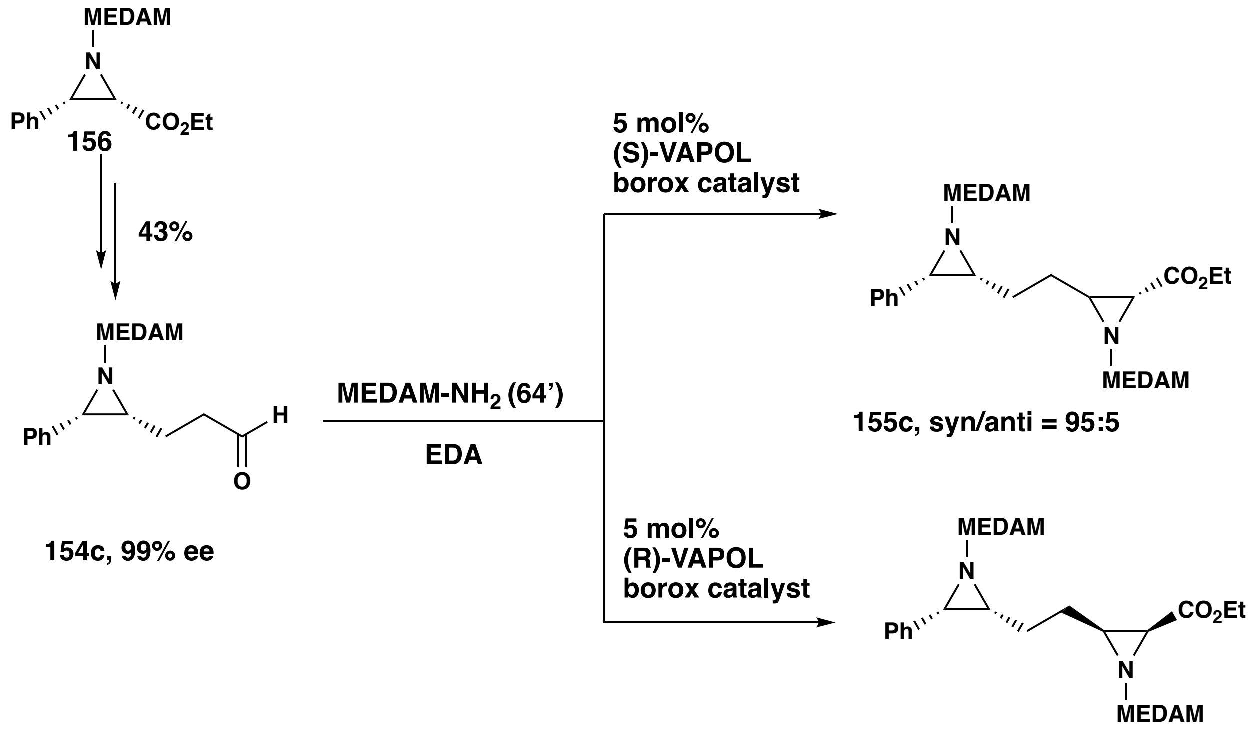
Table 5.2 (continued)

Entry	Cat. (mol%)	Ligand	T (°C)	% Total yield[a]	(2*R*)/(2*S*)
1[b]	5	(*S*)-VAPOL	-10	60	75:25
2[b]	5	(*R*)-VAPOL	-10	50	33:67
3[b]	5	(*S*)-*t*Bu-VANOL	-10	>99	92:8
4[b]	5	(*R*)-*t*Bu-VANOL	-10	80	17:83
5[c]	10	(*S*)-*t*Bu-VANOL	-40	95	96:4
6[c,d]	10	(*R*)-*t*Bu-VANOL	-40	90	4:96

Unless otherwise specified, all reactions were performed with amine **64'** (0.2 mmol, 1.0 equiv.), with EDA (1.2 equiv.), and aldehyde (*R*)-**154b** (1.05 equiv.) at 0.4 M in toluene for 24 in the presence of powdered 4Å molecular sieves, and reached 100% completion. The BOROX catalyst was assembled by heating a solution of **64'** (100 mol%), ligand (10 mol%), and $B(OPh)_3$ (30 mol%) in toluene at 80°C for 0.5 h. After cooling down to the reaction temperature, (*R*)-**154a** and 4Å molecular sieves were added, followed directly by EDA. [a]Yield of **155b**-(2*R*) and **155b'**-(2*S*) isolated together after silica gel chromatography. [b]2.0 equiv. EDA. [d] Reaction time is 48 hours.

γ,δ-Aziridinyl aldehyde (**154c**) was also examined with both (*S*)- and (*R*)-VAPOL catalysts (Scheme 5.2). The aziridine (**154c**) was prepared in 43% yield (4 steps) from aziridine (**156**), which could be synthesized according to the protocol in our previous work in excellent yield and *ee* with (*R*)-VAPOL borox catalyst. [46] With 5 mol% (*S*)-VAPOL catalyst loading, the reaction of aziridine (**154c**), MEDAM amine (**64'**) and ethyl diazoacetate afforded the ethylene diaziridine (**155c**) as a 95:5 mixture of *syn*- and *anti*-diastereomers in 95% yield. While the (*R*)-VAPOL catalyst gave the preferential *anti*-diastereomer (**155c'**) in 74% yield and a 96:4 selectivity.

Scheme 5.2 Catalyst-controlled multicomponent aziridination with γ,δ-aziridinyl aldehyde (154c)



154c, 99% ee

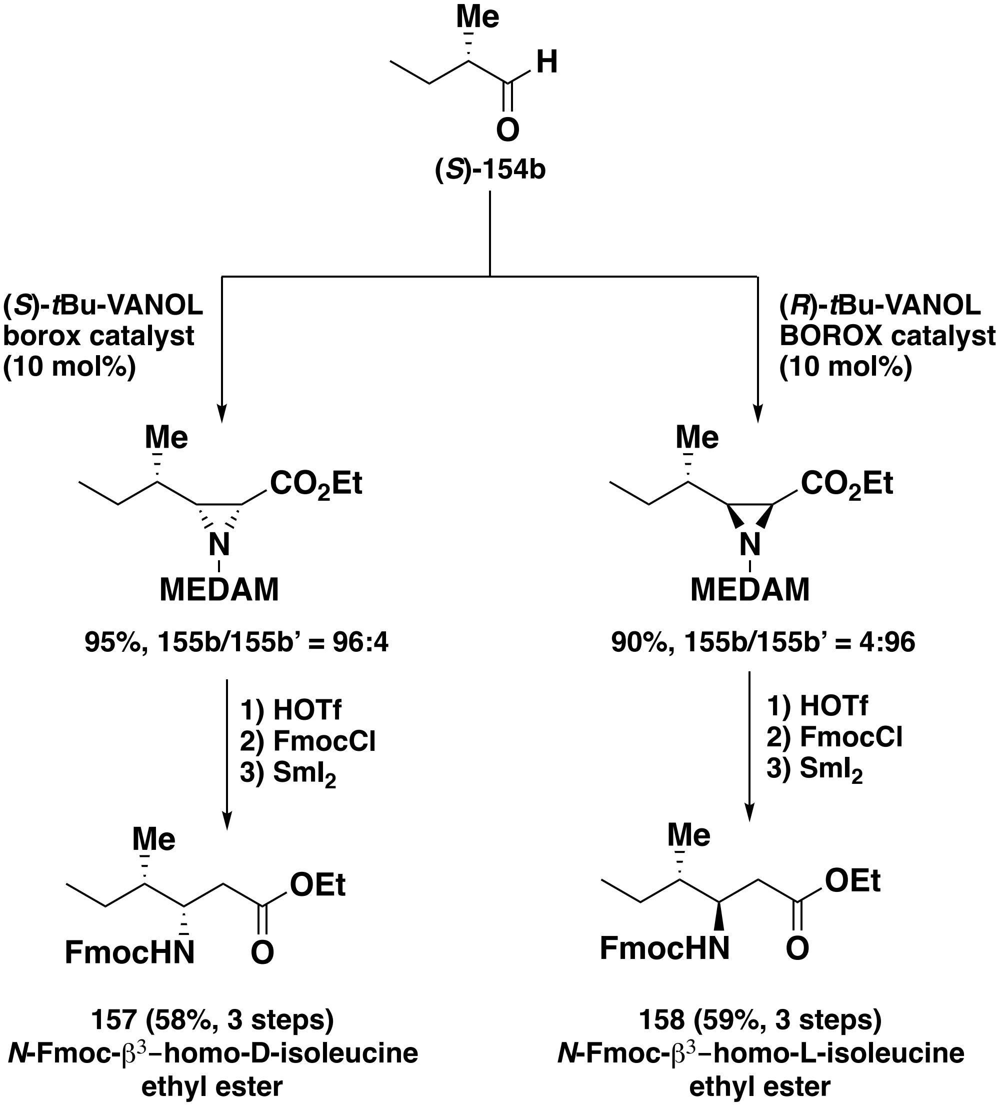
155c, syn/anti = 95:5

155c', syn/anti = 4:96

5.3 Total synthesis of β^3-homo-D-allosisoleucine (157) and β^3-L-isoleucine (158)

β-amino acids attract significant interests in the biochemical and pharmaceutical fields, as the result of the fact that they are important intermediates in the synthesis of β-peptides and β-lactams.[94-98] To display the synthetic utility of the catalyst-controlled multicomponent aziridination of chiral aldehydes, a facile synthesis of β^3-homo-D-allosisoleucine (**157**) and β^3-L-isoleucine (**158**) in protected forms were summarized in Scheme 5.3.

Scheme 5.3 Synthesis of β³-homo-D-allosisoleucine (157) and β³-L-isoleucine (158)



The synthesis commenced with the (*S*)- and (*R*)-*t*Bu-VANOL derived catalyst-controlled aziridinations of MEDAM amine (**64'**), ethyl diazoacetate and aldehyde (**154b**), which was prepared from the commercially available (*S*)-2-methyl-1-butanol. Both reactions afforded the isomer (**155b** and **155b**') with a 96:4 selectivity and in good yields. In the reductive ring opening of *cis*-aziridines, it was found that the substituent on the nitrogen needs to be activating or otherwise the cleavage will take place at both the C-C and C-N bonds. Thus the replacement of the MEDAM group with a Fmoc group was conducted by HOTf and Fmoc chloride in overall 88% and 87% yields (two steps). Subsequent reductive ring-opening reaction by samarium(II) diiodide[99] achieved the final β-amino ester **157** and **158** in good yields as single diastereomers and enantiomers.

5.4 Conclusion

In this chapter, the results of catalyst-controlled aziridination with the α-branched aldehyde (**154b**) and the γ,δ-aziridinyl aldehyde (**154c**) were presented. Excellent diastereoselectivities and yields were obtained with either *t*Bu-VANOL or VAPOL catalysts. An application to the synthesis of β^3-homo-D-allosisoleucine and β^3-L-isoleucine were conducted based on this methodology. These targets were achieved in 55% and 53% yield overall from aldehyde (S)-154b (four steps in total) were achieved, respectively.

CHAPTER SIX

EXPERIMENTAL SECTION

6.1 General information

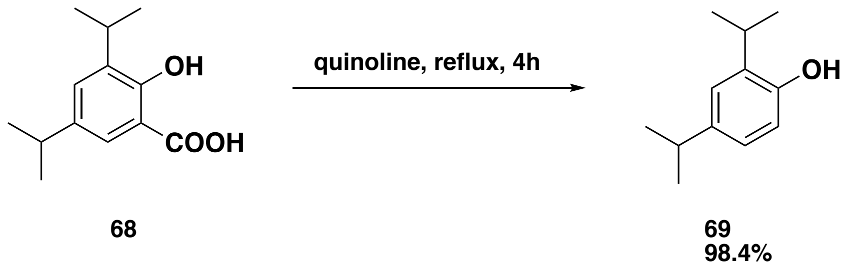
Tetrahydrofuran (THF), diethyl ether and toluene were distilled from sodium metal under nitrogen with benzophenone as indicator. Dichloromethane was distilled from calcium hydride under nitrogen. DMF and acetonitrile were distilled from 4Å molecular sieves under nitrogen. Hexane, ethyl acetate, methanol and ethanol were used as purchased in ACS grade. Commercial available aldehydes and benzoic acids were purified by sublimation or distillation before use. Other reagents were used as purchased from Aldrich or Alfa Aesar. All ligands, including VANOL, VAPOL and their derivatives were prepared according to the literature procedures and were determined to be 99% optical purity.[100-105]

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. IR spectra were taken on ThermoFisher scientific Nicolet iS5 and Jasco FT/IR-6600. ^{1}H NMR and ^{13}C NMR were recorded on a Varian UnityPlus-500 MHz or Varian Inova-600 MHz instrument in $CDCl_3$ unless otherwise noted. $CHCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.26) and ^{13}C NMR (δ = 77.0). HRMS was performed in the Department of Biochemistry at Michigan State University. ECCD was performed by prefessor Babak Borhan's lab. 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, by staining with phosphomolybdic acid in ethanol or with the aid of Iodine vapor in silica gel. Column chromatography was performed with silica gel 60 (230 – 450 mesh). HPLC analyses were carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1.00 mL. Specific rotations are reported in degrees per decimeter at 20 °C.

6.2 Experimental part for chapter two

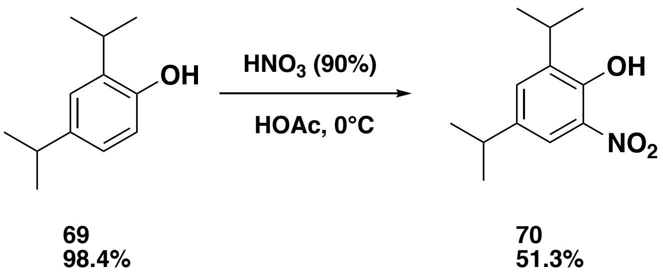
6.2.1 Preparation for the substituted hydroxyanlines 63c, 63d, 63e

*Preparation of aniline **64c***

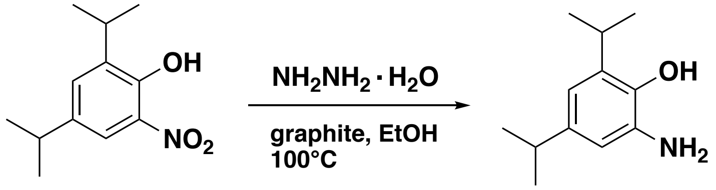


2,4-di*iso*Propylphenol ***69***: To a flame-dried round bottomed flask were added 2-hydroxy-2-hydroxy-3,5-di*iso*propylbenzoic acid **68** (5.00 g, 21.9 mmol, 1.00 equiv.) and quinoline (10.0 mL). The reaction was refluxing for 4 hours under nitrogen. After cooling down to the room temperature, the mixture was diluted by ethyl acetate (40.0 mL) and washed by 1 M HCl (2 x 40.0 mL) until pH reached 1. The resulting organic layer was separated and then washed with brine (40.0 mL) and dried over $NaSO_{4.}$ The following filtration and removal of the volatile to give the crude product as a brown oil. Flash chromatography on silica gel (40 mm x 150 mm, hexane/EtOAc 9:1) provided the purified product as a yellow oil **69**, (3.80 g, 21.6 mmol, 98.4% yield). R_f= 0.8 (7:3 hexane/EtOAc). Spectral data for **69**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 2.3 Hz, 1H), 7.13 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.96 (s, 1H), 3.55 – 3.43 (hept, *J* = 6.9 Hz, 1H), 3.13 – 3.01

(hept, J = 6.9 Hz, 1H), 1.47 (dd, J = 14.0, 7.0 Hz, 12H), ^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.75, 141.29, 134.10, 124.55, 124.15, 115.11, 33.59, 27.20, 24.34 (2C), 22.67 (2C).These spectral data match the previously reported data for this compound.[50]



The general procedure for nitration and synthesis of 2,4-diisopropyl-6-nitrophenol **70**: To a 250 mL Erlenmeyer flask was added a magnetic stir bar, 2,4-di*iso*propylphenol **69** (3.85 g, 24.1 mmol, 1.00 equiv.) and acetic acid (27.0 mL). The flask was cooled in ice bath for 5 min. To another 50 mL Erlenmeyer flask was added acetic acid (9.00 mL) and HNO_3 (1.70 mL, c = 90%) and then the solution was cooled in ice bath for 5 min. The HNO_3 solution was transferred to the 2,4-di*iso*propylphenol **69** solution dropwise with a pipette. After stirring in ice bath for 2 min, H_2O (200 mL) was added in one portion to quench the reaction. The aqueous solution was divided into two portions, and both portions were extracted with DCM (20.0 mL x 4). The combined organic layer was successively washed with H_2O (20.0 mL) and brine (20.0 mL) and dried over $NaSO_4$. The solution was filtered and concentrated under rotary evaporation. The crude product was purified by silica gel column chromatography (40 mm x 100 mm, hexane/EtOAc 95:5). The reaction afforded the product **70** (2.47 g, 11.1 mmol, 52% yield) as a yellow oil. R_f= 0.9 (7:3 hexane/EtOAc). Spectral data for **70**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.96 (s, 1H), 7.80 (d, J = 2.3 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 3.42 (m, J = 7.0 Hz, 1H), 2.90 (hept, J = 6.9 Hz, 1H), 1.26 (dd, J = 9.1, 6.9 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.38, 140.24, 139.21, 133.25, 133.19, 119.10, 33.38, 27.09, 23.79 (2C), 22.31 (2C). These spectral data match the previously reported data for this compound.[106]

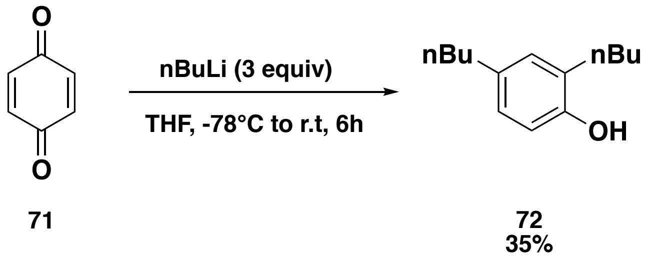


70
51.3%

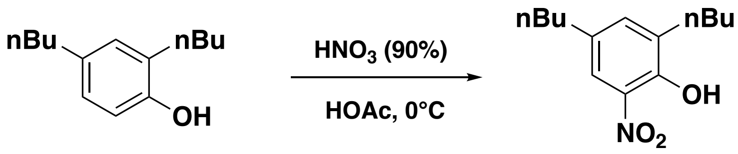
64c
60%

The general procedure of hydrazine reduction and synthesis of 2-hydroxy-3.5-di*iso*propylaniline ***64c***: To a 100 mL round bottomed flask was added 2,4-di*iso*propyl-6-nitrophenol **70** (2.47 g, 11.1 mmol, 1.00 equiv.), graphite (1.58 g), hydrazine monohydrate (1.35 mL, 27.7 mmol, 2.5 equiv.) and ethanol (31.7 mL). The flask was equipped with a condenser and the top was sealed by a septum with a needle attached to it. The flask was heated in a 100 °C for 3.5 h (another 5.00 equiv. of hydrazine monohydrate was added in two equal portions every other hour). The solution was allowed to cool to room temperature, and filtered through celite pad, the filter cake was washed by dichloromethane (50.0 mL). The filtrate was concentrated under rotary evaporation and flash chromatography (40 mm x 160 mm, Hexane/EtOAc 8:2) afford the crude product as a brown solid. The further recrystallization with Hexane/EtOAc (9:1) gave the pure product **64c** as a white solid (1.30 g, 6.64 mmol, 60% yield, mp: 106.8-108.2 °C). R_f= 0.4 (7:3 hexane/EtOAc). Spectral data for **70**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.50 (s, 1H), 6.46 (s, 1H), 3.67-3.64 (br, NH_2), 3.21 (hept, *J* = 6.9 Hz, 1H), 2.73 (hept, *J* = 6.9 Hz, 1H), 1.18 (dd, *J* = 10.5, 6.8 Hz, 13H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.68, 139.62, 136.58, 135.83, 114.53, 112.10, 33.71, 27.20, 24.26 (2C), 22.94 (2C). IR (thin film) 3390s, 3317s, 2956vs, 1740vs, 1592vs, 1486s,1436s, 1215vs, 859vs cm^{-1}. HRMS (ESI-TOF) *m/z* found 194.1554 ([M+H]$^+$); calcd. 194.1545 for $C_{12}H_{20}NO$.

*Preparation of aniline **64d***



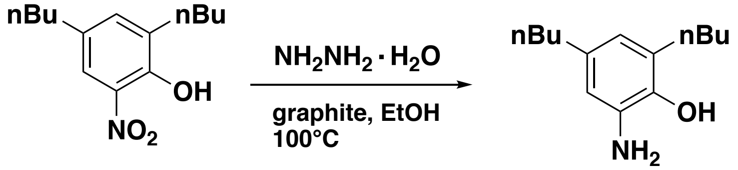
2,4-di*n*Butylphenol ***72***: To a solution of p-benzoquinone **71** (1.00 g, 9.25 mmol, 1.00 equiv.) in THF (25.0 ml) was added the corresponding *n*butyllithium reagent (11.1 mL, 2.5 M in hexane, 3.00 equiv.) at -78°C. The resulting solution was stirred for 6 hours allowing the temperature to rise to 20°C. The resulting mixture was then hydrolyzed with water (20 ml), acidified with 2 N sulfuric acid, and extracted with ether (3 x 20.0 ml). The organic layer was dried over $NaSO_4$ and concentrated to give the crude products **72** (0.67g, 3.23 mmol, 35% yield) as a yellow oil, which were purified by flash chromatography (silica gel, 40 mm x 160 mm, hexane/EtOAc 9:1). R_f= 0.8 (7:3 hexane/EtOAc). Spectral data for **72**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.07 (d, *J* = 2.3 Hz, 1H), 6.99 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.55 (s, 1H, OH), 2.76 – 2.69 (m, 2H), 2.69 – 2.62 (m, 2H), 1.78 – 1.65 (m, 4H), 1.56 – 1.35 (m, 5H), 1.07 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 151.42, 135.12, 130.25, 128.68, 126.71, 115.24, 35.00, 34.15, 32.25, 22.80, 22.50, 14.10 (2C). These spectral data match the previously reported data for this compound[52].



72
35%

73
100%

2,4-di*n*Butyl-6-nitrophenol ***73***: According to the *general procedure of nitration*, 2,4-di*n*Butylphenol **72** (0.67 g, 3.26 mmol), nitric acid (0.25 mL) and acetic acid (4.05 mL + 1.35 mL) were added to the reaction. After purification by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 95:5), the reaction afforded 3,5-di*n*butyl-6-nitrophenol **73** (0.93 g, 3.26 mmol, 100% yield) as an orange oil. R_f= 0.9 (7:3 hexane/EtOAc). Spectral data for **73**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.80 (d, 1H, OH), 7.72 (d, *J* = 2.3 Hz, 1H), 7.26 (d, *J* = 2.2 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.58 – 2.51 (m, 2H), 1.63 – 1.52 (m, 4H), 1.43 – 1.29 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.69, 138.10, 134.04, 133.54, 133.13, 121.22, 34.45, 33.30, 31.52, 29.52, 22.52, 22.18, 13.86, 13.81.



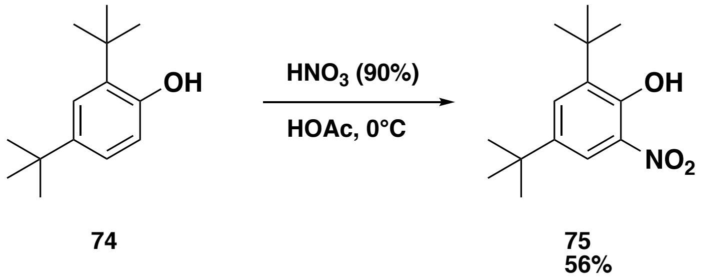
73
100%

64d
49%

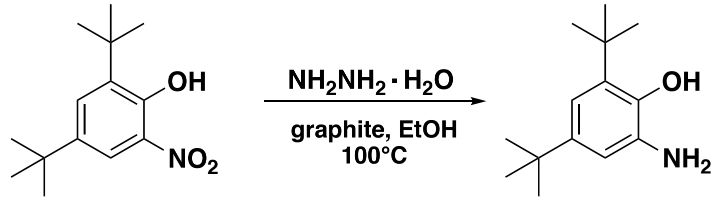
2-Hydroxy-3,5-di*n*butylaniline ***64d***: According to the *general procedure of hydrazine reduction*, 2,4-di*n*butyl-6-nitrophenol **73** (0.82 g, 3.26 mmol, 1.00 equiv.), hydrazine (0.40 mL x 3, 2.5 equiv.) and graphite (0.47 g) were added to the ethanol (9.32 mL). After purification by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 8:2) and recrystallization with hexane/EtOAc (9:1), the reaction afforded the product **64d** (0.35 g, 1.59 mmol, 49% yield) as a yellow oil. R_f= 0.4 (7:3 hexane/EtOAc). Spectral data for

64d: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.50 (d, *J* = 2.1 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 3.52 (s, 2H, NH_2), 2.58 – 2.51 (m, 2H), 2.49 – 2.42 (m, 2H), 1.64 – 1.49 (m, 4H), 1.46 – 1.32 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.64, 135.40, 128.14, 120.82, 115.59, 35.08, 33.94, 32.08, 29.84, 22.69, 22.41, 14.00 (2C). IR (thin film) 3395s, 3313s, 2925vs, 1602vs, 1486vs, 1203vs, 848, 724s cm^{-1}. HRMS (ESI-TOF) *m/z* found 222.1866 ([M+H]$^+$); calcd. 222.1858 for $C_{14}H_{24}NO$.

*Preparation of aniline **64e***



2,4-di*tert*-Butyl-6-nitrophenol ***75***: According to the *general procedure of nitration*, 2,4-di*t*butylphenol **74** (4.97 g, 24.1 mmol, 1.00 equiv.), nitric acid (1.90 mL) and acetic acid (30.0 mL + 10.0 mL) were added to the reaction. After purification by flash chromatography (silica gel, 40 mm x 160 mm, hexane/EtOAc 95:5), the reaction afforded 2,4-di*t*butyl-6-nitrophenol **75** (3.38 g, 13.5 mmol, 56% yield) as a yellow oil. R_f= 0.9 (7:3 hexane/EtOAc). Spectral data for **75**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.47 (d, *J* = 0.6 Hz, 1H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.66 (d, *J* = 2.6 Hz, 1H), 1.46 (s, 9H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.01, 141.93, 139.82, 133.62, 132.59, 118.84, 35.72, 34.51, 31.10 (3C), 29.36 (3C). These spectral data match the previously reported data for this compound.[107]



75
56%

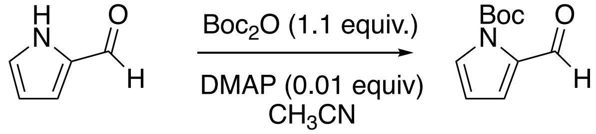
64e
94%

.

2-Hydroxy-3,5-di*t*butylaniline ***64e***: According to the *general procedure of hydrazine reduction*, 2,4-di*t*butyl-6-nitrophenol **75** (3.38 g, 13.5 mmol, 1.00 equiv.), hydrazine (1.64 mL x 3, 2.5 equiv.) and graphite (1.92 g) were added to the ethanol (38.5 mL). After purification by flash chromatography (silica gel, 40 mm x 160 mm, hexane/EtOAc 8:2) and recrystallization with hexane/EtOAc (9:1), the reaction afforded the product **64e** as a light purple solid (1.80 g, 8.14 mmol, 61% yield, mp: 163-168 °C). R_f= 0.4 (7:3 hexane/EtOAc). Spectral data for **64e**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.91 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 3.22 (br, 2H, NH2), 1.42 (s, 9H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.91, 142.48, 135.80, 132.62, 116.88, 115.59, 34.69, 34.26, 31.61(6C), 29.84 (6C). IR (thin film) 3365s, 3289s, 2943vs, 2365s, 1592s, 1486vs, 1418vs, 1331vs, 1237s, 946vs, 741vs cm^{-1}. HRMS (ESI-TOF) *m/z* found 222.1860 ([M+H]$^+$); calcd. 222.1858 for $C_{14}H_{24}NO$.

6.2.2 Preparation for the aldehyde 63i

*Preparation of aldehyde **63i***



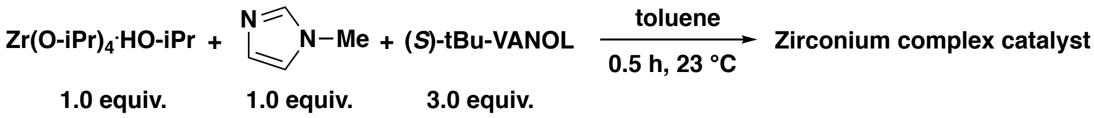
63i'

63i

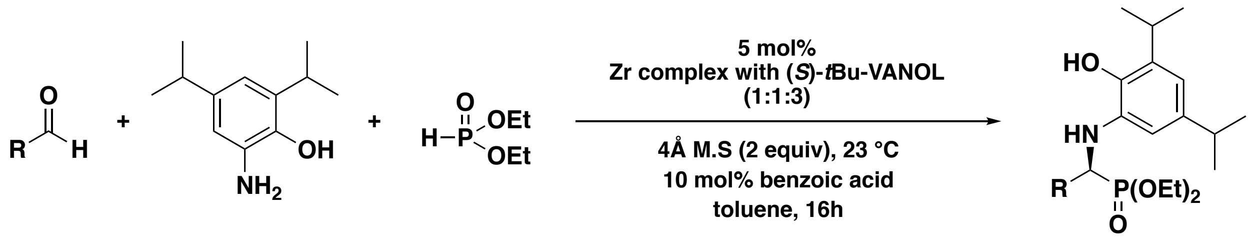
*t*Butyl 2-formyl-1*H*-pyrrole-1-carboxylate **63i**: To an oven-dried 50 mL round bottomed flask were added 1*H*-pyrrole-2-carbaldehyde **63i'** (0.50 g, 5.30 mmol, 1.00 equiv.), Boc anhydride (1.30 g, 5.83 mmol, 1.10 equiv.), 4-Dimethylaminopyridine (DMAP, 6.40 mg, 0.01 equiv.) and acetonitrile (10.0 mL) under nitrogen. After 30 minutes stirring, the reaction was concentrated under rotary evaporation. The resulting crude product was purified with flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 9:1) and afforded the product **63i** (1.03 g, 5.30 mmol, 100% yield) as the colorless oil. R_f= 0.8 (7:3 hexane/EtOAc). Spectral data for **63i**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.31 (d, *J* = 0.7 Hz, 1H), 7.42 (dd, *J* = 3.1, 1.7 Hz, 1H), 7.16 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.26 (ddd, *J* = 3.8, 3.1, 0.7 Hz, 1H), 1.62 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 182.39, 148.38, 134.74, 127.36, 121.23, 111.72, 85.81, 27.96. IR (thin film) 1748 s, 1667 m, 1390 s, 427 vs cm^{-1}. These spectral data match the previously reported data for this compound.[108]

6.2.3 Preparation for Asymmetric Kabachnik-Fields reaction products 67a-m

General procedure A for assembling the tButyl-zirconium catalyst:

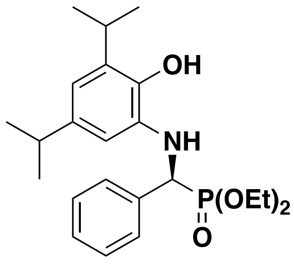


Zr(O*i*Pr)$_4$(HO*i*Pr) zirconium(IV) isopropoxide isopropanol complex (38.8 mg, 0.1 mmol, 1.00 equiv.), (*S*)-*t*Butyl VANOL (165 mg, 0.30 mmol, 3.0 0equiv.), and 4 mL toluene were mixed under air at room temperature in an oven-dried 20-mL vial. After all solids were dissolving in the toluene, the N-methylimidazole (8.00 μL, 0.1 mmol, 1.00 equiv.) was added via a micro syringe. The resulting mixture was stirred at room temperature under air for 30 min before being employed into the asymmetric catalytic Kabachnik-Fields reaction. And the rest of the catalyst can be stored in toluene at -20°C for further uses.



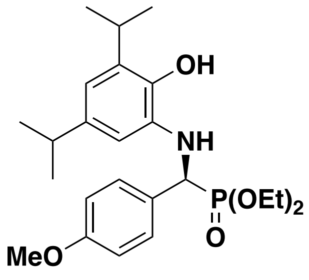
63a-m 1 equiv **64c** 1 equiv **65b** 1 equiv **67a-m**

General procedure B for asymmetric Kabachnik-Fields reaction of aromatic aldehydes: To a 10-mL flame-dried home-made Schlenk flask, prepared from a single necked 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, flushed with nitrogen was added 2-hydroxy-3,5-di*iso*propylaniline **64c** (19.3 mg, 0.10 mmol, 1.00 equiv.), 4 Å molecular sieves (38.6 mg) and benzoic acid (1.20 mg, 0.01 mmol, 0.10 equiv.) Under a nitrogen flow, zirconium catalyst in toluene (0.20 mL, 5 mol%, 0.25 M, prepared from general procedure A), aldehyde (0.10 mmol, 1.00 equiv.) and diethyl phosphite (14.0 μL, 0.10 mmol, 1.00 equiv.) were added to the mixture by syringes. The flask was sealed, and then placed into a liquid nitrogen bath. After the solvent was frozen, the Teflon valve was opened to vacuum and the atmosphere was pumped off for 5 minutes. The flask was sealed again and removed from the liquid nitrogen bath. Gas bubbles could be seen to evolve from the solution during thawing the solvent at the room temperature. When all the solvent melted, the flask was placed back into the liquid nitrogen bath and this Freeze-Pump-Thaw degassing process was repeated for another 2 times. The reaction was then stirring at room temperature for 16 hours and diluted with hexane (5 mL). The mixture was concentrated under rotary evaporation and purified by flash chromatography (silica gel, 10 mm x 100 mm, hexane/EtOAc, 7:3) to yield corresponding α-amino phosphites.



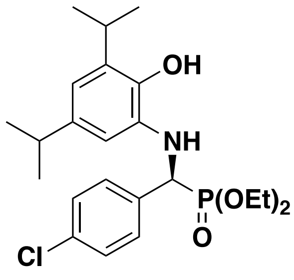
67a

Diethyl (S)-(((2-hydroxy-3,5-diisopropylphenyl)amino)(phenyl)methyl)phosphonate **67a**: Reaction of benzaldehyde **63a** (12.0 μL, 0.10 mmol, 1.00 equiv.) afforded the **67a** (38.6 mg, 0.092 mmol) in 92% yield and 93% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -12.8 (c 1.0, $CHCl_3$); Spectral data for **67a**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 (dd, *J* = 7.2, 3.0 Hz, 2H), 7.31 – 7.23 (m, 3H), 6.55 (d, *J* = 2.2 Hz, 1H), 6.29 (s, 1H), 4.69 (d, *J* = 22.7 Hz, 1H), 4.27 – 4.14 (m, 2H), 4.00 – 3.91 (m, 1H), 3.76 – 3.65 (m, 1H), 3.22 (hept, *J* = 7.0 Hz, 1H), 2.64 (hept, *J* = 7.0 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.72, 140.66, 133.36, 130.15, 128.55, 128.53, 128.40, 128.34, 128.29, 128.03, 116.27, 112.37, 63.56 (d, *J* = 7.1 Hz), 58.42, 57.20, 33.68, 27.18, 24.15, 24.06, 22.86, 22.68, 16.42 (d, *J* = 6.0 Hz), 16.18 (d, *J* = 5.8 Hz). IR (thin film) 3372br, 2959s, 2868s, 1596vs, 1453s, 1200vs, 975s cm^{-1}; HRMS (ESI-TOF) *m/z* found 442.2130 ([M+Na]$^+$); calcd. 442.2123 for $C_{23}H_{34}NO_4PNa$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 10.3 min for the minor peak and 16.9 min for the major peak.



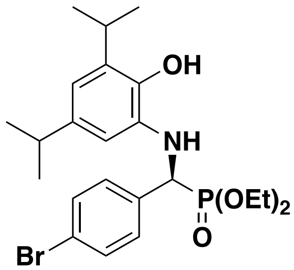
67b

Diethyl (*S*)-(((2-hydroxy-3,5-diisopropylphenyl)amino)(4methoxyphenyl)methyl) phosphonate **67b**: Reaction of 4-methoxybenzaldehyde **63b** (12.4 μL, 0.100 mmol, 1.00 equiv.) afforded the **67b** (40.4 mg, 0.09 mmol) in 90% yield and 90% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -37.6 (c 1.00, $CHCl_3$); Spectral data for **67b**: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.38 (dd, *J* = 8.7, 2.2 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 2.1 Hz, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 4.62 (d, *J* = 22.6 Hz, 1H), 4.18 (tqd, *J* = 10.3, 7.2, 3.4 Hz, 2H), 3.95 (dp, *J* = 10.6, 7.1 Hz, 1H), 3.73 (s, 4H), 3.21 (hept, *J* = 6.8 Hz, 1H), 2.66 (p, *J* = 6.9 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 4H), 1.17 – 1.10 (m, 6H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.30, 141.66, 140.54, 129.47, 129.42, 127.42, 113.99, 113.97, 113.94, 113.92, 63.45 (dd, *J* = 7.2, 4.2 Hz), 57.63, 56.39, 55.20, 33.70, 27.11, 24.20, 24.10, 22.91, 22.68, 16.44 (d, *J* = 5.8 Hz), 16.26 (d, *J* = 5.7 Hz). IR (thin film) 3408br, 2959s, 2065s, 1636vs, 1510s, 1205vs, 974s cm^{-1}; HRMS (ESI-TOF) *m/z* found 450.2410 ($[M+H]^+$); calcd. 450.2409 for $C_{23}H_{37}NO_5P$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 16.4 min for the minor peak and 29.8 min for the major peak.



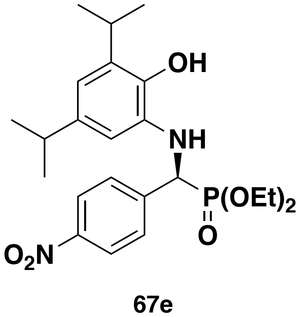
67c

Diethyl (*S*)-((4-chlorophenyl)((2-hydroxy-3,5-diisopropylphenyl)amino)methyl) phosphonate **67c**: Reaction of 4-chlorobenzaldehyde **63c** (11.7 μL, 0.10 mmol, 1.00 equiv.) afforded the **67c** (31.7 mg, 0.07 mmol) in 70% yield and 96% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -18.6 (c 1.00, $CHCl_3$); Spectral data for **67c**: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.45 (m, 1H), 7.42 – 7.37 (m, 1H), 7.28 – 7.18 (m, 3H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.27 (d, *J* = 2.2 Hz, 1H), 4.68 (d, *J* = 22.7 Hz, 1H), 4.23 – 4.12 (m, 2H), 4.06 – 3.96 (m, 1H), 3.88 – 3.77 (m, 1H), 3.19 (hept, *J* = 6.9 Hz, 1H), 2.65 (hept, *J* = 6.9 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.21 (dd, *J* = 11.7, 6.9 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.65, 141.06, 134.45, 129.84, 128.51, 128.47, 126.59, 126.55, 117.01, 112.70, 63.78 (d, *J* = 5.9 Hz), 58.11, 33.67, 27.26, 24.12, 24.06, 22.81, 22.64, 16.38 (d, *J* = 5.8 Hz), 16.28 (d, *J* = 5.7 Hz) (one sp^3 carbon is not located). IR (thin film) 3405br, 2960s, 1653vs, 1507s, 1207s, 1024s cm^{-1}; HRMS (ESI-TOF) *m/z* found 476.1727 ($[M+H]^+$); calcd. 476.1733 for $C_{23}H_{33}NO_4PClNa$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 11.5 min for the minor peak and 19.4 min for the major peak.



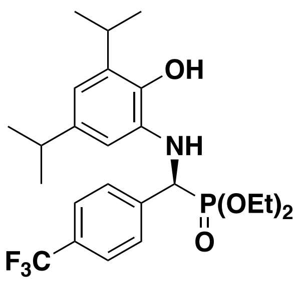
67d

Diethyl (*S*)-((4-bromophenyl)((2-hydroxy-3,5-diisopropylphenyl)amino)methyl) phosphonate **67d**: Reaction of 4-bromobenzaldehyde **63d** (18.3 mg, 0.10 mmol, 1.00 equiv.) afforded the **67d** (34.8 mg, 0.07 mmol) in 70% yield and 96% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -27.5 (c 1.00, $CHCl_3$); Spectral data for **67d**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.21 (m, 4H), 6.50 (d, *J* = 2.0 Hz, 1H), 6.18 (d, *J* = 2.1 Hz, 1H), 4.69 (d, *J* = 24.0 Hz, 1H), 4.30 – 4.16 (m, 2H), 3.98 (dp, *J* = 10.2, 7.1 Hz, 1H), 3.79 (ddq, *J* = 10.2, 8.7, 7.1 Hz, 1H), 3.18 (hept, *J* = 6.9 Hz, 1H), 2.67 (hept, *J* = 6.9 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.23 – 1.12 (m, 6H), 1.13 – 1.03 (m, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.79, 140.60, 134.84, 134.64, 131.54, 131.52, 129.78, 129.74, 121.94, 121.82, 115.00, 110.26, 63.70, 57.03, 55.81, 33.77, 26.92, 24.22, 24.13, 23.05, 22.59, 16.47, 16.25). IR (thin film) 3422br, 1652vs, 1219s, 1053s, 771s cm^{-1} HRMS (ESI-TOF) *m/z* found 520.1243 ($[M+Na]^+$); calcd. 520.1228 for $C_{23}H_{33}NO_4PBrNa$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 10.0 min for the minor peak and 29.7 min for the major peak.



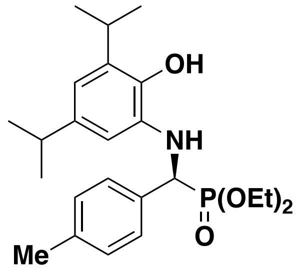
67e

Diethyl (*S*)-(((2-hydroxy-3,5-diisopropylphenyl)amino)(4-nitrophenyl)methyl) phosphonate **67e**: Reaction of 4-nitrobenzaldehyde **63e** (15.1 mg, 0.10 mmol, 1.00 equiv.) afforded the **67e** (26.0 mg, 0.056 mmol) in 56% yield as yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -3.1 (c 0.68, $CHCl_3$); Spectral data for **67e**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.60 – 8.32 (m, 1H), 8.20 – 8.04 (m, 2H), 7.81 – 7.57 (m, 1H), 6.52 (s, 1H), 6.12 (s, 1H), 4.80 (d, *J* = 24.3 Hz, 1H), 4.28 – 4.00 (m, 3H), 3.92 (q, *J* = 9.5, 8.7 Hz, 1H), 3.12 (p, *J* = 6.9 Hz, 1H), 2.64 (p, *J* = 6.9 Hz, 1H), 1.36 – 1.27 (m, 6H), 1.23 – 1.16 (m, 6H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 130.16, 128.85, 128.17, 124.19, 123.67, 122.90, 115.22, 114.96, 110.37, 63.94, 63.47, 34.37, 33.72, 29.71, 27.30, 24.44, 22.63, 16.29, 16.00 (one sp^2 carbon and two sp^3 carbons is not located). IR (thin film) 3421br, 2095s, 1652vs, 1034s cm^{-1}. HRMS (ESI-TOF) *m/z* found 465.2130 ($[M+H]^+$); calcd. 465.2154 for $C_{23}H_{34}N_2O_6P$. *ee* can not determined by HPLC.



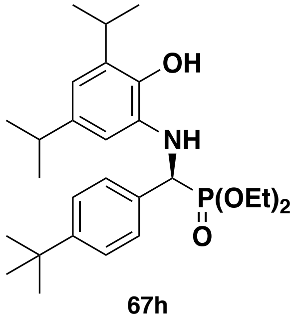
67f

Diethyl (*S*)-(((2-hydroxy-3,5-diisopropylphenyl)amino)(4-(trifluoromethyl)phenyl)methyl) phosphonate **67f**: Reaction of 4-trifluoromethylbenzaldehyde **63f** (11.2 μL, 0.10 mmol, 1.00 equiv.) afforded the **67f** (35.1 mg, 0.072 mmol) in 72% yield and 90% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -12.3 (c 1.00, $CHCl_3$); Spectral data for **67f**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.51 (s, 1H), 6.16 (s, 1H), 4.74 (d, *J* = 23.8 Hz, 1H), 4.28 – 4.10 (m, 2H), 4.10 – 3.94 (m, 1H), 3.94 – 3.81 (m, 1H), 3.12 (hept, *J* = 7.1 Hz, 1H), 2.64 (hept, *J* = 6.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.04, 140.80, 128.46, 127.69, 125.89, 125.40, 122.37, 115.54, 114.73, 111.03, 76.75, 63.61 (dd, *J* = 52.8, 7.0 Hz), 57.70, 56.49, 33.70, 29.70, 27.17, 24.13, 23.98, 22.56, 16.43 (d, *J* = 5.6 Hz), 16.21 (d, *J* = 5.8 Hz); IR (thin film) 3422br, 2095s, 1653vs, 1457 m cm^{-1}; HRMS (ESI-TOF) *m/z* found 488.2180 ([M+H]$^{+}$); calcd. 488.2178 for $C_{24}H_{34}NO_4F_3P$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 10.8 min for the minor peak and 28.8 min for the major peak.



67g

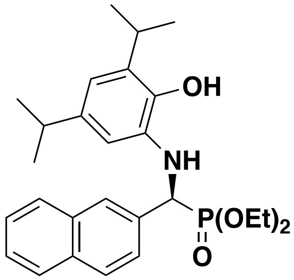
Diethyl (*S*)-(((2-hydroxy-3,5-diisopropylphenyl)amino)(*p*-tolyl)methyl) phosphonate **67g**: Reaction of 4-methylbenzaldehyde **63g** (11.8 μL, 0.10 mmol, 1.00 equiv.) and benzoic acid (0.60 mg, 0.005 mmol, 0.05 equiv.) afforded the **67g** (41.6 mg, 0.096 mmol) in 96% yield and 81% *ee* as a yellow oil; R$_f$ = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -40.2 (c 1.00, CHCl$_3$); Spectral data for **67g**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.29 (m, 2H), 7.02 (d, *J* = 7.7 Hz, 2H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 4.68 (d, *J* = 24.0 Hz, 1H), 4.30 – 4.13 (m, 2H), 4.02 – 3.89 (m, 1H), 3.77 – 3.66 (m, 1H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.66 (hept, *J* = 6.9 Hz, 1H), 2.28 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.13 (t, *J* = 7.3 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.32, 140.41, 137.46, 134.42, 132.71, 129.18, 128.09, 128.04, 115.16, 111.27, 77.29, 77.03, 76.78, 63.56 (dd, *J* = 18.2, 7.1 Hz), 57.70, 56.47, 33.73, 27.02, 24.21, 24.12, 22.95, 22.69, 21.11, 16.45 (d, *J* = 6.0 Hz), 16.23 (d, *J* = 5.7 Hz).). IR (thin film) 3374br, 2959s, 1598s, 1511s, 1206vs, 975s cm^{-1}. HRMS (ESI-TOF) *m/z* found 434.2457 ([M+H]$^+$); calcd 434.2460 for $C_{24}H_{37}NO_4P$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 11.6 min for the minor peak and 20.1 min for the major peak.



67h

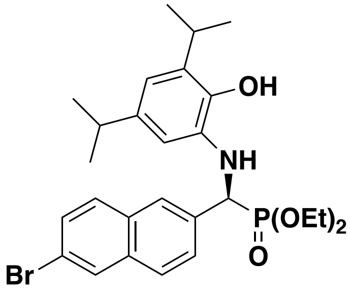
Diethyl (*S*)-((4-(*tert*-butyl)phenyl)((2-hydroxy-3,5 diisopropylphenyl)amino)methyl) phosphonate **67h**: Reaction of 4-(*tert*-butyl)benzaldehyde **63h** (16.8 μL, 0.10 mmol, 1.00 equiv.) afforded the **67h** (43.2 mg, 0.091 mmol) in 91% yield and 91% *ee* as a yellow oil. R$_f$ = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -2.5 (c 1.00, CHCl$_3$); Spectral data for **67h**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 6.3 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.50 (s, 1H), 6.26 (s, 1H), 4.67 (d, *J* = 23.2 Hz, 1H), 4.27 – 4.12 (m, 2H), 4.00 – 3.89 (m, 1H), 3.75 – 3.64 (m, 1H), 3.21 (hept, *J* = 6.8 Hz, 1H), 2.65 (hept, *J* = 6.8, 5.7 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 9H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 6H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-

d) δ 150.77, 141.41, 140.34, 134.37, 132.48, 127.90, 127.85, 125.36, 115.37, 111.51, 63.48 (dd, *J* = 24.4, 7.0 Hz), 57.69, 56.46, 34.45, 33.69, 31.27 (3C), 27.00, 24.21, 24.00, 22.97, 22.65, 16.45 (d, *J* = 5.9 Hz), 16.13 (d, *J* = 5.7 Hz). IR (thin film) 3420br, 2962s, 1636vs, 1186s, 1038s cm^{-1}; HRMS (ESI-TOF) *m/z* found 498.2716 ([M+Na]$^+$); calcd. 498.2749 for $C_{27}H_{42}NO_4PNa$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 9.1 min for the minor peak and 16.7 min for the major peak.



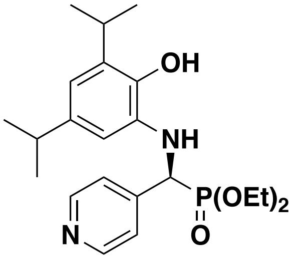
67i

Diethyl (*S*)-(((2-hydroxy-3,5-diisopropylphenyl)amino)(naphthalen-2-yl)methyl) phosphonate **67i**: Reaction of 2-naphthaldehyde **63i** (15.6 mg, 0.10 mmol, 1.00 equiv.) afforded the **67i** (38.0 mg, 0.081 mmol) in 81% yield and 95% *ee* as a yellow oil. R$_f$ = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -25.3 (c 1.00, CHCl$_3$); Spectral data for **67i**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.74 (dd, *J* = 8.4, 3.9 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.38 (d, *J* = 2.1 Hz, 1H), 4.92 (d, *J* = 22.3 Hz, 1H), 4.30 – 4.15 (m, 2H), 4.01 – 3.91 (m, 1H), 3.77 – 3.66 (m, 1H), 3.22 (hept, *J* = 6.4 Hz, 1H), 2.58 (hept, *J* = 7.0 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.13 – 1.04 (m, 5H), 0.97 (t, *J* = 6.7 Hz, 5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.84, 133.14, 128.32, 128.06, 127.90, 127.85, 127.50, 126.15, 126.09, 126.03, 125.99, 63.73, 58.81, 57.58, 33.59, 27.16, 24.02, 22.90, 22.57, 16.45, 16.41, 16.23, 16.18, (four sp^2 carbon are not located). IR (thin film) 3372br, 2959s, 1597vs, 1508s, 1198vs, 1024vs, 976s cm^{-1}; HRMS (ESI-TOF) *m/z* found 470.2462 ([M+H]$^+$); calcd. 470.2460 for $C_{27}H_{37}NO_4P$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 5:95, 0.7 mL/min flow rate, 245 nm), 15.5 min for the minor peak and 26,7 min for the major peak.



67j

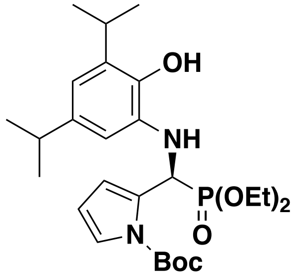
Diethyl (*S*)-((6-bromonaphthalen-2-yl)((2-hydroxy-3,5-diisopropylphenyl)amino)methyl) phosphonate **67j**: Reaction of 6-bromo-2-naphthaldehyde **63j** (23.5 mg, 0.10 mmol, 1.00 equiv.) afforded the **67j** (47.1 mg, 0.086 mmol) in 86% yield and 98% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -54.9 (c 1.00, $CHCl_3$); Spectral data for **67j**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 17.0 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 6.41 (s, 1H), 6.34 (s, 1H), 4.96 (d, *J* = 24.5 Hz, 1H), 4.41 – 4.25 (m, 2H), 3.97 – 3.85 (m, 1H), 3.72 – 3.57 (m, 1H), 3.21 (hept, *J* = 7.0 Hz, 1H), 2.66 (hept, *J* = 7.3 Hz, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.15 – 1.01 (m, 9H), 0.87 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.54, 134.38, 133.76, 131.44, 129.44, 129.11, 129.04, 127.33, 127.17, 127.12, 127.01, 119.84, 114.83, 109.81, 63.79 (dd, *J* = 110.9, 7.0 Hz), 57.25, 56.03, 33.76, 26.58, 24.33, 24.14, 23.33, 22.49, 16.50 (d, *J* = 5.9 Hz), 16.17 (d, *J* = 5.6 Hz) (four sp^2 carbon are not located). IR (thin film) 3408br, 2960s, 1653vs, 1507s, 1197vs,1053vs, 975s cm^{-1}; HRMS (ESI-TOF) *m/z* found 570.1372 ([M+Na]$^{+}$); calcd. 570.1358 for $C_{237}H_{35}NO_4PBrNa$. HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 17.6 min for the minor peak and 26.3 min for the major peak.



67k

Diethyl (*S*)-(((2-hydroxy-3,5-diisopropylphenyl)amino)(pyridin-4-yl)methyl)phosphonate **67k**: Reaction of isonicotinaldehyde **63k** (9.90 μL, 0.10 mmol, 1.00 equiv.) afforded the **67k** (14.7 mg, 0.035 mmol) in 35% yield and 17% *ee* as a yellow oil; R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -7.9 (c 1.00, $CHCl_3$); Spectral data for **67k**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.46 (dt, *J* = 3.6, 1.8 Hz, 1H), 7.86 (dq, *J* = 8.0, 2.1 Hz, 2H), 7.13 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.49 (d, *J* = 2.1 Hz, 1H), 6.18 (d, *J* = 2.0 Hz, 1H), 4.80 (d, *J* = 24.1 Hz, 1H), 4.36 – 4.13 (m, 2H), 4.08 – 3.96 (m, 1H), 3.88 (m, *J* = 10.1, 8.4, 7.0 Hz, 1H), 3.20 (p, *J* = 6.9 Hz, 1H), 2.65 (p, *J* = 6.9 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.43, 148.88, 123.26, 122.94, 122.45, 122.10, 121.39, 120.98, 114.97, 63.73, 57.17, 55.98, 30.00, 27.20, 24.43, 24.18, 22.78, 22.59, 16.32, 16.19. IR (thin film) 3423br, 2100s, 1646vs, 1208vs,1041vs cm^{-1}; HRMS (ESI-TOF) *m/z* found 421.2278 ([M+H]$^{+}$); calcd.

421.2256 for $C_{22}H_{34}N_2O_4P$. HPLC: DAICEL CHIRALPAK AS-H (Hexane/*i*PrOH = 5:95, 1 mL/min flow rate, 245 nm), 11.4 min for the minor peak and 18.9 min for the major peak.



67l

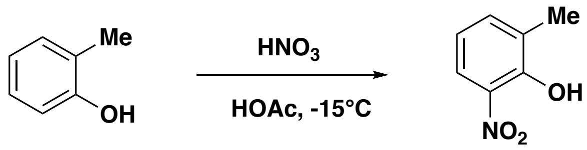
tert-Butyl (*S*)-2-((diethoxyphosphoryl)((2-hydroxy-3,5-diisopropylphenyl)amino)methyl)-1*H*-pyrrole-1-carboxylate **67l**: Reaction of *tert*-butyl 2-formyl-1*H*-pyrrole-1-carboxylate **63l** (18.1 mg, 0.1 mmol, 1.00 equiv.) afforded the **67l** (46.7 mg, 0.092 mmol) in 92% yield and 77% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -1.1 (c 1.00, $CHCl_3$); Spectral data for **67l**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.25 (s, 1H), 6.56 – 6.51 (m, 2H), 6.41 (s, 1H), 6.10 – 6.06 (m, 1H), 4.80 (br, 1H, NH), 4.18 (dt, *J* = 14.1, 6.9 Hz, 2H), 3.98 (dt, *J* = 9.9, 6.9 Hz, 1H), 3.76 (dt, *J* = 14.5, 7.4 Hz, 1H), 3.26 (hept, *J* = 7.0 Hz, 1H), 2.71 (hept, *J* = 7.0 Hz, 1H), 1.60 (s, 9H), 1.31 – 1.24 (m, 4H), 1.23 – 1.17 (m, 6H), 1.16 – 1.10 (m, 8H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.51, 141.89, 140.41, 134.37, 130.18, 122.35, 115.80, 114.13, 111.71, 110.66, 84.32, 63.29, 63.23, 63.17, 33.75, 27.90, 27.07, 24.26, 24.21, 22.93, 22.79, 16.43 (d, *J* = 5.9 Hz), 16.28 (d, *J* = 5.7 Hz) (one sp^2 carbon is not located). IR (thin film) 3420br, 2091s, 1645vs, 1320vs, 1023s, 973s cm^{-1}. HRMS (ESI-TOF) *m/z* found 509.2802 ([M+H]$^+$); calcd. 509.2780 for $C_{26}H_{42}N_2O_6P$.

HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 95:5, 0.7 mL/min flow rate, 245 nm), 12.4 min for the minor peak and 24.1 min for the major peak.

6.3 Experimental part for chapter three

6.3.1 Preparation for the substituted hydroxyanlines 64f, 64k, 64k, 64m

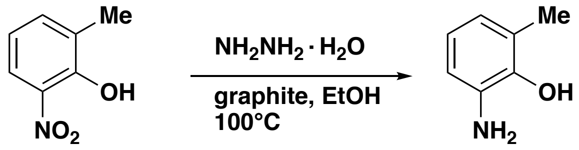
*Preparation of aniline **64f***



159

160
20%

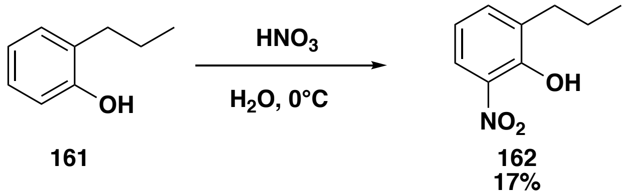
2-Methyl-6-nitrophenol **160**: According to the *general procedure of nitration*, 2-methylphenol **159** (1.00 g, 9.25 mmol), nitric acid (1.37 mL) and acetic acid (2.75 mL + 1.53 mL) were added to the reaction and stirred at -15°C. After purification by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 95:5), the reaction afforded 2-methyl-6-nitrophenol **160** (0.28 g, 1.85 mmol, 20% yield) as a yellow oil. R_f= 0.9 (7:3 hexane/EtOAc). Spectral data for **160**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.92 (d, *J* = 0.6 Hz, 1H, OH), 7.96 (ddd, *J* = 8.6, 1.7, 0.7 Hz, 1H), 7.45 (ddq, *J* = 7.4, 1.7, 0.8 Hz, 1H), 6.88 (dd, *J* = 8.6, 7.3 Hz, 1H), 2.34 (d, *J* = 0.7 Hz, 3H). The spectral data match the previously reported data for this compound.[53]



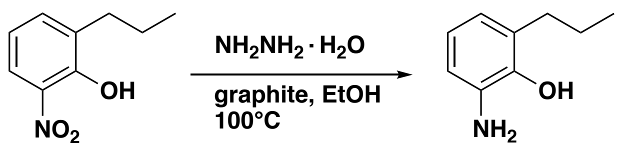
160

64f
70%

2-Hydroxy-3-methylaniline **64f**: According to the *general procedure of hydrazine reduction*, 2-methyl-6-nitrophenol **160** (0.22 g, 1.43 mmol, 1.00 equiv.), hydrazine (0.17 mL x 3, 2.5 equiv.) and graphite (0.21 g) were added to the ethanol (4.10 mL). After purification by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 8:2) and recrystallization with hexane/EtOAc (9:1), the reaction afforded the product **64f** as a yellow solid (0.12 g, 1.0 mmol, 70% yield, mp: 82.8-85.6 °C). R_f= 0.4 (7:3 hexane/EtOAc). Spectral data for **64f**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.89 – 6.42 (m, 3H), 3.56 (br, 2H, NH_2), 2.24 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.71, 132.64, 122.84, 118.72, 112.84, 17.28 (one sp^2 carbon is not located). IR (thin film) 3396s, 3314s, 2924s, 1582vs, 1480vs, 13330s, 1205vs, 804vs, 724vs cm^{-1}. HRMS (ESI-TOF) *m/z* found 124.0773 ([M+H]$^+$); calcd. 124.0762 for $C_7H_{10}NO$.



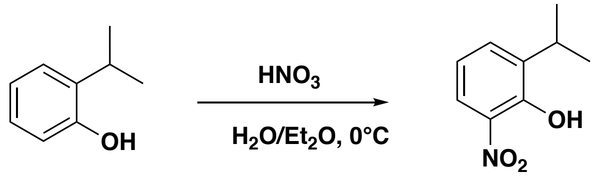
2-*n*Propyl-6-nitrophenol **162**: To an oven-dried 25 mL round bottomed flask were added 2-*n*propyl-phenol **161** (1.00 g, 7.30 mmol), nitric acid (1.10 mL) and water (5.00 mL) at 0°C under nitrogen. Then the mixture was allowed to stir at room temperature for 2 hours. Diethyl ether (5.00 mL x 3) was added to extract the aqueous layers. The combined organic layers were dried over $NaSO_4$ and concentrated under rotary evaporation. After purification of the crude product by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 95:5), the reaction afforded 2-*n*propyl-6-nitrophenol **162** (0.22 g, 1.24 mmol, 17% yield) as a yellow oil. R_f= 0.9 (7:3 hexane/EtOAc). Spectral data for **162**:^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.92 (s, 1H, OH), 7.93 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 1H), 6.88 (t, *J* = 7.9 Hz, 1H), 2.68 (t, *J* = 7.7 Hz, 2H), 1.76 – 1.57 (m, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). The spectral data match the previously reported data for this compound.[54]



162

64j
70%

2-Hydroxy-3-*n*propylaniline **64j**: According to the *general procedure of hydrazine reduction*, 2-*n*propyl-6-nitrophenol **162** (0.23 g, 1.24 mmol, 1.00 equiv.), hydrazine (0.15 mL x 3, 2.5 equiv.) and graphite (0.18 g) were added to the ethanol (3.60 mL). After purification by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 8:2) and recrystallization with pure hexane, the reaction afforded the product **64j** as a light yellow solid (0.13 g, 0.87 mmol, 70% yield, mp: 55.2-54.3 °C). R_f= 0.4 (7:3 hexane/EtOAc). Spectral data for **64j**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.76 – 6.59 (m, 3H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.64 (h, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.04, 133.88, 128.08, 121.16, 120.68, 115.83, 32.01, 22.93, 14.06. IR (thin film) 3392s, 3299s, 2928vs, 1477vs, 1328s, 1193vs, 806vs, 726vs cm^1. HRMS (ESI-TOF) *m/z* found 152.1077 ([M+H]$^+$); calcd. 152.1075 for $C_9H_{14}NO$.

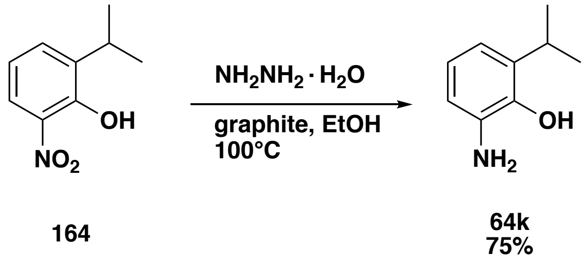


163

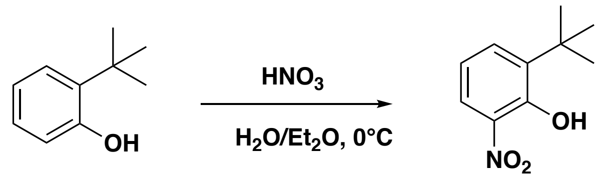
164
25%

2-*iso*Propyl-6-nitrophenol **164**: To an oven-dried 25 mL round bottomed flask were added 2-*n*propyl-phenol **163** (2.00 g, 14.6 mmol), nitric acid (2.20 mL), water (20.0 mL) and diethyl ether (20 mL) at room temperature under nitrogen. Then the mixture was stirring for 2 days and the aqueous layer was extracted by diethyl ether (20.0 mL x 3). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation.

After purification of the crude product by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 95:5), the reaction afforded 2-*iso*propyl-6-nitrophenol **164** (0.66 g, 3.65 mmol, 25% yield) as a yellow oil. R_f= 0.9 (7:3 hexane/EtOAc. Spectral data for **164**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.07 (d, *J* = 0.6 Hz, 1H, OH), 7.96 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.52 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.97 – 6.91 (m, 1H), 3.50 – 3.39 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 6H). The spectral data match the previously reported data for this compound.[55]

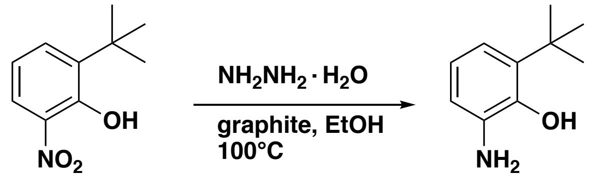


2-Hydroxy-3-*iso*propylaniline **64k**: According to the *general procedure of hydrazine reduction*, 2-*iso*propyl-6-nitrophenol **164** (0.65 g, 3.58 mmol, 1.00 equiv.), hydrazine (0.43 mL x 3, 2.5 equiv.) and graphite (0.51 g) were added to the ethanol (10.3 mL). After purification by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 8:2) and recrystallization with hexane/EtOAc (9:1), the reaction afforded the product **64j** as a organge solid (0.41 g, 2.69 mmol, 75% yield, mp: 75.6-77.3 °C). R_f= 0.4 (7:3 hexane/EtOAc). Spectral data for **64k**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.82 – 6.62 (m, 3H), 3.12 (hept, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.85, 134.26, 133.60, 120.84, 117.64, 116.09, 27.23, 22.67. IR (thin film) 3385s, 3286s, 2961s, 1583s, 1475vs, 1194vs, 897s, 841s, 732vs cm^{-1}. HRMS (ESI-TOF) *m/z* found 152.1078 ([M+H]$^+$); calcd. 152.1075 for $C_9H_{14}NO$.



165 **166** **55%**

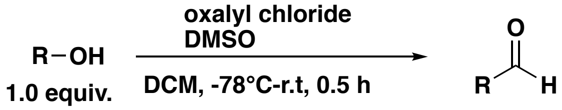
2-*tert-Butyl*-6-nitrophenol ***166***: To an oven-dried 25 mL round bottomed flask were added 2-*tert-Butyl*-phenol **165** (4.40 g, 29.2 mmol), nitric acid (4.4 0mL), water (40.0 mL) and diethyl ether (40.0 mL) at room temperature under nitrogen. Then the mixture was stirring for 2 days and the aqueous layer was extracted by diethyl ether (40.0 mL x 3). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. After purification of the crude product by flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 95:5), the reaction afforded 2-*iso*propyl-6-nitrophenol **166** (3.13 g, 16.6 mmol, 55% yield) as a yellow oil. R_f= 0.9 (7:3 hexane/EtOAc). Spectral data for **166**: ^1H NMR (500 MHz, Chloroform-*d*) δ 11.56 (d, *J* = 0.6 Hz, 1H, OH), 8.01 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.59 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.90 (dd, *J* = 8.5, 7.6 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.00, 140.60, 134.63, 123.05, 119.09, 35.55, 29.28 (one sp^2 carbon is not located). These spectral data match the previously reported data for this compound.[56]



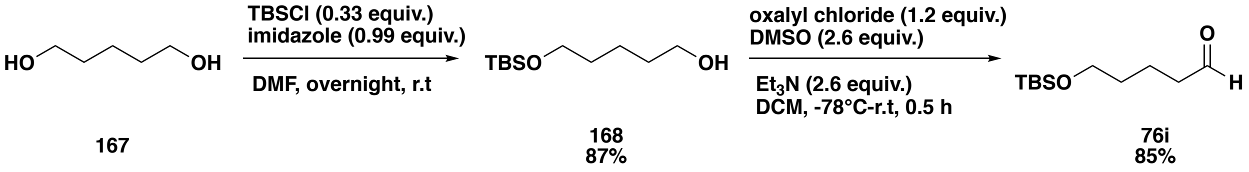
166 **64m** **70%**

2-Hydroxy-*tert-butyl*aniline ***64m***: According to the *general procedure of hydrazine reduction*, 2-*iso*propyl-6-nitrophenol **166** (0.80 g, 4.1 mmol, 1.00 equiv.), hydrazine (0.49 mL x 3, 2.5 equiv.) and graphite (0.58 g) were added to the ethanol (11.7 mL). After purification by flash chromatography (silica gel, 40 mm x 160 mm, hexane/EtOAc 8:2) and recrystallization with hexane/EtOAc (9:1), the reaction afforded the product **64m** as a pink solid (0.47 g, 2.87 mmol, 70% yield, mp: 97.8-99.0 °C). R_f= 0.4 (7:3 hexane/EtOAc). Spectral data for **64m**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.91 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.85 – 6.70 (m, 2H), 4.33 (br, 2H, NH_2, OH), 1.42 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.56, 136.91, 132.97, 120.33, 119.99, 118.69, 34.48, 29.74. IR (thin film) 3382s, 3308s, 2960vs, 1740s, 1595vs, 1448vs, 1273vs, 1198s, 788vs, 734vs cm^{-1}. HRMS (ESI-TOF) *m/z* found 166.1241 ([M+H]$^+$); calcd. 166.1232 for $C_{10}H_{16}NO$.

6.3.2 Preparation for aldehyde 76i-76r

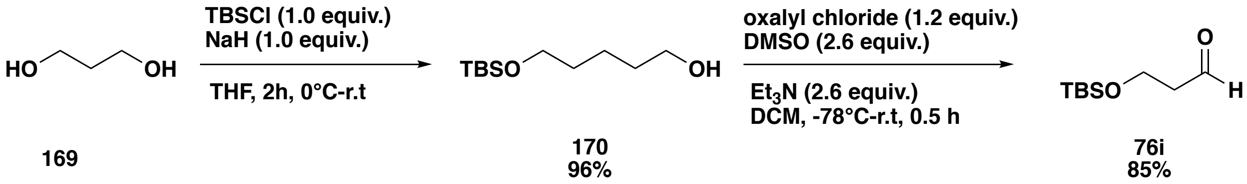


General procedure for Swern oxidation of alcohol: To a solution of oxalyl chloride in dichloromethane at –78 °C under nitrogen was added dimethyl sulfoxide. After 15 min, a solution of the corresponding alcohol (1.00 equiv.) in dichloromethane was added. The mixture was stirred for 30 min before triethylamine was added. The resulting mixture was then warmed up to room temperature and diluted with dichloromethane. The reaction was quenched by sat. $NaHCO_3$. The organic phase was separated, dried with $NaSO_4$ and concentrated. Purification of the crude aldehyde by silica gel chromatography (hexane/EtOAc as eluent) afforded the resulting aldehyde.



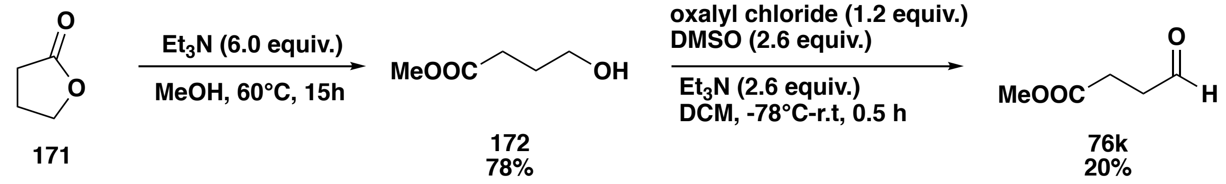
5-((*tert*-Butyldimethylsilyl)oxy)pentanal **76i**: To an oven-dried 250 mL round bottomed flask were added pentane-1,5-diol **167** (10.0 mL, 95.4 mmol, 1.00 equiv.), imidazole (6.46 g, 94.8 mmol, 0.99 equiv.) and DMF (40 mL). After all solids were dissolving, TBSCl (4.84 g, 32.0 mmol, 0.33 equiv.) in another 40 mL DMF was dropwisely added to it. The whole mixture was stirring overnight at the room temperature and quenched with water (40.0 mL) and pentane (40.0 mL). The aqueous layer was extract with pentane (20.0 mL x 3) and the combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 60 mm x 200 mm, hexane/EtOAc 80:20) afforded the pure mono-protected diol **168** (18.1 g, 83.0 mmol, 87%) as a colorless oil. R_f= 0.6 (5:5 hexane/EtOAc). Spectral data for **168**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.60 (dt, *J* = 8.2, 6.6 Hz, 4H), 1.62 – 1.44 (m, 4H), 1.43 – 1.31 (m, 2H), 0.86 (d, *J* = 1.2 Hz, 9H), 0.05 – -0.04 (m, 6H). The spectral data match the previously reported data for this compound.[109]

Following the *General procedure for Swern oxidation of alcohol*, the reaction of **168** (6.0 g, 21.0 mmol, 1.00 equiv.), oxalyl chloride (2.31 mL, 25.2 mmol,1.2 equiv.), DMSO (3.76 mL, 54.6 mmol, 2.60 equiv.) and triethylamine (7.50 mL, 54.6 mmol, 2.60 equiv.) in dichloromethane (52.0 mL x 2) afford the product **76i** (3.85 g, 17.9 mmol, 85%) as a colorless oil. R_f= 0.8 (7:3 hexane/EtOAc). Spectral data for **76i**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.76 (s, 1H), 3.61 (td, *J* = 6.3, 1.1 Hz, 2H), 2.45 (td, *J* = 7.4, 1.8 Hz, 2H), 1.74 – 1.64 (m, 2H), 1.59 – 1.48 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H). These spectral data match the previously reported data for this compound.[109]



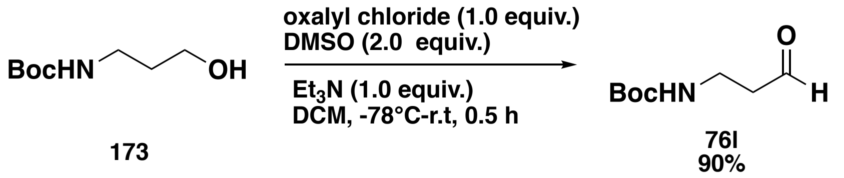
3-((*tert*-Butyldimethylsilyl)oxy)propanal **76j**: To the THF (12.5 mL) solution of propane-1,3-diol **169** (1.8 mL, 25 mmol, 1.00 equiv.) was added THF (25 mL) solution of NaH (1 g, 25 mmol, 1.00 equiv.) dropwisely at 0°C. The mixture was stirring 45 minutes at room temperature and was added TBSCl (3.75 g, 25.0 mmol, 1.00 equiv.) solution in THF (12.5 mL). The reaction stirred 1 hour and quenched with sat. $NaHCO_3$ at 0°C. After two layers was separated, the aqueous layer was extracted with diethyl ether (15.0 mL x 3). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 75:25) afforded the pure mono-protected diol **170** (4.60 g, 24.0 mmol, 96%) as a colorless oil. R_f= 0.2 (7:3 hexane/EtOAc). Spectral data for **170**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.87 – 3.76 (m, 4H), 1.77 (p, *J* = 5.6 Hz, 2H), 0.89 (s, 9H), 0.10 – 0.05 (m, 6H). These spectral data match the previously reported data for this compound.[47]

Following the *General procedure for Swern oxidation of alcohol*, the reaction of **170** (4.60 g, 24.0 mmol, 1.00 equiv.), oxalyl chloride (2.60 mL, 28.8 mmol,1.20 equiv.), DMSO (4.3 mL, 62.4 mmol, 2.6 equiv.) and triethylamine (8.50 mL, 62.4 mmol, 2.6 equiv.) in dichloromethane (59.0 mL x 2) afford the product **76j** (3.60 g, 19.2 mmol, 80%) as a colorless oil. R_f= 0.8 (7:3 hexane/EtOAc). Spectral data for **76j**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.80 (s, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 2.59 (td, *J* = 6.1, 2.0 Hz, 2H), 0.88 (s, 9H), 0.06 (s, 6H). These spectral data match the previously reported data for this compound.[47]

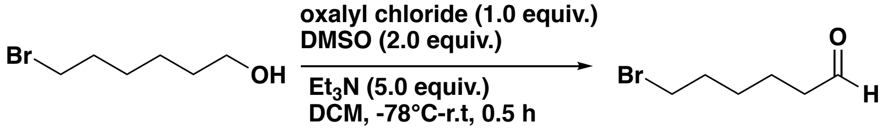


Methyl 4-oxobutanoate **76k**: To the solution of methanol (50 mL) of dihydrofuran-2(3*H*)-one **171** (0.76 mL, 10 mmol, 1.00 equiv.) was added triethylamine (8.40 mL, 60.0 mmol, 6.0 equiv.). The reaction was then heated up to 60°C and stirring for 15 hours. After the mixture was cool down to the room temperature, it was diluted with hexane (50 mL) and concentrated under the rotary evaporation. The crude product **172** (0.90 g, 7.80 mmol, 78%) can be directly used into the further reaction without purification. R_f= 0.2 (5:5 hexane/EtOAc).

Following the *General procedure for Swern oxidation of alcohol*, the reaction of **172** (0.92 g, 7.80 mmol, 1.00 equiv.), oxalyl chloride (0.68 mL, 9.40 mmol,1.20 equiv.), DMSO (1.10 mL, 20.3 mmol, 2.60 equiv.) and triethylamine (5.4 mL, 20.3 mmol, 2.60 equiv.) in dichloromethane (11.7 mL x 2) afford the product **76k** (0.18 g, 1.6 mmol, 20%) as a colorless oil. The low yield was due to the loss of the product during the rotary evaporation as the low boiling point of the product. R_f= 0.7 (5:5 hexane/EtOAc). Spectral data for **76k**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.82 (s, 1H), 3.70 (s, 3H), 2.81 (t, *J* = 6.6 Hz, 2H), 2.64 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 199.95, 172.70, 51.95, 38.52, 26.30. These spectral data match the previously reported data for this compound.[47]



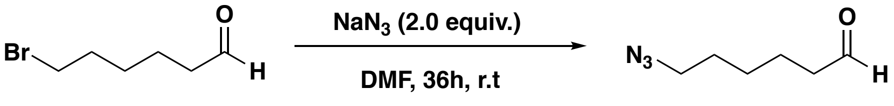
tert-Butyl (3-oxopropyl)carbamate **76l**: Following the *General procedure for Swern oxidation of alcohol*, the reaction of **173** (3.50 g, 20.1 mmol, 1.00 equiv.), oxalyl chloride (1.50 mL, 24.1 mmol,1.20 equiv.), DMSO (3.60 mL, 51.0 mmol, 2.00 equiv.) and triethylamine (5.40 mL, 20.3 mmol, 1.00 equiv.) in dichloromethane (20.0 mL x 2) afford the product **76l** (3.1 g, 18.1 mmol, 90%) as a colorless oil. R_f= 0.5 (5:5 hexane/EtOAc). Spectral data for **76l**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.77 (s, 1H), 3.38 (t, *J* = 5.9 Hz, 2H), 2.67 (t, *J* = 6.1 Hz, 2H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 201.45, 44.32, 33.98, 28.41 (one sp^2 and one sp^3 carbon are not located). These spectral data match the previously reported data for this compound.[47]



174

76m
70%

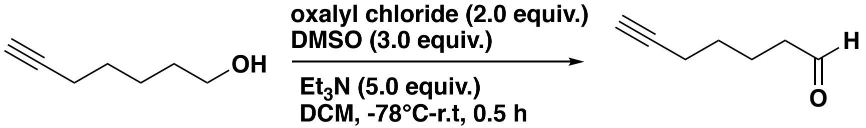
6-Bromohexanal **76m**: Following the *General procedure for Swern oxidation of alcohol*, the reaction of 6-bromohexan-1-ol **174** (1.30 mL g, 10.0 mmol, 1.00 equiv.), oxalyl chloride (0.87 mL, 10.0 mmol,1.00 equiv.), DMSO (1.40 mL, 20.0 mmol, 2.00 equiv.) and triethylamine (6.90 mL, 50.0 mmol, 5.0 equiv.) in dichloromethane (20.0 mL x 2) afford the product **76m** (1.24 g, 7.00 mmol, 70%) as a colorless oil. R_f= 0.5 (7:3 hexane/EtOAc). Spectral data for **76m**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.76 (s, 1H), 3.39 (t, *J* = 6.7 Hz, 2H), 2.50 – 2.40 (m, 2H), 1.92 – 1.82 (m, 2H), 1.73 – 1.59 (m, 2H), 1.55 – 1.40 (m, 2H). These spectral data match the previously reported data for this compound.[110]



76m

76n
70%

6-azidohexanal **76n**: To an oven-dried 50 mL round bottomed flask were added 6-Bromohexanal **76m** (0.35 g, 2.00 mmol, 1.00 equiv.), sodium azide (0.26 g, 4.00 mmol, 2.00 equiv.) and DMF (8.0 mL). The reaction was stirring at room temperature for 16 hours and washed with water/diethyl ether (10.0 mL x 3, 1:1). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 3:7) afforded the pure **76n** (0.20 g, 1.40 mmol, 70%) as a colorless oil. R_f= 0.2 (7:3 hexane/EtOAc). Spectral data for **76n**: ^1H NMR (500 MHz, Chloroform-*d*) δ 9.78 (s, 1H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.50 – 2.43 (m, 2H), 1.71 – 1.59 (m, 4H), 1.47 – 1.36 (m, 3H). The spectral data match the previously reported data for this compound.[111]



175

76o
85%

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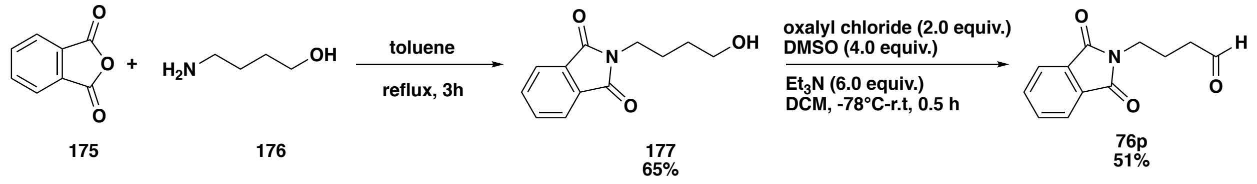
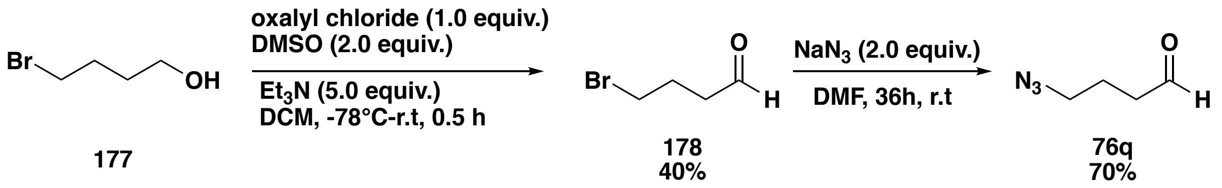
Hept-6-ynal **76o**: Following the *General procedure for Swern oxidation of alcohol*, the reaction of hept-6-yn-1-ol **175** (1.00 g, 8.90 mmol, 1.00 equiv.), oxalyl chloride (1.53 mL, 17.8 mmol, 2.0 equiv.), DMSO (1.90 mL, 26.7 mmol, 3.0 equiv.) and triethylamine (6.20 mL, 50.0 mmol, 5.00 equiv.) in dichloromethane (35.0 mL x 2) afford the product **76o** (0.83 g, 7.60 mmol, 85%) as a colorless oil. R_f= 0.5 (7:3 hexane/EtOAc). Spectral data for **76o**: ^1H NMR (500 MHz, Chloroform-*d*) δ 9.78 (t, *J* = 1.7 Hz, 1H), 2.47 (td, *J* = 7.3, 1.7 Hz, 2H), 2.23 (td, *J* = 7.0, 2.7 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.82 – 1.71 (m, 2H), 1.64 – 1.46 (m, 2H). The spectral data match the previously reported data for this compound.[112]



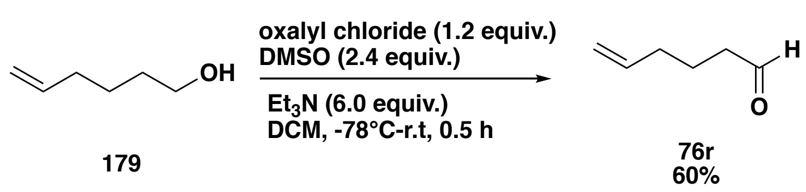
4-(1,3-Dioxoisoindolin-2-yl)butanal **76p**: To an oven-dried 50 mL round bottomed flask were added isobenzofuran-1,3-dione **175** (0.74 g, 5.00 mmol, 1.00 equiv.), 4-aminobutan-1-ol **176** (0.45 g, 5.00 mmol, 1.00 equiv.) and toluene (20.0 mL). The reaction was refluxed for 3 hours and concentrated under rotary evaporation. Flash chromatography (silica gel, 20 mm x 160 mm, pure EtOAc) afforded the pure **177** (0.71 g, 3.30 mmol, 65%) as a white solid. R_f= 0.1 (pure EtOAc). Spectral data for **177**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.87 – 7.80 (m, 2H), 7.75 – 7.67 (m, 2H), 3.74 (t, *J* = 7.2 Hz, 2H), 3.69 (t, *J* = 6.4 Hz, 2H), 1.78 (p, *J* = 7.3 Hz, 2H), 1.62 (p, *J* = 7.3 Hz, 2H). The spectral data match the previously reported data for this compound.[113]

Following the *General procedure for Swern oxidation of alcohol*, the reaction of 2-(4-hydroxybutyl)isoindoline-1,3-dione **177** (0.72 g, 3.30 mmol, 1.00 equiv.), oxalyl chloride (0.57 mL, 6.60 mmol, 2.0 equiv.), DMSO (0.93 mL, 13.2 mmol, 4.0 equiv.) and triethylamine (2.74 mL, 19.8 mmol, 6.0 equiv.) in dichloromethane (15.0 mL x 2) afford the product **76p** (0.37 g, 1.70 mmol, 51%) as a colorless oil. R_f= 0.8 (pure EtOAc). Spectral data for **76p**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.77 (s, 1H), 7.94 – 7.79 (m, 2H), 7.75 – 7.69 (m, 2H), 3.74 (t, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.02 (p, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 200.86, 168.37, 134.03, 131.97, 123.29, 41.09, 37.11, 21.16. These spectral data match the previously reported data for this compound.[113]



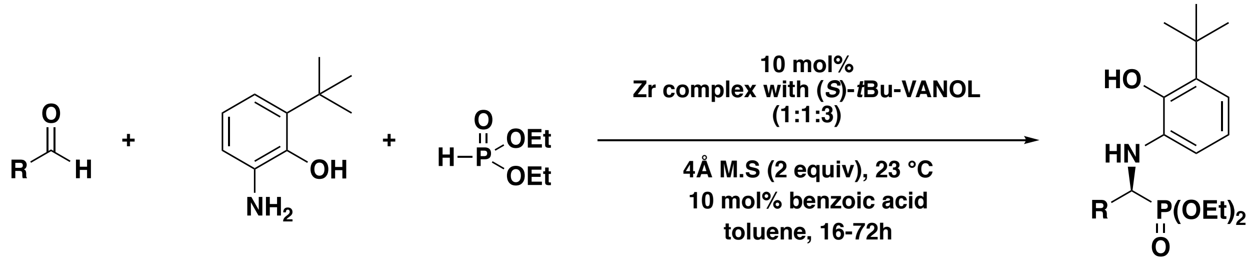
4-Azidobutanal **76q**: Following the *General procedure for Swern oxidation of alcohol*, the reaction of 4-bromobutan-1-ol **177** (1.1 mL g, 10.0 mmol, 1.00 equiv.), oxalyl chloride (0.87 mL, 10.0 mmol,1.00 equiv.), DMSO (1.4 mL, 20.0 mmol, 2.00 equiv.) and triethylamine (6.9 mL, 50.0 mmol, 5.0 equiv.) in dichloromethane (15 mL x 2) afford the product **178** (0.6 g, 4.0 mmol, 40%) as a colorless oil. R_f= 0.5 (7:3 hexane/EtOAc). Spectral data for **178**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.82 (s, 1H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 7.0 Hz, 2H), 2.18 (p, *J* = 6.7 Hz, 2H). The spectral data match the previously reported data for this compound.[114]

To an oven-dried 50 mL round bottomed flask were added 4-bromobutanal **178** (0.6 g, 4.0 mmol, 1.00 equiv.), sodium azide (0.51 g, 8.0 mmol, 2.00 equiv.) and DMF (16.0 mL). The reaction was stirring at room temperature for 16 hours and washed with water/diethyl ether (20.0 mL x 3, 1:1). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 3:7) afforded the pure **76q** (0.32 g, 2.80 mmol, 70%) as a colorless oil. R_f= 0.2 (7:3 hexane/EtOAc). Spectral data for **76q**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.80 (s, 1H), 3.35 (d, *J* = 6.7 Hz, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 1.92 (p, *J* = 6.9 Hz, 2H). The spectral data match the previously reported data for this compound.[115]



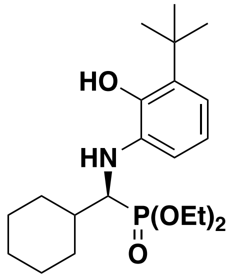
Hex-5-enal **76r**: Following the *General procedure for Swern oxidation of alcohol*, the reaction of hex-5-en-1-ol **179** (1.2 mL g, 10.0 mmol, 1.00 equiv.), oxalyl chloride (1.0 mL, 12.0 mmol,1.2 equiv.), DMSO (1.68 mL, 24.0 mmol, 2.40 equiv.) and triethylamine (8.30 mL, 60.0 mmol, 6.00 equiv.) in dichloromethane (15.0 mL x 2) afford the product **76r** (0.69 g, 7.00 mmol, 70%) as a colorless oil. R_f= 0.7 (7:3 hexane/EtOAc). Spectral data for **76r**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.78 (d, *J* = 1.8 Hz, 1H), 5.90 – 5.64 (m, 1H), 5.08 – 4.93 (m, 2H), 2.45 (td, *J* = 7.3, 1.7 Hz, 2H), 2.12 – 2.06 (m, 2H), 1.74 (p, *J* = 7.4 Hz, 2H). The spectral data match the previously reported data for this compound.[116]

6.3.3 Preparation for Asymmetric Kabachnik-Fields reaction products 78a-s



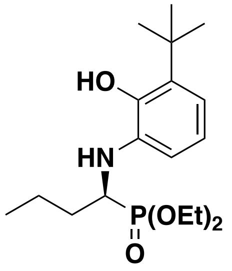
76a-s **1 equiv** **64m** **1 equiv** **65b** **1 equiv** **78a-s**

General procedure C for asymmetric Kabachnik-Fields reaction of aliphatic aldehydes: To a 10-mL flame-dried home-made Schlenk flask, prepared from a single necked 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, flushed with nitrogen was added 2-hydroxy-3-*tert*-propylaniline **64m** (16.5 mg, 0.1 mmol, 1.00 equiv.), 4 Å molecular sieves (33.0 mg) and benzoic acid (1.20 mg, 0.01 mmol, 0.10 equiv.) Under a nitrogen flow, zirconium catalyst in toluene (0.40 mL, 10 mol%, 0.25 M, prepared from general procedure A), aldehyde (0.10 mmol, 1.00 equiv.) and diethyl phosphite (14.0 μL, 0.10 mmol, 1.00 equiv.) were added to the mixture by syringes. The flask was sealed, and then placed into a liquid nitrogen bath. After the solvent was frozen, the Teflon valve was opened to vacuum and the atmosphere was pumped off for 5 minutes. The flask was sealed again and removed from the liquid nitrogen bath. Gas bubbles could be seen to evolve from the solution during thawing the solvent at the room temperature. When all the solvent melted, the flask was placed back into the liquid nitrogen bath and this Freeze-Pump-Thaw degassing process was repeated for another 2 times. The reaction was then stirring at room temperature for 16-72 hours and diluted with hexane (5.00 mL). The mixture was concentrated under rotary evaporation and purified by flash chromatography (silica gel, 10 mm x 100 mm, hexane/EtOAc, 7:3) to yield corresponding α-amino phosphites.



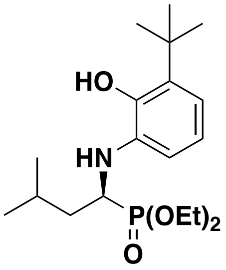
78a

Diethyl (*S*)-(((3-(*tert*-butyl)-2-hydroxyphenyl)amino)(cyclohexyl)methyl)phosphonate **78a**: Reaction of cyclohexanecarbaldehyde **76a** (12.0 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78a** (20.6 mg, 0.052 mmol) in 52% yield and 91% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3). Spectral data for **78a**:^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.02 (br, 1H, NH), 6.89 – 6.79 (m, 1H), 6.79 – 6.69 (m, 2H), 4.13 (p, *J* = 7.2 Hz, 2H), 4.08 – 4.00 (m, 1H), 3.97 – 3.87 (m, 1H), 3.42 (dd, *J* = 17.1, 3.8 Hz, 1H), 1.98 – 1.82 (m, 2H), 1.82 – 1.68 (m, 3H), 1.69 – 1.61 (m, 1H), 1.40 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 5H), 1.27 – 1.21 (m, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.39, 137.51, 136.44, 119.81, 119.28, 116.75, 62.37 (dd, *J* = 36.2, 7.5 Hz), 60.06, 58.87, 39.72, 39.68, 34.65, 30.59, 30.50, 29.78 (3C), 28.67, 28.64, 26.46, 26.35, 26.07,16.34 (d, *J* = 5.8 Hz), 16.31 (d, *J* = 5.8 Hz). IR (thin film) 3370br, 2924vs, 2096vs, 1713s, 1205s, 1021vs, 754s cm^{-}1; HRMS (ESI-TOF) *m/z* found 398.2432 ([M+H]$^{+}$); calcd. 398.2460 for $C_{21}H_{37}NO_4P$; HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 8.3 min for the minor peak and 10.9 min for the major peak.



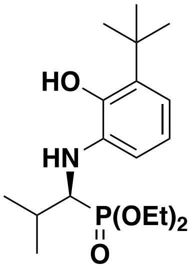
78b

Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)butyl)phosphonate **78b**: Reaction of butyraldehyde **76b** (9.00 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78b** (28.6 mg, 0.080 mmol) in 80% yield and 89% *ee* as a yellow oil; R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78b**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.24 – 7.03 (m, 1H, NH), 6.89 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 4.21 – 3.95 (m, 4H), 3.51-3.45 (m, 1H), 1.89-1.82 (m, 1H), 1.736-1.71 (m, 1H), 1.65 – 1.55 (m, 1H), 1.53-1.48 (m, 1H), 1.38 (s, 9H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.17, 137.30, 135.46, 120.09, 119.57, 117.55, 62.37 (dd, *J* = 36.2, 7.5 Hz), 54.65, 53.42, 34.67, 32.78, 29.71 (3C), 19.39 16.43 (2C), 13.94; IR (thin film) 3091br, 2399s, 1708s, 1213s, 748vs cm^{-}1; HRMS (ESI-TOF) *m/z* found 358.2147 ([M+H]$^{+}$); calcd. 358.2147 for $C_{18}H_{33}NO_4P$; HPLC: DAICEL CHIRALPAK AS-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 8.4 min for the minor peak and 11.0 min for the major peak.



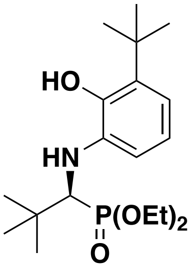
78c

Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-3-methylbutyl)phosphonate **78c**: Reaction of 3-methylbutanal **76c** (10.7 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78c** (30.6 mg, 0.083 mmol) in 83% yield and 91% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78c**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.88 (br, 1H, NH), 6.82 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 4.17 – 3.91 (m, 4H), 3.61 – 3.52 (m, 1H), 1.97 – 1.84 (m, 1H), 1.72 – 1.64 (m, 2H), 1.40 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.81, 137.29, 135.87, 119.71, 119.66, 117.12, 62.52 (dd, *J* = 45.4, 7.6 Hz), 52.87, 51.64, 39.94, 34.62, 29.74, 24.51, 24.42, 23.16, 21.65, 6.43 (d, *J* = 5.7 Hz), 16.34 (d, *J* = 5.6 Hz). IR (thin film) 3380br, 2927s, 2097vs, 1711s, 1213vs, 1022s, 750vs cm$^-$1; HRMS (ESI-TOF) *m/z* found 394.2138 ([M+Na]$^+$); calcd. 394.2123 for $C_{19}H_{34}NO_4PNa$; HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 222 nm), 17.8 min for the minor peak and 20.6 min for the major peak.



78d

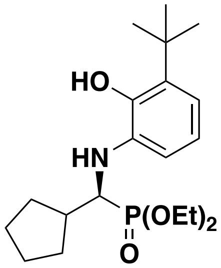
Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-2-methylpropyl)phosphonate **78d**: Reaction of *iso*butyraldehyde **76d** (9.10 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78d** (17.1 mg, 0.048 mmol) in 48% yield and 80% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78d**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.87 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.82 (br, 1H, NH), 6.80 – 6.73 (m, 2H), 4.17 – 4.09 (m, 2H), 4.06 – 3.86 (m, 2H), 3.38 (dd, *J* = 16.3, 3.7 Hz, 1H), 2.33 – 2.20 (m, 1H), 1.40 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.10, 139.83, 137.33, 136.56, 119.88, 118.04, (dd, *J* = 15.8, 7.0 Hz), 60.90, 59.73, 34.61, 29.77 (3C), 20.38, 20.29, 18.24, 16.41 (d, *J* = 5.7 Hz), 16.28 (d, *J* = 5.7 Hz). IR (thin film) 3375br, 3308br, 2923vs, 2356s, 1585s, 1422vs, 1204vs, 1021vs, 732s cm^{-}1; HRMS (ESI-TOF) *m/z* found 380.1967 ([M+Na]$^+$); calcd. 380.1967 for $C_{18}H_{32}NO_4PNa$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 11.0 min for the minor peak and 13.0 min for the major peak.



78e

Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-2,2-dimethylpropyl)phosphonate **78e**: Reaction of pivalaldehyde **76e** (10.7 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78e** (10.4 mg, 0.028 mmol) in 28% yield and 97% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78e**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.82 – 6.70 (m, 3H), 4.09 (p, *J* = 7.3 Hz, 2H), 4.06 – 3.98 (m, 1H), 3.97 – 3.87 (m, 1H), 3.37

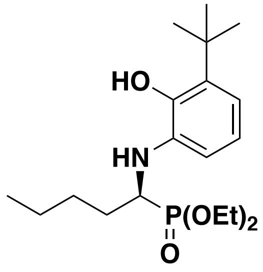
(d, *J* = 16.9 Hz, 1H), 1.41 (s, 9H), 1.27 – 1.23 (m, 6H), 1.15 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 120.65, 62.54, 62.20, 61.83, 34.56, 29.97, 29.70 (3C), 27.81, 16.31, 16.26 (five sp^2 carbons are not located). IR (thin film) 3378br, 2958s, 2280s, 1712s, 1213vs, 1021vs, 751s cm$^-$1; HRMS (ESI-TOF) *m/z* found 372.2299 ([M+H]$^+$); calcd. 372.2304 for $C_{19}H_{34}NO_4P$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 9.8 min for the minor peak and 11.9 min for the major peak.



78f

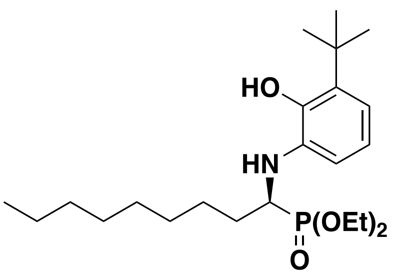
Diethyl (*S*)-(((3-(*tert*-butyl)-2-hydroxyphenyl)amino)(cyclopentyl)methyl)phosphonate **78f**: Reaction of cyclopentanecarbaldehyde **76f** (11.0 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78f** (15.3 mg, 0.040 mmol) in 40% yield and 71% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78f**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.90 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.84 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.74 (td, *J* = 7.8, 1.6 Hz, 1H), 4.15 – 4.02 (m, 3H), 4.01 – 3.88 (m, 1H), 3.54 (dd, *J* = 14.0, 6.3 Hz, 1H), 2.38 (dq, *J* = 16.3, 8.2 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.70 – 1.61 (m, 2H), 1.61 – 1.46 (m, 4H), 1.40 (s, 9H), 1.32 – 1.23 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.20, 147.24, 134.53, 120.14, 118.86, 118.74, 62.64, 59.30, 58.00, 40.99, 34.74, 30.08, 29.79, 29.17 (3C), 25.30, 25.17, 16.35, 16.31. IR (thin film) 3370br, 2923vs, 1715s, 1443s, 1258s, 1017vs, 756vs cm$^-$1; HRMS (ESI-TOF) *m/z* found 406.2133 ([M+Na]$^+$); calcd.

406.2123 for $C_{20}H_{34}NO_4PNa$; HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 18.2 min for the minor peak and 23.0 min for the major peak.



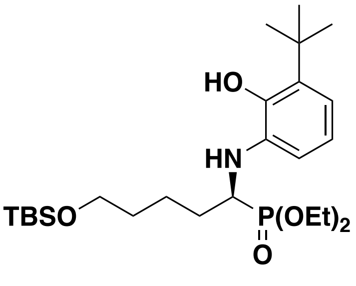
78g

Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)pentyl)phosphonate **78g**: Reaction of pentanal **76g** (10.6 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78g** (26.0 mg, 0.07 mmol) in 70% yield and 90% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78g**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.09 (br, 1H, NH), 6.93 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.85 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 4.19 – 3.96 (m, 4H), 3.46 (ddd, *J* = 13.6, 8.0, 5.4 Hz, 1H), 1.98 – 1.84 (m, 1H), 1.81 – 1.68 (m, 1H), 1.59 – 1.50 (m, 1H), 1.40 (s, 9H), 1.33-1.30 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.68, 137.44, 134.80, 120.93, 119.61, 118.61, 62.54 (dd, *J* = 18.6, 7.3 Hz), 55.28, 54.05, 34.67, 30.14, 29.69 (3C), 28.24, 28.17, 22.54, 16.44, 16.34, 13.85. IR (thin film) 3373br, 3306br, 2924vs, 1698vs, 1442s, 1206s,1166s, 1020vs, 754s cm$^-$1; HRMS (ESI-TOF) *m/z* found 372.2294 ([M+H]$^+$); calcd. 372.2304 for $C_{19}H_{35}NO_4P$; HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 8.5 min for the minor peak and 9.9 min for the major peak.zz



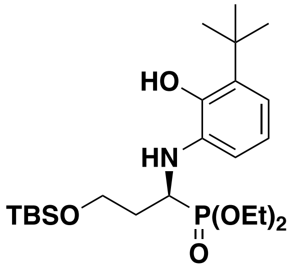
78h

Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)nonyl)phosphonate **78h**: Reaction of nonanal **76h** (17.2 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78h** (33.0 mg, 0.078 mmol) in 78% yield and 81% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78h**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.17 – 7.06 (br, 1H, NH), 6.95 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.86 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.76 (t, *J* = 7.8 Hz, 1H), 4.22 – 3.98 (m, 4H), 3.50 – 3.44 (m, 1H), 1.97 – 1.83 (m, 1H), 1.81 – 1.71 (m, 1H), 1.60 – 1.52 (m, 1H), 1.42 (s, 9H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.30 – 1.17 (m, 14H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.74, 121.06, 119.65, 118.74, 62.59 (dd, *J* = 20.2, 7.3 Hz), 55.33, 54.11, 34.70, 31.82, 30.40, 29.70 (3C), 29.44, 29.31, 29.21, 26.09, 22.65, 16.41 (2C), 14.11 (two carbons are not located). IR (thin film) 3370br, 2924vs, 2096vs, 1713s, 1205s, 1021vs, 754s cm^{-}1; HRMS (ESI-TOF) *m/z* found 428.2935 ([M+H]$^{+}$); calcd. 428.2930 for $C_{23}H_{43}NO_4P$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 16.3 min for the minor peak and 18.8 min for the major peak.



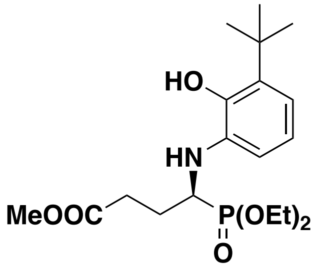
78i

Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-5-((*tert* butyldimethylsilyl)oxy) pentyl) phosphonate **78i**: Reaction of 5-((*tert*-butyldimethylsilyl)oxy)pentanal **76i** (21.6 mg, 0.1 mmol, 1.00 equiv.) for 48 hours afforded the **78i** (22.0 mg, 0.044 mmol) in 44% yield and 85% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -7.19 (c 1.05, $CHCl_3$); Spectral data for **78i**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.00 (br, 1H, NH), 6.93 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.84 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 4.20 – 3.98 (m, 4H), 3.59 (t, *J* = 6.1 Hz, 2H), 3.50 – 3.38 (m, 1H), 1.99 – 1.83 (m, 1H), 1.83 – 1.68 (m, 1H), 1.67 – 1.56 (m, 1H), 1.56 – 1.48 (m, 3H), 1.41 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.77, 137.30, 134.97, 120.90, 119.60, 118.76, 62.79, 62.52 (dd, *J* = 20.2, 7.3 Hz), 55.38, 54.15, 34.66, 32.61, 30.38, 29.70 (3C), 25.96, 22.51, 18.34, 16.40 (2C), -5.29 (2C). IR (thin film) 3373br, 3307br, 2926vs, 1702s, 1441s, 1213s, 1022vs, 752s cm$^-$1; HRMS (ESI-TOF) *m/z* found 502.3120 ($[M+H]^+$); calcd. 502.3118 for $C_{25}H_{49}NO_5SiP$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 12.3 min for the minor peak and 13.7 min for the major peak.



78j

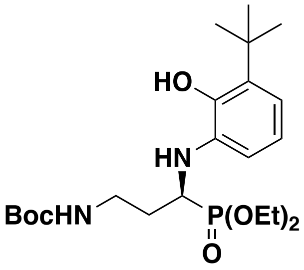
Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-3-((*tert*-butyldimethylsilyl)oxy) propyl)phosphonate **78j**: Reaction of 3-((*tert*-butyldimethylsilyl)oxy)propane **76j** (18.8 mg, 0.10 mmol, 1.00 equiv.) for 24 hours afforded the **78j** (25.1 mg, 0.053 mmol) in 53% yield and 83% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78j**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.00 – 6.89 (m, 2H), 6.73 (t, *J* = 7.8 Hz, 1H), 4.11 – 3.89 (m, 5H), 3.89 – 3.74 (m, 2H), 2.24 (m, 1H), 1.91 – 1.80 (m, 1H), 1.39 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.09, 128.89, 127.41, 126.37, 120.24, 119.43, 62.43, 59.67, 59.58, 34.74, 32.20, 29.63 (3C), 25.91, 18.33, 16.24, -5.36, -5.51 IR (thin film) 3374br, 3307br, 2926vs, 1701vs, 1442s, 1208s, 1021vs, 753vs cm^{-}1; HRMS (ESI-TOF) *m/z* found 474.2813 ([M+H]$^+$); calcd. 474.2805 for $C_{23}H_{45}NO_5SiP$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 17.4 min for the minor peak and 19.6 min for the major peak.



78k

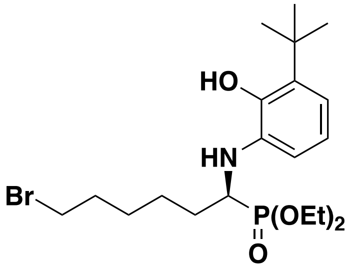
Methyl (*S*)-4-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-4-(diethoxyphosphoryl)butanoate **78k**: Reaction of methyl 4-oxobutanoate **76k** (11.6 mg, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78k** (13.2 mg, 0.033 mmol) in 33% yield and 93% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78k**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.99 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.92 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.79 (t, *J* = 7.9 Hz, 1H), 4.16 – 4.10 (m, 2H), 4.08 – 3.93 (m, 2H), 3.78 – 3.71 (m, 1H), 3.66 (s, 3H), 2.70 – 2.57 (m, 2H), 2.36 – 2.24 (m, 1H), 2.18 – 2.06 (m, 1H), 1.41 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.71, 147.54, 127.43, 126.39, 122.00, 120.29, 119.01, 62.91 (d, *J* = 6.9 Hz), 54.44, 53.23, 51.84, 34.78, 30.53, 29.75

(3C), 25.12, 16.34 (2C). IR (thin film) 3376br, 2956s, 1707s, 1213vs, 1023s, 748vs cm^{-}1; HRMS (ESI-TOF) *m/z* found 402.2048 ([M+H]$^+$); calcd. 402.2045 for $C_{19}H_{33}NO_6P$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 99:1, 1 mL/min flow rate, 245 nm), 14.9 min for the minor peak and 15.9 min for the major peak.



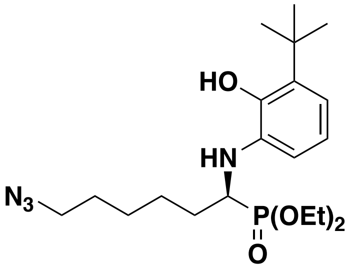
78l

tert-Butyl (*S*)-(3-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-3-(diethoxyphosphoryl)propyl) carbamate **78l**: Reaction of *tert*-butyl (3-oxopropyl)carbamate **76l** (17.3 mg, 0.1 mmol, 1.00 equiv.) for 16 hours afforded the **78l** (29.3 mg, 0.064 mmol) in 64% yield and 95% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78l**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.89 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.75 (t, *J* = 7.8 Hz, 1H), 4.93 (br, 1H, NH), 4.19 – 3.95 (m, 4H), 3.63 – 3.53 (m, 1H), 3.37 – 3.28 (m, 2H), 2.18 – 2.07 (m, 1H), 1.95 – 1.85 (m, 1H), 1.41 (s, 9H), 1.39 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.06, 146.85, 137.99, 135.66, 127.43, 120.09, 117.56, 62.72 (dd, *J* = 35.1, 7.0 Hz), 52.82, 51.59, 37.42, 34.69, 30.93, 29.75 (3C), 28.37, 16.37 (2C). IR (thin film) 3373br, 2925vs, 2096vs, 1713s, 1585s, 1442s, 1210vs, 1022vs, 751vs cm^{-}1; HRMS (ESI-TOF) *m/z* found 459.2634 ([M+H]$^+$); calcd. 459.2624 for $C_{22}H_{40}N_2O_6P$; HPLC: DAICEL CHIRALPAK AS-H (Hexane/*i*PrOH = 98:2, 1 mL/min flow rate, 245 nm), 11.4 min for the minor peak and 14.8 min for the major peak.



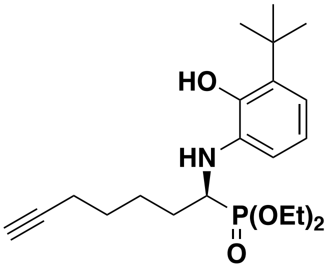
78m

Diethyl (*S*)-(5-bromo-1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)pentyl)phosphonate **78m**: Reaction of 5-bromopentanal **76m** (17.8 mg, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78m** (27.8 mg, 0.060 mmol) in 60% yield and 86% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78m**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.96 (d, *J* = 7.9 Hz, 1H), 6.86 (t, *J* = 10.2 Hz, 1H), 6.82 – 6.74 (m, 1H), 4.21 – 3.98 (m, 4H), 3.52 (dt, *J* = 14.2, 6.7 Hz, 1H), 3.42 – 3.31 (m, 2H), 1.82 (td, *J* = 12.9, 11.6, 5.8 Hz, 3H), 1.63 – 1.42 (m, 5H), 1.38 (s, 9H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.52, 121.48, 119.92, 118.64, 62.76 (dd, *J* = 27.5, 7.1 Hz), 55.16, 53.93, 34.73, 33.68, 32.36, 29.71(3C), 27.89, 25.25, 16.39 (2C) (three sp^2 carbons are not located). IR (thin film) 3373br, 2953s, 1735vs, 1439s, 1203vs, 1020vs, 753s cm^{-}1; HRMS (ESI-TOF) *m/z* found 464.1573 ([M+H]$^+$); calcd. 464.1565 for $C_{20}H_{36}NO_4PBr$; HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 98:2, 1 mL/min flow rate, 245 nm), 17.9 min for the minor peak and 27.8 min for the major peak.



78n

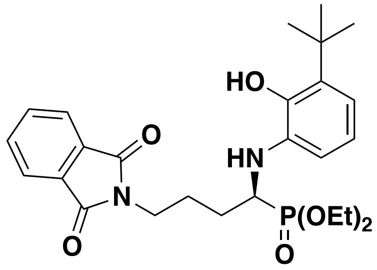
Diethyl (*S*)-(5-azido-1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)pentyl)phosphonate **78n**: Reaction of 5-azidopentanal **76n** (14.0 mg, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78n** (25.8 mg, 0.063 mmol) in 63% yield and 91% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= -7.19 (c 1.05, CHCl3); Spectral data for **78n**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.00 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.77 (t, *J* = 7.9 Hz, 1H), 4.18 – 4.00 (m, 4H), 3.56 (dt, *J* = 14.0, 6.6 Hz, 1H), 3.22 (t, *J* = 6.9 Hz, 2H), 1.95 (m, 1H), 1.87 – 1.76 (m, 1H), 1.63 – 1.48 (m, 5H), 1.40 (s, 9H), 1.37 – 1.33 (m, 3H), 1.31 – 1.21 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.81, 120.14, 119.45, 62.87 (dd, *J* = 17.6, 7.0 Hz), 55.51, 54.29, 51.24, 34.80, 29.71 (3C), 28.50, 26.44, 25.59, 16.39, 16.34. IR (thin film) 3375br, 2959vs, 2096vs, 1602s, 1441s, 1206vs, 1022vs, 752s cm^{-}1; HRMS (ESI-TOF) *m/z* found 427.2475 ($[M+H]^+$); calcd. 427.2474 for $C_{20}H_{36}N_4O_4P$; HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 98:2, 1 mL/min flow rate, 245 nm), 18.4 min for the minor peak and 27.0 min for the major peak.



78o

Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)hept-6-yn-1-yl)phosphonate **78o**: Reaction of hept-6-ynal **76o** (11.0 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78o** (18.9 mg, 0.050 mmol) in 50% yield and 91% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78o**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.98 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.77 (t, *J* = 7.9 Hz, 1H), 4.26 – 3.96

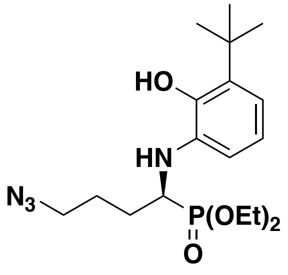
(m, 4H), 3.57 – 3.48 (m, 1H), 2.17 (td, *J* = 7.0, 2.7 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.87 – 1.73 (m, 1H), 1.73 – 1.59 (m, 2H), 1.57 – 1.50 (m, 2H), 1.41 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.74, 138.21, 129.65, 121.73, 119.93, 119.06, 84.13, 68.51, 62.85, 62.79, 62.74, 62.68, 55.33, 54.10, 34.75, 29.71 (3C), 29.61, 28.17, 25.22, 18.14, 16.39 (2C). IR (thin film) 3375br, 3308br, 2923vs, 2399s, 1722s, 1585s, 1443s, 1210s, 1022vs, 751s cm^{-}1; HRMS (ESI-TOF) *m/z* found 396.2303 ([M+H]$^{+}$); calcd. 396.2304 for $C_{21}H_{35}NO_4P$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 98:2, 1 mL/min flow rate, 245 nm), 16.2 min for the minor peak and 18.3 min for the major peak.



78p

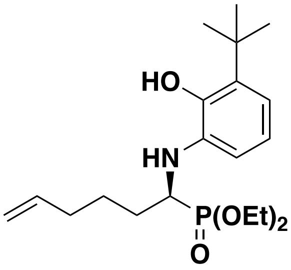
Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)-4-(1,3-dioxoisoindolin-2-yl)butyl) phosphonate **78p**: Reaction of 4-(1,3-dioxoisoindolin-2-yl)butanal **76p** (21.9 mg, 0.1 mmol, 1.00 equiv.) for 72 hours afforded the **78p** (26.6 mg, 0.053 mmol) in 53% yield and 91% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78p**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (dt, *J* = 7.7, 3.8 Hz, 2H), 7.80 – 7.66 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.82 – 6.66 (m, 3H), 4.19 – 4.01 (m, 4H), 3.70 (t, *J* = 6.6 Hz, 2H), 3.56 – 3.44 (m, 1H), 2.02 – 1.86 (m, 3H), 1.85 – 1.72 (m, 1H), 1.36 (d, *J* = 7.1 Hz, 9H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.33, 147.18, 137.22, 135.52, 135.46, 133.93, 132.03, 123.21, 120.26, 119.78, 117.96, 62.56 (dd, *J* = 18.2, 7.3 Hz), 54.53, 53.30, 37.56, 34.59, 29.72 (3C), 27.78, 25.19, 25.12, 16.38

(2C). IR (thin film) 3374br, 2926vs, 2095vs, 1713s, 1442s, 1210vs, 1022vs, 752s cm-1; HRMS (ESI-TOF) *m/z* found 503.2325 ([M+H]$^+$); calcd. 503.2311 for $C_{26}H_{36}N_2O_6P$; HPLC: DAICEL CHIRALPAK AS-H (Hexane/*i*PrOH = 5:95, 1 mL/min flow rate, 245 nm), 11.4 min for the minor peak and 18.9 min for the major peak.



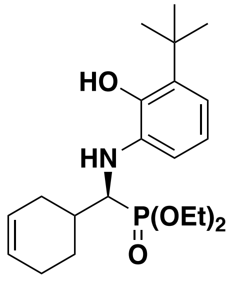
78q

Diethyl (*S*)-(4-azido-1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)butyl)phosphonate **78q**: Reaction of 4-azidobutanal **76q** (11.3 mg, 0.10 mmol, 1.00 equiv.) for 48 hours afforded the **78q** (19.9 mg, 0.052mmol) in 52% yield and 90% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78q**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.94 (d, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.77 (q, *J* = 7.7 Hz, 1H), 4.19 – 3.99 (m, 4H), 3.58 – 3.49 (m, 1H), 3.29 (t, *J* = 6.3 Hz, 2H), 2.06 – 1.94 (m, 1H), 1.90 – 1.75 (m, 3H), 1.40 (s, 9H), 1.34 – 1.28 (m, 3H), 1.24 – 1.19 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.22, 137.80, 134.64, 120.91, 119.97, 117.99, 62.81 (dd, *J* = 25.1, 7.1 Hz), 54.64, 53.40, 51.16, 34.68, 27.69 (3C), 25.65, 16.40 (2C). IR (thin film) 3370br, 2927vs, 2095vs, 1712vs, 1212vs, 1021vs, 751vs cm-1; HRMS (ESI-TOF) *m/z* found 399.2166 ([M+H]$^+$); calcd. 399.2161 for $C_{18}H_{32}N_4O_4P$; HPLC: DAICEL CHIRALPA IA-H (Hexane/*i*PrOH = 98:2, 1 mL/min flow rate, 245 nm), 17.9 min for the minor peak and 26.2 min for the major peak.



78r

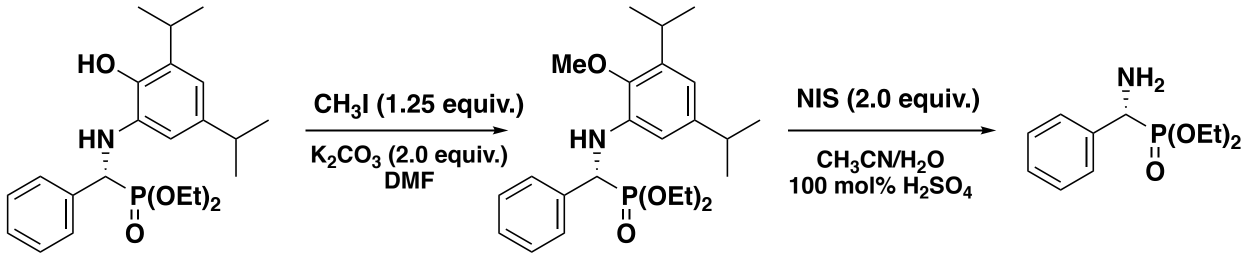
Diethyl (*S*)-(1-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)hex-5-en-1-yl)phosphonate **78r**: Reaction of 4-azidobutanal **76r** (12.0 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78r** (7.6 mg, 0.020mmol) in 20% yield and 88% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78r**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.91 (d, *J* = 7.8 Hz, 1H), 6.84 – 6.78 (m, 1H), 6.74 (t, *J* = 7.9 Hz, 1H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.08 – 4.83 (m, 2H), 4.19 – 3.97 (m, 4H), 3.40 (m, 1H), 2.13 – 2.01 (m, 2H), 1.95 – 1.84 (m, 1H), 1.80 – 1.61 (m, 2H), 1.61 – 1.51 (m, 1H), 1.40 (s, 9H), 1.32 (q, *J* = 7.4 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.72, 138.06, 136.99, 135.36, 120.64, 119.55, 118.60, 115.03, 62.48, 55.14, 53.91, 34.61, 33.48, 30.10, 29.70 (3C), 25.37, 16.37 (2C). IR (thin film) 3372br, 3308br, 2926s, 1586s, 1458s, 1213vs, 1024vs, 747vs cm$^-$1; HRMS (ESI-TOF) *m/z* found 384.2307 ([M+H]$^+$); calcd. 384.2304 for $C_{20}H_{35}NO_4P$; HPLC: DAICEL CHIRALPAK IA-H (Hexane/*i*PrOH = 95: 5, 1 mL/min flow rate, 245 nm), 8.8 min for the minor peak and 9.8 min for the major peak.



78s

Diethyl ((1*S*)-((3-(*tert*-butyl)-2-hydroxyphenyl)amino)(cyclohex-3-en-1-yl)methyl) phosphonate **78s**: Reaction of cyclohex-3-ene-1-carbaldehyde **76s** (11.7 μL, 0.10 mmol, 1.00 equiv.) for 16 hours afforded the **78q** (7.90 mg, 0.025mmol) in 25% yield and 3% *ee* as a yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Spectral data for **78s**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.94 (m, 2H), 6.75 (td, *J* = 7.9, 3.1 Hz, 1H), 5.69 – 5.62 (m, 2H), 4.19 – 3.88 (m, 4H), 3.72 – 3.55 (m, 1H), 2.36 – 2.23 (m, 2H), 2.20 – 1.95 (m, 4H), 1.41 (s, 9H), 1.30 – 1.20 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 126.66, 125.87, 125.74, 120.76, 120.64, 62.88, 60.82, 59.64, 35.21, 29.81 (3C), 27.87, 25.50, 24.99, 16.35 (2C) (two sp^2 and one sp^3 carbons are not located). IR (thin film) 3378br, 2957vs, 2097s, 1713s, 1211vs, 1022vs, 751s cm^{-}1; HRMS (ESI-TOF) *m/z* found 396.2296 ([M+H]$^+$); calcd. 396.2304 for $C_{21}H_{35}NO_4P$; HPLC: DAICEL CHIRALPAK AD-H (Hexane/*i*PrOH = 98:2, 1 mL/min flow rate, 245 nm), 17.4 min for the minor peak and 20.7 min for the major peak.

6.3.4 Deprotection of 67a and 76c



67a

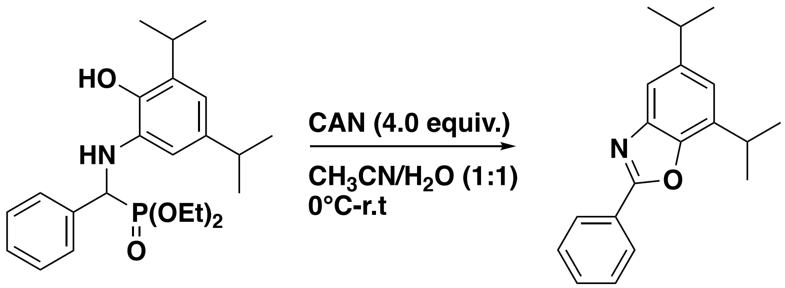
79
80%

80
80%

Diethyl (((3,5-diisopropyl-2-methoxyphenyl)amino)(phenyl)methyl)phosphonates **79**: To a oven-dried 25 mL round bottom flask were added **67a** (0.42 g, 1.00 mmol, 1.00 equiv.), potassium carbonate (0.28 g, 2.00 mmol, 2.00 equiv.) and dried DMF (5.00 mL). The mixture was stirring for 5 minutes followed by the addition of methyl iodine (92.3 μL, 1.25 mmol, 1.25 equiv.). The reaction was stirring for 6 hours at room temperature and quenched with water (5.0 mL). The organic layer was washed by water (3 x 5.00 mL) and the aqueous layer was extracted with diethyl ether (3 x 5.00 mL). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 10 mm x 100 mm, hexane/EtOAc, 7:3) afforded the **79** (0.35 g, 0.80 mmol, 80%) as a light yellow oil. R_f = 0.30 (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20}$= +5.6 (c 1.0, $CHCl_3$); Spectral data for **79**: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.47 (m, 2H), 7.38 – 7.29 (m, 2H), 7.29 – 7.21 (m, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 6.17 (d, *J* = 2.1 Hz, 1H), 4.75 (d, *J* = 23.7 Hz, 1H), 4.18 – 3.93 (m, 3H), 3.79 (s, 3H), 3.78 – 3.74 (m, 1H), 3.28 (hept, *J* = 6.9 Hz, 1H), 2.66 (hept, *J* = 6.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.17 (m, 6H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.88, 142.61, 140.65, 139.14, 139.03, 136.27, 128.52, 127.94, 127.90, 127.83, 113.34, 108.00, 63.12 (t, *J* = 7.6 Hz), 60.50, 56.64, 55.44, 33.98, 26.39, 24.11, 23.93, 23.84, 23.82, 6.46 (d, *J* = 5.8 Hz), 16.25 (d, *J* = 5.9 Hz). IR (thin film) 2956s, 1740vs, 1591s, 1442s, 1366vs, 1263vs, 733vs cm^-1; HRMS (ESI-TOF) *m/z* found 434.2460 ($[M+H]^+$); calcd. 434.2460 for $C_{24}H_{37}NO_4P$.

Diethyl (amino(phenyl)methyl)phosphonates **80**: To an oven-dried 5 mL round bottom flask were added **79** (22.0 mg, 0.05 mmol, 1.00 equiv.), NIS (8.70 mg, 0.10 mmol, 2.0 equiv.), sulfuric acid (1 M, 0.05 mL, 0.05 mmol, 1.00 equiv.) and acetonitrile/water (1.00 mL, 1:1). The reaction was stirring for 3 hours at room temperature and quenched with sodium bicarbonate (1.0 mL). The aqueous layer was extracted with diethyl ether (3 x 2.00 mL). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 10 mm x 100 mm, $CHCl_3$/MeOH, 9:1) afforded the **80** (9.6 mg, 0.08 mmol, 80%) as a light yellow oil. R_f = 0.1 (EtOAc);

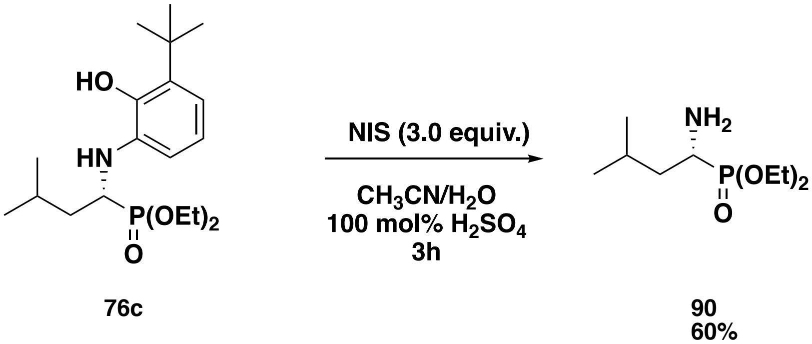
Specific Rotation: $[\alpha]_{D}^{20}$ =+10.1 (c 0.9, $CHCl_3$); Spectral data for **80**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.43 (m, 2H), 7.38 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 4.26 (d, *J* = 17.1 Hz, 1H), 4.09 – 3.96 (m, 3H), 3.91 – 3.83 (m, 1H),2.49-2.19 (br, 1H, NH^2), 1.28 (t, *J* = 7.1, 0.5 Hz, 3H), 1.18 (t, *J* = 7.1, 0.6 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 128.46, 128.44, 127.87, 127.84, 127.72, 127.67, 62.77 (dd, *J* = 18.8, 7.2 Hz), 54.65, 53.47, 16.44 (d, *J* = 5.7 Hz), 16.32 (d, *J* = 5.7 Hz). IR (thin film) 3400br, 2925vs, 2359vs, 1650s, 1258s, 1026vs, 798s cm^{-}1; HRMS (ESI-TOF) *m/z* found 266.0924 [(M+Na)$^+$; calcd. 266.0922 for $C_{11}H_{18}NO_3PNa$. The absolute configuration was determined to be (*R*) by comparing the optical rotation with literature reported same compound[60] and ECCD spectrum.



67a

81
34% (major side product)

5,7-Di*iso*propyl-2-phenylbenzo[*d*]oxazole **81**: To an oven-dried 5 mL round bottom flask were added **67a** (42.8 mg, 0.10 mmol, 1.00 equiv.), CAN (0.22 g, 0.40 mmol, 4.0 equiv.), and acetonitrile/water (0.80 mL, 1:1). The reaction was stirring for 6 hours at room temperature and quenched with sodium bicarbonate (1.0 mL). The aqueous layer was extracted with diethyl ether (3 x 2.00 mL). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 10 mm x 100 mm, EtOAc/Hexane, 2:8) afforded the **81** (9.4mg, 0.034 mmol, 34%) as a light yellow oil. R_f = 0.7 (hexane/EtOAc 7:3); Spectral data for **81**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 – 8.25 (m, 2H), 7.56 – 7.51 (m, 3H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.08 – 7.05 (m, 1H), 3.38 (hept, *J* = 7.0 Hz, 1H), 3.03 (hept, *J* = 6.9 Hz, 1H), 1.45 (d, *J* = 7.0 Hz, 6H), 1.32 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.71, 147.21, 145.86, 142.10, 131.50, 131.25, 128.86, 127.47, 121.66, 114.43, 34.35, 30.08, 24.50, 22.62 (one sp2 carbon is not located). IR (thin film) 2960vs, 2925vs, 1555s, 1450s, 1058s, 1026vs, 798s cm^{-}1; HRMS (ESI-TOF) *m/z* found 280.1705 [(M+H)$^+$; calcd. 280.1701 for $C_{19}H_{22}NO$.

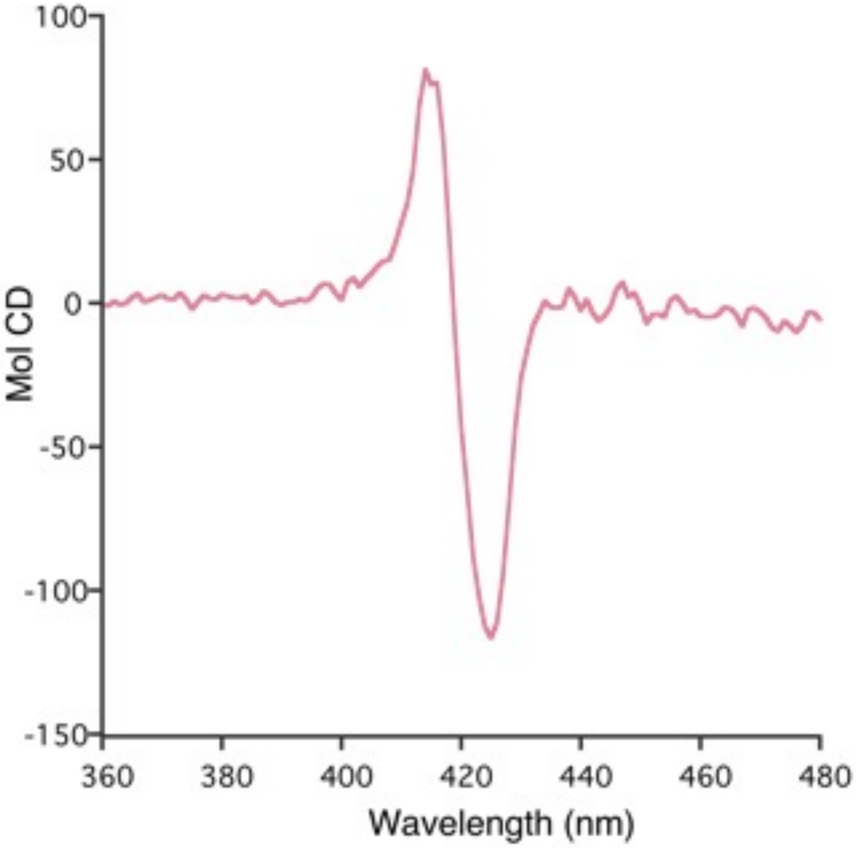


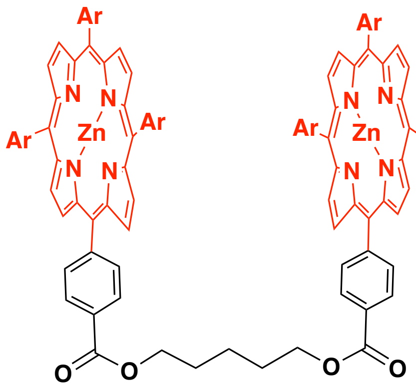
76c

90
60%

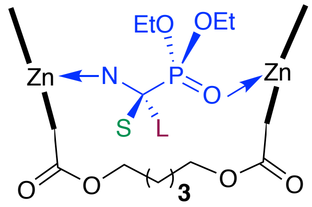
Diethyl (1-amino-3-methylbutyl)phosphonates **90**: To an oven-dried 5 mL round bottom flask were added **76c** (20.8 mg, 0.06mmol, 1.00 equiv.), NIS (37.8 mg, 0.18 mmol, 3.0 equiv.), sulfuric acid (1 M, 0.06 mL, 0.06 mmol, 1.00 equiv.) and acetonitrile/water (1.12 mL, 1:1). The reaction was stirring for 3 hours at room temperature and quenched with sodium bicarbonate (1.0 mL). The aqueous layer was extracted with diethyl ether (3.0 mL x 2). The combined organic layer was dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 10 mm x 100 mm, $CHCl_3$/MeOH, 9:1) afforded the **90** (7.2 mg, 0.032 mmol, 60%) as a light yellow oil. $[\alpha]_D^{20}$= -36.7 (c 0.72, $CHCl_3$); R_f = 0.1 (EtOAc). Spectral data for **90**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.17 (s, 4H), 3.10 (s, 1H), 1.93 (s, 1H), 1.54 (s, 2H), 1.35 (t, *J* = 6.5 Hz, 6H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 63.33, 46.00, 39.08, 24.37, 23.24, 21.37, 16.60. IR (thin film) 3396br, 2921vs, 1653s, 1223s, 1023vs; HRMS (ESI-TOF) *m/z* found 246.1238 ([M+Na]$^+$); calcd. 246.1235 for $C_9H_{22}NO_3PNa$; The absolute configuration was determined to be (*R*) by comparing the optical rotation with literature reported same compound[62] and ECCD spectrum.

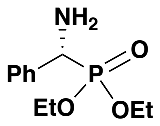
Figure 35.1 CD spectrum of α-amino phosphonate 80





Ar = C_6F_5





80

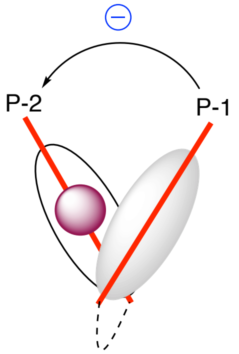
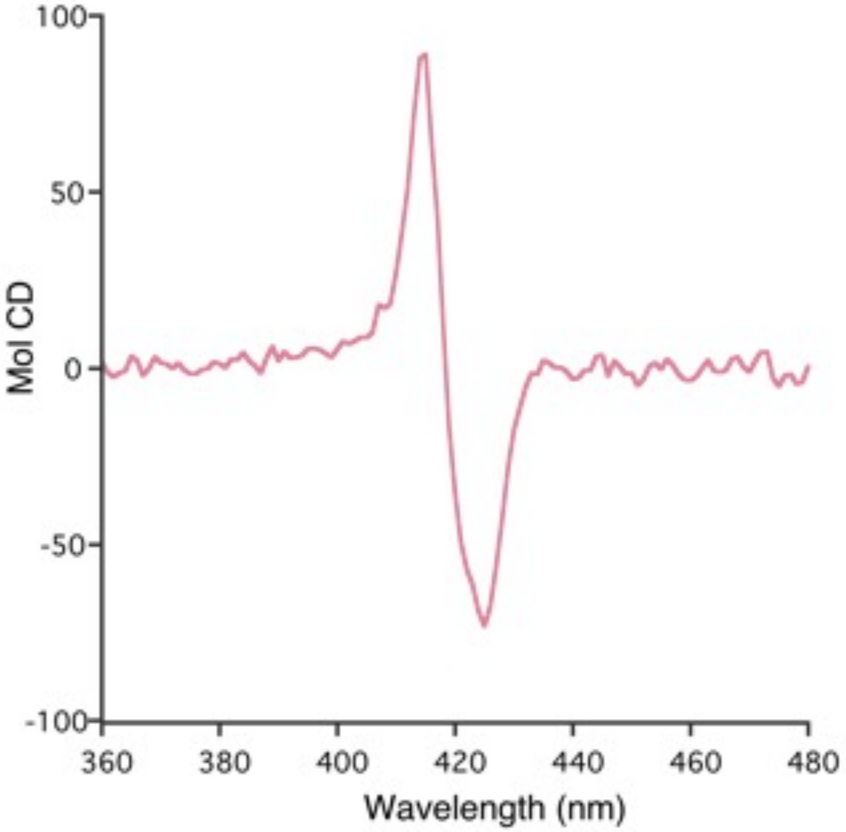
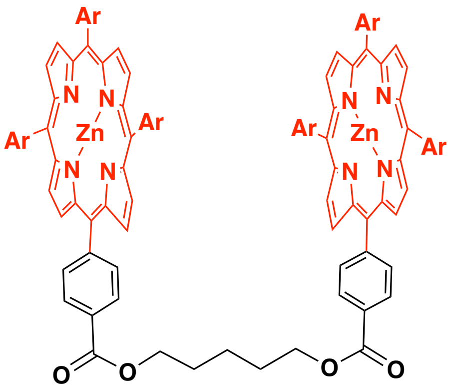
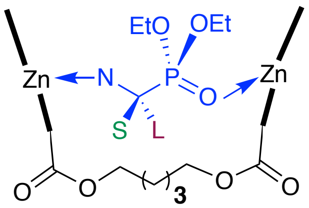


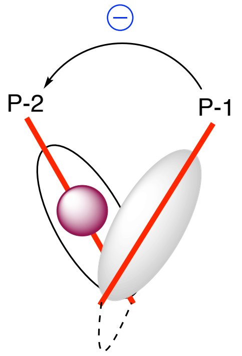
Figure 35.2 CD spectrum of α-amino phosphonate 90

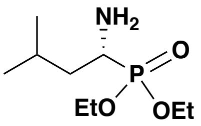




Ar = C_6F_5



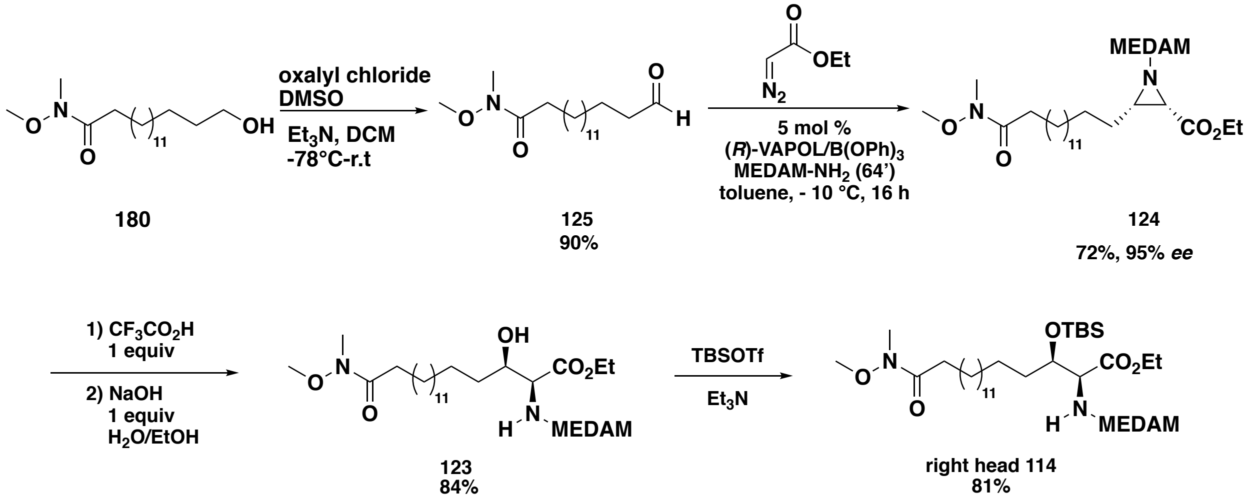


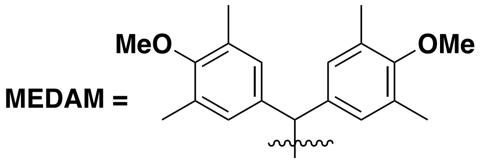


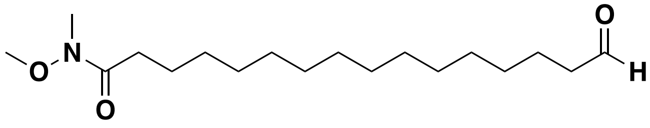
90

6.4 Experimental part for chapter four

6.4.1 Synthesis of right head 114

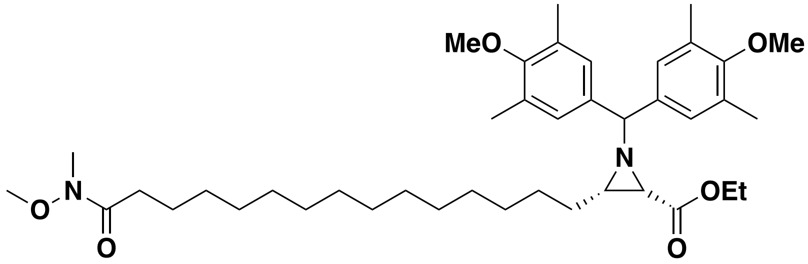






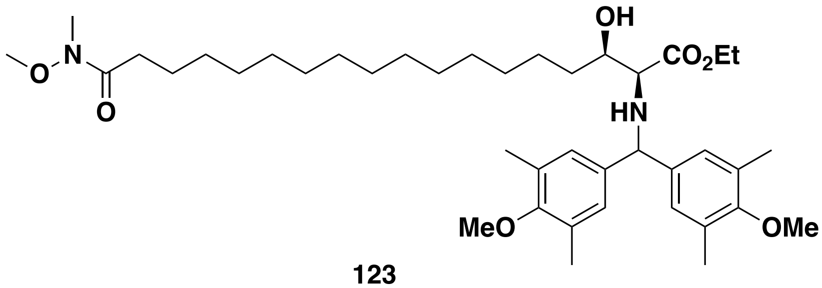
125

N-methoxy-*N*-methyl-16-oxohexadecanamide ***125***: Following the *General procedure for Swern oxidation of alcohol* (6.3.2), the reaction of **180**[51] (3.15 g, 10.0 mmol, 1.00 equiv.), oxalyl chloride (1.10 mL, 12.5 mmol,1.25 equiv.), DMSO (1.85 mL, 26.0 mmol, 2.6 equiv.) and triethylamine (3.60 mL, 26.0 mmol, 2.6 equiv.) in dichloromethane (26.0 mL x 2) afford the product **125** (2.80 g, 9.00 mmol, 90%) as a white solid. R_f= 0.2 (7:3 hexane/EtOAc). m. p. = 34-36°C. Spectral data for **125**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 3.56 (s, 3H), 3.05 (s, 3H), 2.36 – 2.19 (m, 4H), 1.56 – 1.41 (m, 4H), 1.14 (d, *J* = 9.6 Hz, 20H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 202.97, 61.16, 43.89, 29.59, 29.53, 29.57, 29.47, 29.43, 29.40, 29.38, 29.31, 29.13, 25.70, 24.63, 22.05, (one sp^2 and two sp^3 carbons are not located); These spectral data match the previously reported data for this compound.[51]



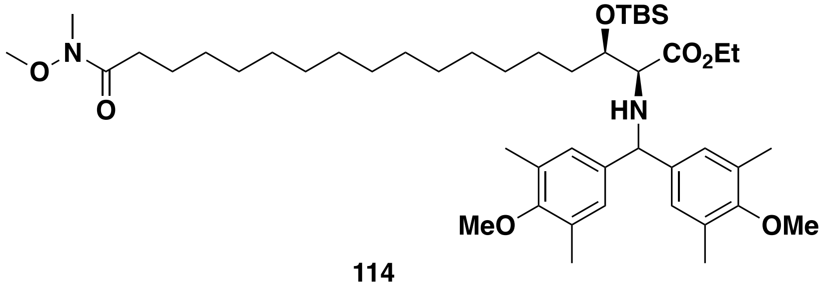
124

Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(15-(methoxy(methyl)amino)-15-oxopentadecyl)aziridine-2-carboxylate **124**: To a flame-dried 50mL Schlenk flask equipped with a magnetic stir bar and filled with nitrogen gas was added (*R*)-VAPOL (0.18 g, 0.34 mmol, 5 mol%), $B(OPh)_3$ (0.29 g, 1.0 mmol, 15 mol%) and MEDAM-NH_2 **64’** (2.01 g, 6.73 mmol, 1.00 equiv.) and 13.46 mL toluene. The flask was sealed and the resulting mixture was heated at 80°C for 1 hour. Then it was cooled to room temperature and followed by cooling at -10°C with an immersion cooler. A nitrogen flow was introduced to the neck of the flask to avoid absorption of moisture. The flask was opened, and 4Å molecular (2.0 g) sieve, aldehyde **125** (2.32 g, 7.41 mmol, 1.1 equiv.) and ethyl diazoacetate (3.07 mL, 26.9 mmol, 4.0 equiv.) was successively added at -10°C. The flask was sealed again. The resulting reaction mixture was stirred at -10°C for 16 hours. Then it was warmed up to room temperature and diluted with 15 mL hexane, filtered through celite pad in sintered glass funnel. The filtrate was concentrated under reduced pressure and followed by exposure to high vacuum for 1 hour. The crude oil was purified by silica gel column chromatography, 8:2 hexane/EtOAc as eluent (R_f = 0.3 in 7:3 hexane/EtOAc), affording the product (4.73 g, 6.40 mmol, 95%) as a yellow oil. It was determined to be 95% *ee* by chiral HPLC analysis, CHIRAL OD-H column, 97:3 hexane:isopropanol at 222nm, flow rate: 1.0mL/min, retention time: R_t = 8.28 min as the major enantiomer and R_t = 6.52min as the minor enantiomer. Spectral data for **124**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.10 (s, 2H), 7.01 (s, 2H), 4.25 – 4.12 (m, 2H), 3.79 – 3.61 (3s, 9H), 3.41 (s, 1H), 3.18 (s, 3H), 2.42 (t, *J* = 7.6 Hz, 2H), 2.24 (s, 12H), 2.21 (d, *J* = 6.7 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.63 (p, *J* = 7.6 Hz, 2H), 1.55 – 1.42 (m, 2H), 1.39 – 0.92 (m, 23H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.55, 156.05, 155.69, 138.10, 137.68, 130.32, 130.27, 127.99, 127.29, 77.22, 61.04, 60.49, 59.42, 46.88, 43.44, 31.81, 29.53, 29.51, 29.50, 29.49, 29.43, 29.39, 29.34, 29.31, 29.05, 27.84, 27.12, 24.55, 16.03, 15.99, 14.22 (one sp^2 and three sp^3 carbons are not located). These spectral data match the previously reported data for this compound.[51]



123

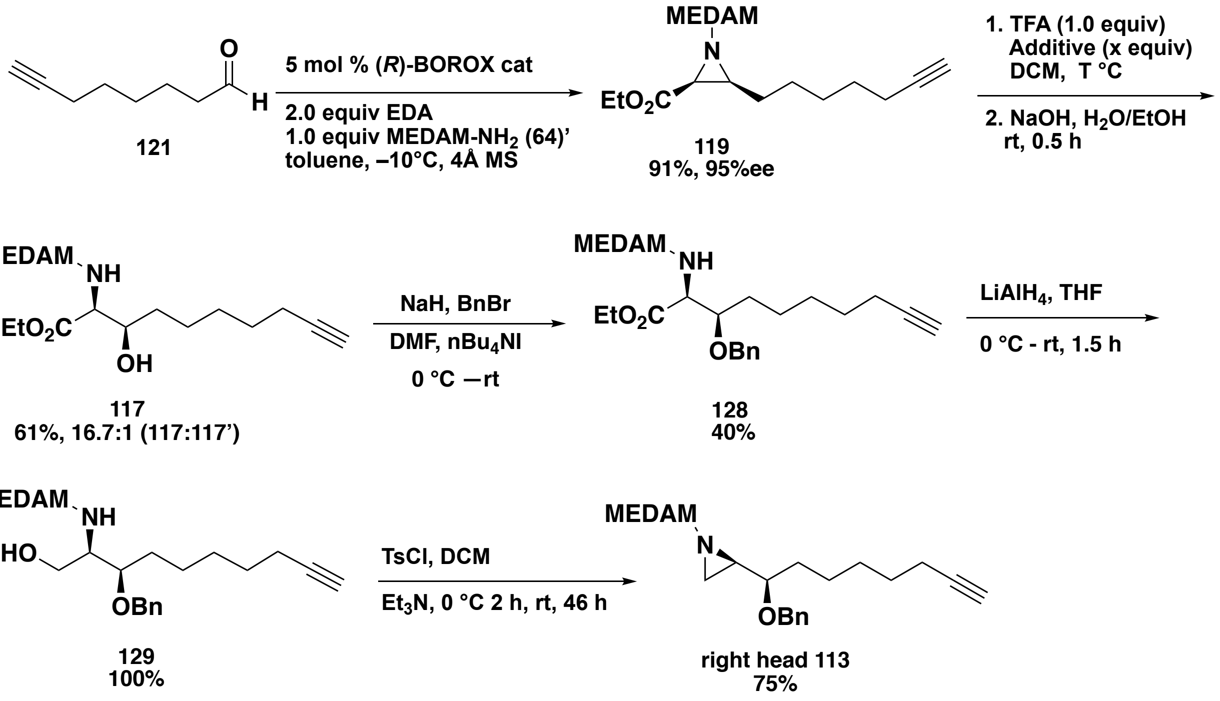
Ethyl (2*S*,3*R*)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxy-18-(methoxy(methyl)amino)-18-oxooctadecanoate **123**: To a flame-dried 250 mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added the aziridine **124** (4.37 g, 6.42 mmol, 1.00 equiv.), 64 mL CH_2Cl_2 and CF_3COOH (0.49 mL 6.42 mmol, 1.00 equiv.). The flask was quickly equipped with a condenser and the top was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. The resulting mixture was refluxed at room temperature for 65 hours. Then it was cooled to room temperature, the volatiles were removed under reduced pressure. A solution of 0.26 g NaOH in 3.80 mL water and 32.5 mL ethanol was added to the flask containing the residue after removal of the volatile. It was stirred at room temperature for 0.5 hours, then ethanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (60 mL×3), the combined organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography, 7.5:2.5 hexane/EtOAc as eluent (R_f = 0.4 in 7:3 hexane/EtOAc), affording the product (4.11 g, 5.90 mmol, 92%, >10:1 regioselectivity) as a colorless oil. Spectral data for **123**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.97 (s, 2H), 6.94 (s, 2H), 4.54 (s, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.66 – 3.61 (m, 1H), 3.58 (3s, 9H), 3.17 (br, NH), 3.07 (s, 3H), 3.01 (d, *J* = 5.1 Hz, 1H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.17 (2s, 6H), 1.61 – 1.43 (m, 4H), 1.39 – 1.07 (m, 25H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.00, 155.94, 155.89, 139.47, 137.63, 130.53, 127.80, 127.37, 72.46, 64.69, 63.40, 61.01, 60.67, 60.67, 60.22, 59.36, 59.34, 53.45, 33.87, 31.93, 31.75, 29.60, 29.57, 29.52, 29.46, 29.38, 25.65, 24.59, 16.14, 16.06, 14.22 (two sp^2 and two sp^3 carbons are not located). Spectral data for *regioisomer*- **123**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.89 (s, 2H), 6.87 (s, 2H), 5.21 (s, 1H), 4.61 (d, *J* = 9.0 Hz, 1H), 4.17 – 4.09 (m, 1H), 4.01 – 3.88 (m, 2H), 3.69 (3s, 9H), 3.18 (s, 3H), 2.41 (t, *J* = 7.8 Hz, 2H), 2.26 (s, 12H), 1.71 – 1.56 (m, 3H), 1.51 – 1.18 (m, 23H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.34, 156.52, 156.32, 137.02, 136.45, 130.79, 130.69, 127.64, 127.12, 80.97, 75.88, 61.90, 61.18, 59.62, 59.54, 54.68, 32.11, 31.90, 31.01, 29.64, 29.52, 29.46, 29.36, 25.21, 24.67, 16.22, 13.86 (two sp^2 and seven sp^3 carbons are not located). These spectral data match the previously reported data for this compound.[51]

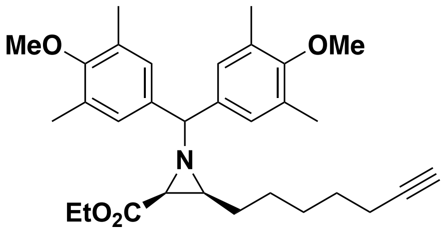


114

Ethyl (2*S*,3*R*)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-18-(methoxy(methyl)amino)-18-oxooctadecanoate **114**: To a flame-dried 100 mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added a solution of compound **123** (4.11 g, 6.10 mmol, 1.00 equiv.) in 58.8 mL THF. The flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. It was then added TBSOTf (1.39 mL, 1.20 mmol, 1.03 equiv.) and Et_3N (1.46 mL, 10.59 mmol, 1.8 equiv.) via syringe. The resulting mixture was stirred at room temperature for 30min. The volatiles were removed under reduced pressure and the crude product was purified by silica gel column chromatography, 85:15 hexane/EtOAc as eluent (R_f = 0.5 in 7:3 hexane/EtOAc). The product (3.8 g, 4.7 mmol, 80%) was obtained as colorless oil. Specific Rotation: $[\alpha]_D^{20}$ = –20.0 (*c* 1.0, CH_2Cl_2). Spectral data for **114**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.03 (s, 4H), 4.66 (s, 1H), 4.23 – 4.12 (m, 2H), 3.91 (dt, *J* = 5.3, 2.5 Hz, 1H), 3.74 – 3.61 (3s, 9H), 3.19 (s, 3H), 3.10 (d, *J* = 2.4 Hz, 1H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.25 (s, 12H), 2.07 – 1.90 (m, 2H), 1.72 – 1.55 (m, 3H), 1.35 – 1.21 (m, 22H), 1.11 – 0.99 (m, 2H), 0.84 (s, 9H), 0.01 (s,3), -0.08 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.18, 155.90, 155.73, 140.38, 138.20, 130.57, 130.43, 128.16, 127.43, 74.52, 64.01, 61.81, 61.20, 60.46, 59.60, 59.58, 34.11, 32.12, 31.92, 29.90, 29.78, 29.71, 29.67, 29.63, 29.56, 29.49, 29.47, 25.86, 25.78, 24.68, 17.98, 16.23, 16.21, 14.33, -4.26, -5.04 (one sp^2 and two sp^3 carbons are not located). These spectral data match the previously reported data for this compound.[51]

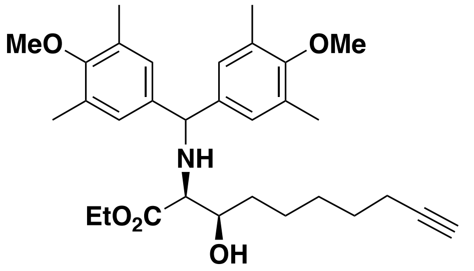
6.4.2 Synthesis of left head 113





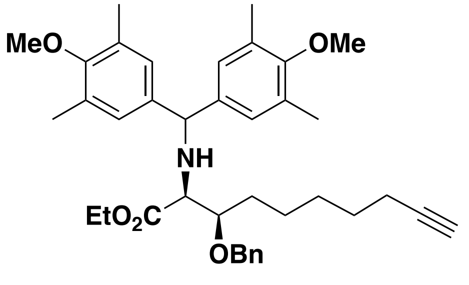
119

Ethyl (2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(hept-6-yn-1-yl)aziridine-2-carboxylate **119**: A 50 mL Schlenk flask equipped with a stir bar was flame dried, cooled to room temperature under N_2 and charged with (*R*)-VAPOL (0.48 g, 0.83 mmol, 0.05 equiv.), p-methoxylphenol (0.21 g, 1.66 mmol, 0.1 equiv.), dry toluene (17.0 mL), H_2O (45.0 µL, 2.49 mmol, 0.15 equiv.), and $BH_3{\cdot}SMe_2$ (2M, 1.25 mL, 2.49 mmol, 0.15 equiv.). The Schlenk flask was sealed by closing the Teflon valve, and the mixture was heated at 100 °C for 1 h. After the reaction was cooled to room temperature, MEDAM-NH_2 **64'** (4.96 g, 16.6 mmol, 1.00 equiv.) and dry toluene (17.0 mL) was added to the mixture under a N_2 stream and the resulting mixture was stirred at room temperature for 30 min. After the mixture was cooled to – 10 °C, 4Å Molecular Sieves (5.00 g) and the aldehyde **121**[117] (2.20 g, 17.4 mmol, 1.05 equiv.) were added to the flask followed by the addition of ethyl diazoacetate (EDA) (85%, 4.25 mL, 33.2 mmol, 2.0 equiv.). The Teflon valve was then closed, and the resulting mixture was stirred at room temperature for 16 h. Upon completion, the reaction was diluted by addition of hexane (25 mL). The reaction mixture was then filtered through a Celite pad to a 250-mL round bottom flask. The reaction flask was rinsed with EtOAc (10.0 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacum followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine **119** as a viscous yellow oil. The product was purified by column chromatography (silica gel, 40 × 250 mm, hexane/EtOAc 9:1) to afford compound **119** as a light-yellow oil (7.4 g, 15.1 mmol, 87%, 95% *ee*). R_f = 0.34 (hexane:EtOAc 3:1); Specific Rotation: $[\alpha]_D^{20}$= -85.5 (*c* 1.0, CH_2Cl_2). The optical purity of **119** was determined to be 95% *ee* by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 0.7 mL/min); Retention times: R_t = 5.70 min (minor enantiomer, *ent*-**119**) and R_t = 7.15 min (major enantiomer, **119**). ^1H NMR (500 MHz, $CDCl_3$) δ 0.93-1.04 (m, 1H), 1.06-1.16 (m, 1H), 1.17-1.28 (m, 5H), 1.29-1.38 (m, 2H), 1.40-1.55 (m, 2H), 1.88 (t, 1H, *J* = 2.6 Hz), 1.94 (q, 1H, *J* = 6.6 Hz), 2.04 (td, 2H, *J* = 7.2 Hz, *J* = 2.2 Hz), 2.19 (d, 1H, *J* = 6.8 Hz), 2.215 (s, 6H), 2.220 (s, 6H), 3.38 (s, 1H), 3.657 (s, 3H), 3.665 (s, 3H), 4.10-4.25 (m, 2H), 6.99 (s, 2H), 7.07 (s, 2H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.63, 156.12, 155.76, 138.14, 137.68, 130.50, 130.47, 128.10, 127.32, 84.49, 77.33, 68.12, 60.72, 59.62, 59.59, 46.77, 43.56, 28.38, 28.15, 27.72, 26.69, 18.16, 16.18, 16.14, 14.35. These spectral data match the previously reported data for this compound.[86]



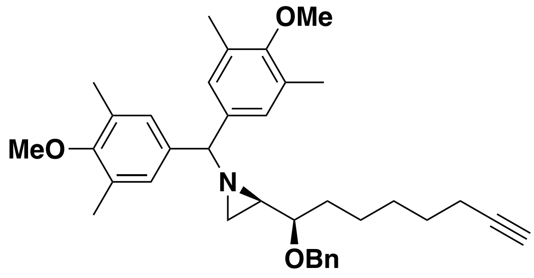
117

Ethyl (2*S*,3*R*)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxydec-9-ynoateD **117**: To a flame-dried 500 mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added the aziridine **119** (7.44 g 15.1 mmol, 1.00 equiv.), CH_2Cl_2 (302 mL, 0.05 M) and CF_3COOH (1.16 mL, 15.1 mmol, 1.00 equiv.). The flask was equipped with a condenser, sealed with a septum to which a nitrogen balloon was attached via a needle, and stirred for 48 hours at room temperature. Then the volatile was removed under reduced pressure. 85 mL 15:2 EtOH/H_2O solution with NaOH (0.6 g, 15.1 mmol, 1.00 equiv.) was added to the flask and stirred at room temperature for 0.5 hours. Thereafter, ethanol was removed under reduced pressure. The residue was extracted with ethyl acetate (30 mL x 3), the combined organic layers were dried over $NaSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, 4:1 hexane/EtOAc as eluent (R_f = 0.19), affording the product (4.8 g, 9.4 mmol, 62%, >10:1 regioselectivity) as a colorless oil. Specific Rotation: $[\alpha]_D^{20}$= -25.8 (*c* 1.0, CH_2Cl_2. Spectral data for **117**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.00 (s, 2H), 6.96 (s, 2H), 4.58 (s, 1H), 4.31 – 4.25 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.63 (q, *J* = 6.0 Hz, 1H), 3.05 (d, *J* = 6.2 Hz, 1H), 2.26 (s, 6H), 2.25 – 2.24 (s, 6H), 2.18 (td, *J* = 7.0, 2.7 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.56 – 1.47 (m, 4H), 1.34 – 1.28 (m, 5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.99. 156.06, 156.02, 139.13, 137.24, 130.81, 130.73, 127.81, 127.38, 84.55, 72.24, 68.16, 64.78, 63.71, 60.95, 59.59, 59.56, 33.57, 28.65, 28.35, 25.07, 18.30, 16.27, 16.18, 14.31. These spectral data match the previously reported data for this compound.[86]



128

Ethyl (2*S*,3*R*)-3-(benzyloxy)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)dec-9-ynoate **128**: To a flame-dried 10mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added α-amino-β-alcohol ester **117** (4.77 g, 9.4 mmol, 1.00 equiv.), DMF (27 mL), BnBr (1.90 mL, 15.9 mmol, 1.70 equiv.) and Bu_4NI (0.7 g, 1.9 mmol, 0.2 equiv.). The flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. It was cooled in ice bath for 10min. Then 60% NaH in mineral oil (0.42 g, 10.3 mmol, 1.1 equiv.) suspended in 5.0 mL DMF was added via syringe slowly. The reaction mixture was stirred for 18 hours (The ice melted and the temperature rose to room temperature in about 4 hours). Thereafter, the reaction was quenched with 50 mL distilled water, and it was extracted with CH_2Cl_2 (50.0 mL x 3). The combined organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. After silica gel column chromatography, 4:1 hexane/EtOAc as eluent (R_f=0.19), compound **128** (2.00 g, 3.30 mmol, 36%) was obtained as colorless oil and 1.00 g starting material. Specific Rotation: $[\alpha]_D^{20}$= -26.2 (*c* 1.0 CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 7.04 (s, 2H), 7.03 (s, 2H), 4.64 (s, 1H), 4.53 (d, 1H, *J* = 12.0 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.19-4.06 (m, 2H), 3.68 (s, 3H), 3.65 (s, 3H), 3.19 (s, 1H), 2.23 (s, 12H), 2.16 (dt, 2H, *J* = 2.5 Hz, 7.5 Hz), 1.94 (t, 1H, *J* = 2.5 Hz), 1.85-1.80 (m, 2H), 1.76-1.69 (m, 2H), 1.50 (q, 2H, *J* = 6.0 Hz), 1.40 (q, 2H, *J* = 6.0 Hz), 1.29-1.25 (m, 1H), 1.22 (t, 2H, *J* = 6.0 Hz), 1.09-1.19 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.07. 155.93, 155.86, 140.00, 138.32, 138.19, 130.55, 130.47, 128.22, 127.98, 127.83, 127.55, 127.46, 84.49, 80.71, 72.05, 68.22, 64.65, 61.07, 60.60, 59.56, 59.52, 30.82, 28.82, 28.42, 25.38, 18.35, 16.24, 16.17, 14.28. These spectral data match the previously reported data for this compound.[86]

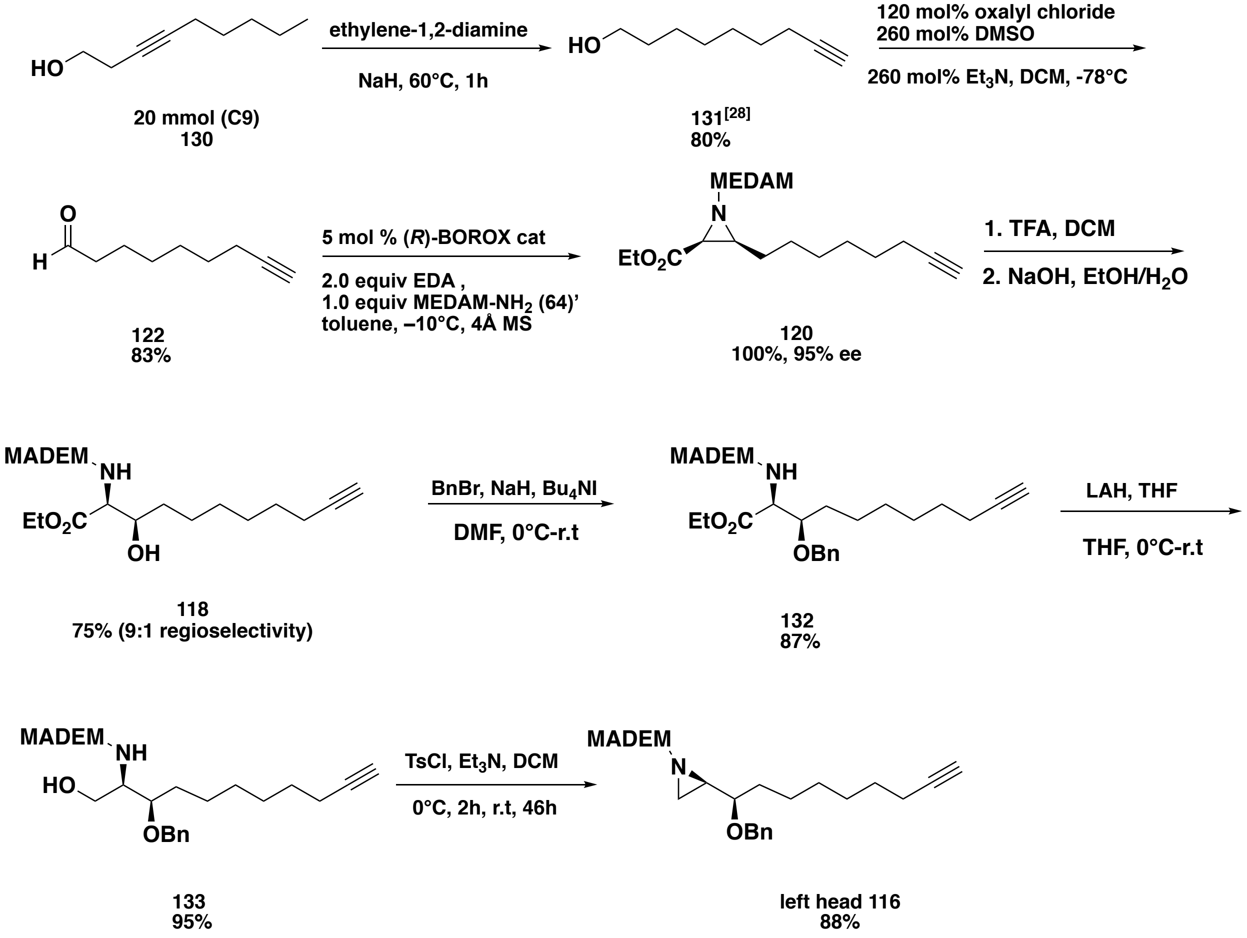


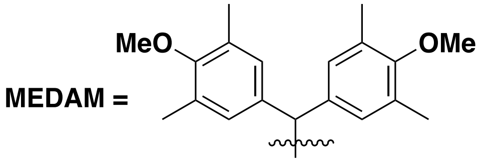
113

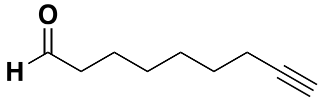
(*R*)-2-((*R*)-1-(benzyloxy)oct-7-yn-1-yl)-1-(bis(4-methoxy-3,5 dimethylphenyl)methyl) aziridine **113**: To an oven-dried 50 mL round bottom flask filled with nitrogen was added $LiAlH_4$ (0.2 g, 5.3 mmol, 1.60 equiv.) and THF (12.3 mL). After the suspension was cooled to 0 °C, a solution of compound **128** (2.0 g, 3.34 mmol, 1.00 equiv.) in THF (8.80 mL) was added dropwise into the reaction flask at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 1 hour. It was quenched by addition of H_2O (1.00 mL), followed by addition of aq. NaOH (15%, 0.3 mL) and then another two portions of H_2O (1.00 mL x 2). After the mixture was vigorously stirred at room temperature for 30 min, it became a white emulsion, which was filtered through a celite pad. The celite pad was washed with ethyl acetate several times until TLC indicated there was no product in the rinse. The combined organic solution was concentrated to give the crude product **129** (> 100% yield) as an opaque oil, which could be directly used into the next step without further purification.

To an oven-dried 50 mL round bottom flask were added compound **129** (1.90 g, 3.30 mmol, 1.00 equiv.) and dichloromethane (16.7 mL). After the solution was cooled to 0 °C, Et_3N (0.51 mL, 3.7 mmol, 1.10 equiv.) and tosyl chloride (0.70 g, 3.70 mmol, 1.10 equiv.) were added to the reaction flask. The reaction mixture was stirred at 0 °C for 2 h and then room temperature for 24 hours, which was then added another portion of Et_3N (3.12 mL, 22.2 mmol, 6.72 equiv.) and tosyl chloride (0.95 g, 5.00 mmol, 1.5 equiv.). After the mixture was stirred for another 24 hours at room temperature, it was quenched by the addition of $NaHCO_3$ (60.0 mL). The organic layer was separated and the aqueous layer was extracted with DCM (60.0 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography (40 x 250 mm, hexanes/EtOAc 9:1) gave the desired product **113** as a colorless oil (1.40 g, 2.50 mmol, 75%). $R_f = 0.8$ (hexane/EtOAc 7:3). Spectral data for **113**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 (td, *J* = 15.3, 13.2, 8.0 Hz, 2H), 7.22 (dd, *J* = 17.0, 7.1 Hz, 2H), 7.09 (s, 2H), 7.04 (d, *J* = 10.2 Hz, 3H), 4.14 – 4.07 (m, 2H), 3.71 (s, 3H), 3.56 (s, 3H), 3.28 (s, 1H), 3.05 (td, *J* = 8.2, 3.2 Hz, 1H), 2.27 (s, 6H), 2.19 (s, 6H), 2.14 (td, *J* = 7.2, 2.6 Hz, 2H), 2.06 (s, 1H), 1.94 – 1.90 (m, 1H), 1.81 (td, *J* = 7.0, 3.6 Hz, 1H), 1.46 (dt, *J* = 17.7, 6.7 Hz, 3H), 1.29 (dt, *J* = 23.3, 7.6 Hz, 4H), 1.13 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.15, 155.63, 139.15, 138.64, 138.55, 130.54, 130.42, 128.48, 128.01, 127.40, 127.34, 127.06, 84.64, 80.69, 78.22, 78.21, 70.91, 68.10, 59.62, 59.57, 59.45, 59.41, 44.58, 33.26, 30.58, 28.63, 28.35, 25.10, 18.31, 16.24, 16.22, 16.20, 16.17. Specific Rotation: $[\alpha]_D^{20} = -16.7$ (*c* 1.0, CH_2Cl_2) on 95% *ee* material. These spectral data match the previously reported data for this compound.[86]

6.4.3 Synthesis of left head 116



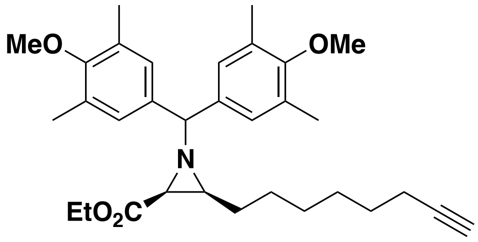




122

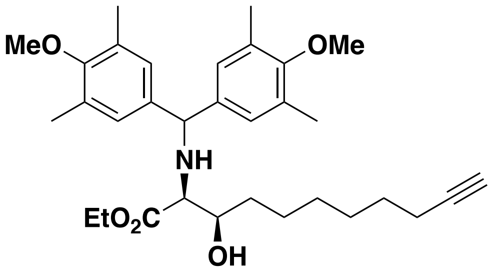
Following the *General procedure for Swern oxidation of alcohol* (6.3.2), the reaction of the alcohol **131**[118](2.90 g, 20.7 mmol, 1.00 equiv.), oxalyl chloride (2.10 mL, 25.9 mmol,1.25 equiv.), DMSO (3.70 mL, 53.8 mmol, 2.6 equiv.) and triethylamine (7.20 mL, 53.8 mmol, 2.6 equiv.) in dichloromethane (52.0 mL x 2) afford the product **122** (2.40 g, 17.2 mmol, 83%) as a colorless oil. R_f= 0.7 (7:3 hexane/EtOAc). Spectral data for **122**:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.76 (t, *J* = 1.8 Hz, 1H), 2.43 (td, *J* = 7.4, 1.8 Hz, 2H), 2.18 (td, *J* = 7.0, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.64 (p, *J* = 7.4 Hz, 2H), 1.56 – 1.49 (m, 2H), 1.46 – 1.38 (m, 2H), 1.38 – 1.31 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 202.73, 84.45, 68.28, 43.80, 28.59, 28.39, 28.16, 21.89, 18.30. These spectral data match the previously reported data for this compound.[119]



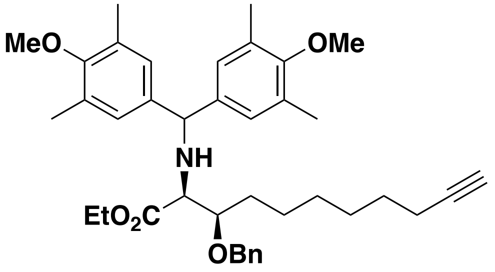
120

Ethyl (2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(oct-7-yn-1-yl)aziridine-2-carboxylate **120**: A 50 mL Schlenk flask equipped with a stir bar was flame dried, cooled to room temperature under N_2 and charged with (*R*)-VAPOL (0.50 g, 0.93 mmol, 0.05 equiv.), p-methoxylphenol (0.23 g, 1.86 mmol, 0.1 equiv.), dry toluene (18.6 mL), H_2O (50.0 µL, 2.79 mmol, 0.15 equiv.), and $BH_3 \cdot SMe_2$ (2M, 1.4 mL, 2.79 mmol, 0.15 equiv.). The Schlenk flask was sealed by closing the Teflon valve, and the mixture was heated at 100 °C for 1 h. After the reaction was cooled to room temperature, MEDAM-NH_2 **64'** (4.95 g, 16.6 mmol, 1.00 equiv.) and dry toluene (18.6 mL) was added to the mixture under a N_2 stream and the resulting mixture was stirred at room temperature for 30 min. After the mixture was cooled to -10 °C, 4Å molecular Sieves (5.0 g) and the aldehyde **132** (2.4 g, 17.3 mmol, 1.05 equiv.) were added to the flask followed by the addition of ethyl diazoacetate (EDA) (85%, 4.23 mL, 33.1 mmol, 2.0 equiv.). The Teflon valve was then closed, and the resulting mixture was stirred at room temperature for 16 h. Upon completion, the reaction was diluted by addition of hexane (25.0 mL). The reaction mixture was then filtered through a Celite pad to a 250-mL round bottom flask. The reaction flask was rinsed with EtOAc (10.0 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine **120** as a viscous yellow oil. The product was purified by column chromatography (silica gel, 40 × 250 mm, hexane:EtOAc 9:1) to afford compound **120** as a light yellow oil (8.40 g, 16.6 mmol, 100%, 95% *ee*). $R_f = 0.4$ (hexane/EtOAc 7:3); Specific Rotation: $[\alpha]_D^{20} = -63.53$ (*c* 5.0, CH_2Cl_2). Spectral data for **120**: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.11 (s, 2H), 7.03 (s, 2H), 4.27 – 4.12 (m, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 3.42 (s, 1H), 2.25 (s, 6H), 2.24 (s, 6H), 2.22 (d, *J* = 6.8 Hz, 1H), 2.11 (td, *J* = 7.2, 2.6 Hz, 2H), 1.98 (td, *J* = 7.0, 5.8 Hz, 1H), 1.91 (t, *J* = 2.7 Hz, 1H), 1.58 – 1.45 (m, 2H), 1.41 (p, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.24-1.20 (m, 1H), 1.14 (ddt, *J* = 8.4, 5.6, 2.9 Hz, 3H), 1.06 – 0.99 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.65, 156.16, 155.80, 138.20, 137.76, 130.49, 130.45, 128.13, 127.36, 84.55, 76.92, 68.21, 60.69, 59.57, 59.54, 46.87, 43.57, 28.66, 28.57, 28.24, 27.85, 27.10, 18.30, 16.19, 16.14, 14.36. IR (thin film) 3288br, 2933vs, 2857s, 1742vs, 1483vs, 1221s, 1183s, 1014vs cm^-1; HRMS (ESI-TOF) *m/z* found 528.3095 ($[M+Na]^+$); calcd. 528.3090 for $C_{32}H_{43}NO_4Na$. The optical purity of **120** was determined to be 95% *ee* by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 222 nm, flow-rate 0.7 mL/min); Retention times: R_t = 5.70 min as minor enantiomer and R_t = 7.15 min as major enantiomer.



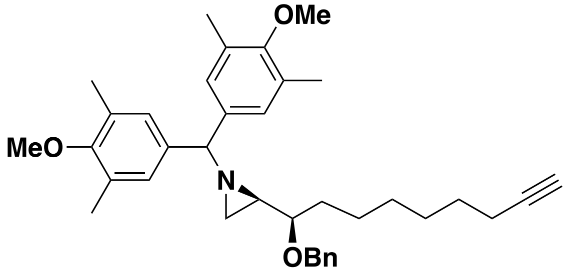
118

Ethyl (2*S*,3*R*)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxyundec-10-ynoate **118**: To a flame-dried 500 mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added the aziridine **120** (3.90 g 7.82 mmol, 1.00 equiv.), CH_2Cl_2 (156.4 mL, 0.05 M) and CF_3COOH (0.59 mL, 7.82 mmol, 1.00 equiv.). The flask was equipped with a condenser, sealed with a septum to which a nitrogen balloon was attached via a needle, and stirred for 48 hours at room temperature. Then the volatile was removed under reduced pressure. 44.3 mL 15:2 EtOH/H_2O solution with NaOH (0.31 g, 7.82 mmol, 1.00 equiv.) was added to the flask and stirred at room temperature for 0.5 hours. Thereafter, ethanol was removed under reduced pressure. The residue was extracted with ethyl acetate (15.0 mL x 3), the combined organic layers were dried over $NaSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, 4:1 hexane/EtOAc as eluent (R_f = 0.2), affording the product (3.10 g, 5.60 mmol, 71%, 9:1 regioselectivity) as a colorless oil. Specific Rotation: $[\alpha]_D^{20}$= -15.8 (*c* 1.0, CH_2Cl_2). Spectral data for **118**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.01 (s, 2H), 6.99 (s,2H), 4.59 (s, 1H), 4.20 (qd, *J* = 7.2, 2.3 Hz, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.67 – 3.62 (m, 1H), 3.07 (dd, *J* = 6.1, 2.3 Hz, 1H), 2.26 (t, *J* = 3.0 Hz, 12H), 2.18 (m, 3H), 1.97 – 1.92 (m, 1H), 1.55 – 1.47 (m, 4H), 1.42 – 1.37 (m, 2H), 1.33 – 1.24 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.97, 156.10, 156.07, 130.87, 130.79, 127.85, 127.43, 84.67, 72.29, 68.15, 64.84, 63.74, 61.02, 59.62, 59.60, 33.67, 29.06, 28.63, 28.38, 25.46, 18.36, 16.31, 16.22, 14.34 (two sp^2 carbons are not located). 59.57, 59.54, 46.87, 43.57, 28.66, 28.57, 28.24, 27.85, 27.10, 18.30, 16.19, 16.14, 14.36. IR (thin film) 3291br, 2934vs, 2857s, 1731s, 1483s, 1221s, 1188s, 1143s, 1013vs cm$^-$1; HRMS (ESI-TOF) *m/z* found 546.3189 ([M+Na]$^+$); calcd. 546.3195 for $C_{39}H_{45}NO_5Na$.



132

Ethyl (2*S*,3*R*)-3-(benzyloxy)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)undec-10-ynoate **132**: To a flame-dried 10mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added α-amino-β-alcohol ester **118** (2.88 g, 5.50 mmol, 1.00 equiv.), DMF (16.1 mL), BnBr (1.10 mL, 8.30 mmol, 1.7 equiv.) and Bu_4NI (0.41 g, 1.10 mmol, 0.2 equiv.). The flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. It was cooled in ice bath for 10min. Then 60% NaH in mineral oil (0.33 g, 8.30 mmol, 1.1 equiv.) suspended in 5.0 mL DMF was added via syringe slowly. The reaction mixture was stirred for 18 hours (The ice melted and the temperature rose to room temperature in about 4 hours). Thereafter, the reaction was quenched with 50 mL distilled water, and it was extracted with CH_2Cl_2 (30.0 mL x 3). The combined organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. After silica gel column chromatography, 9:1 hexane/EtOAc as eluent (R_f =0.8, 7:3 hexane/EtOAc), compound **132** (2.90 g, 4.60 mmol, 87%) was obtained as colorless oil. Specific Rotation: $[\alpha]_D^{20}$= -0.5 (*c* 1.0 CH_2Cl_2). Spectral data for **132**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 – 7.31 (m, 2H), 7.29 – 7.24 (m, 3H), 7.06 (s, 2H), 7.05 (s, 2H), 4.65 (s, 1H), 4.52 – 4.40 (m, 2H), 4.19 – 4.08 (m, 2H), 3.69 (s, 3H), 3.67 (s, 3H), 3.20 (d, *J* = 2.7 Hz, 1H), 2.25 (d, *J* = 0.9 Hz, 12H), 2.19 (td, *J* = 7.1, 2.6 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.85 (dddd, *J* = 12.6, 9.9, 7.1, 5.4 Hz, 1H), 1.74 (dddd, *J* = 13.2, 10.7, 6.2, 4.9 Hz, 1H), 1.56 – 1.49 (m, 2H), 1.41 – 1.31 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.15 (tdd, *J* = 13.6, 9.2, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.15, 155.91, 155.85, 140.06, 138.35, 138.22, 130.60, 130.51, 128.26, 127.98, 127.87, 127.59, 127.49, 84.66, 80.77, 72.02, 68.19, 64.63, 61.01, 60.65, 59.61, 59.57, 30.85, 29.28, 28.75, 28.45, 25.79, 18.39, 16.29, 16.22, 14.32. IR (thin film) 3414br, 2934vs, 2858s, 1734vs, 1653s, 1484s, 1454s, 1221s, 1159s, 1014vs cm^{-}1; HRMS (ESI-TOF) *m/z* found 636.3698 ($[M+Na]^+$); calcd. 636.3665 for $C_{39}H_{51}NO_5Na$.



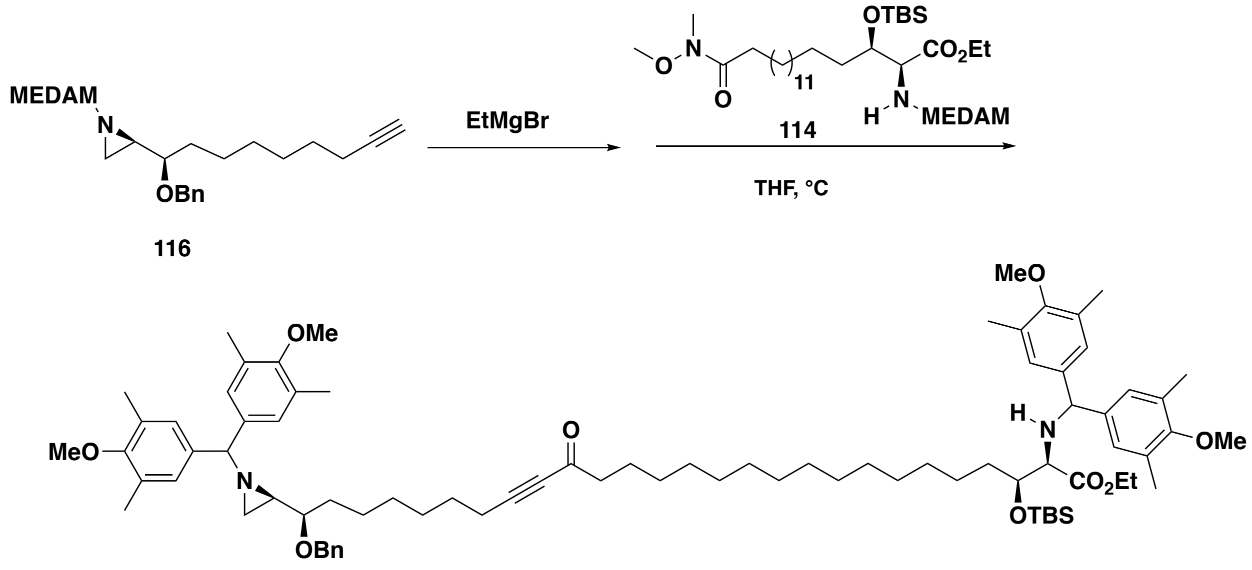
116

(*R*)-2-((*R*)-1-(benzyloxy)non-8-yn-1-yl)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl) aziridine **116**: To an oven-dried 50 mL round bottom flask filled with nitrogen was added $LiAlH_4$ (0.29 g, 7.60 mmol, 1.60 equiv.) and THF (17.0 mL). After the suspension was cooled to 0 °C, a solution of compound **132** (2.90 g, 4.6 mmol, 1.00 equiv.) in THF (12.6 mL) was added dropwise into the reaction flask at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 1 hour. It was quenched by addition of H_2O (2.00 mL), followed by addition of aq. NaOH (15%, 0.5 mL) and then another two portions of H_2O (2.00 mL x 2). After the mixture was vigorously stirred at room temperature for 30 min, it became a white emulsion, which was filtered through a celite pad. The celite pad was washed with ethyl acetate several times until TLC indicated there was no product in the rinse. The combined organic solution was concentrated to give the crude product **133** (> 100% yield) as an opaque oil, which could be directly used into the next step without further purification.

To an oven-dried 100 mL round bottom flask were added compound **133** (2.80 g, 5.10 mmol, 1.00 equiv.) and dichloromethane (25.0 mL). After the solution was cooled to 0 °C, Et_3N (0.77 mL, 5.58 mmol, 1.10 equiv.) and tosyl chloride (1.10 g, 5.58 mmol, 1.10 equiv.) were added to the reaction flask. The reaction mixture was stirred at 0 °C for 2 h and then room temperature for 24 hours, which was then added another portion of Et_3N (4.70 mL, 34.1 mmol, 6.72 equiv.) and tosyl chloride (1.45 g, 7.62 mmol, 1.50 equiv.). After the mixture was stirred for another 24 hours at room temperature, it was quenched by the addition of $NaHCO_3$ (80.0 mL). The organic layer was separated and the aqueous layer was extracted with DCM (80.0 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography (40 x 250 mm, hexanes/EtOAc 9:1) gave the desired product **116** as a colorless oil (2.50 g, 4.50 mmol, 88%). R_f = 0.8 (hexane/EtOAc 7:3). Specific Rotation: $[\alpha]_D^{20}$= -4.8 (*c* 1.0 CH_2Cl_2). Spectral data for **116**: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.26 (m, 2H), 7.25 – 7.20 (m, 1H), 7.14 (s, 2H), 7.11 – 7.06 (m, 4H), 4.20 – 4.13 (m, 2H), 3.73 (s, 3H), 3.59 (s, 3H), 3.33 (s, 1H), 3.10 (ddd, *J* = 8.4, 7.0, 3.7 Hz, 1H), 2.34 (s, 6H), 2.23 (s, 6H), 2.19 (td, *J* =

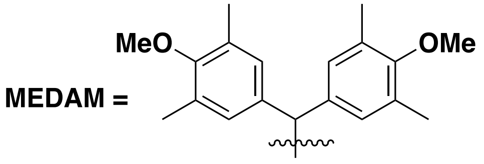
7.1, 2.7 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.86 (td, *J* = 7.0, 3.6 Hz, 1H), 1.75 (d, *J* = 3.6 Hz, 1H), 1.64 – 1.54 (m, 1H), 1.54 – 1.44 (m, 4H), 1.42 – 1.35 (m, 3H), 1.35 – 1.30 (m, 1H), 1.30 – 1.22 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.20, 155.68, 139.24, 138.70, 138.60, 130.57, 130.45, 128.53, 128.04, 127.43, 127.39, 127.09, 84.74, 80.80, 78.26, 70.92, 68.11, 59.63, 59.46, 44.65, 33.39, 30.63, 29.03, 28.65, 28.41, 25.50, 18.37, 16.26, 16.22. $[\alpha]_D^{20}$ = – 16.7° (*c* 1.0, CH_2Cl_2) on 95% *ee* material. IR (thin film) 3427br, 2934vs, 2858s, 1652s, 1483vs, 1453s, 1325s, 1221vs, 1144s, 1014vs cm^{-}1; HRMS (ESI-TOF) *m/z* found 554.3625 ($[M+H]^+$); calcd. 554.3634 for $C_{37}H_{48}NO_3$.

6.4.4 Later stage synthesis of rhizochalinin D 111

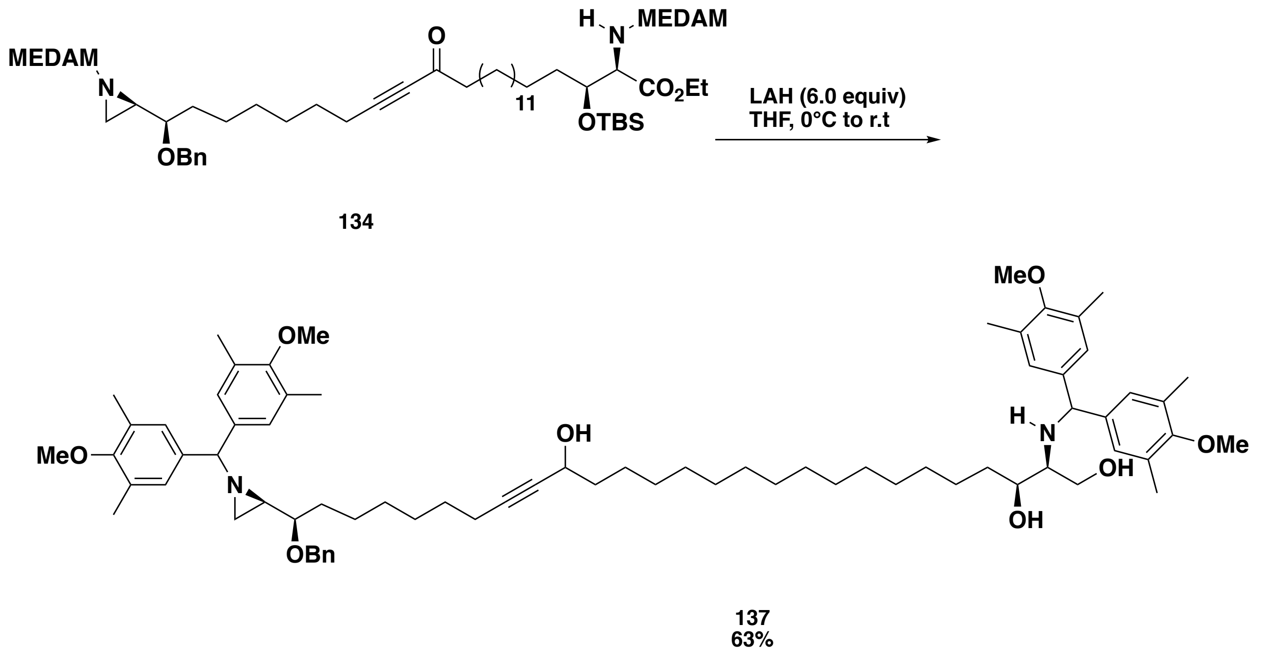


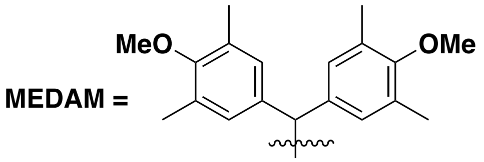
116

134
35%



(1*R*,25*S*,26*S*)-1-(benzyloxy)-26-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-1-((*R*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)aziridin-2-yl)-25-((*tert*-butyldimethylsilyl)oxy)-27-(ethylperoxy)-27λ^2-heptacos-8-yn-10-one **132**: The procedure of the coupling was according to the Wenjun's procedure.[86] To a solution of compound **116** (0.29 g, 0.50 mmol, 1.00 equiv.) in THF (1.30 mL) was added ethyl magnesium bromide (2.5 M in diethyl ether, 1.60 mL, 0.50 mmol, 1.00 equiv.) dropwise at 0 °C. After this solution was stirred at 0 °C for 20 min, it was transferred via a syringe to a solution of compound **114** (0.43 g, 0.50 mmol, 1.00 equiv.) in THF (1.0 mL) at 0 °C. The mixture was then heated up to 65 °C and stirred for 5 h. After it was cooled to room temperature, the mixture was treated with aq. NaH_2PO_4 (1 M, 2.50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (5.00 mL x 3). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by column chromatography (25 x 160 mm, hexanes/EtOAc 5:1) gave the desired product **134** as a colorless oil (0.22 g, 0.18 mmol, 35%). R_f = 0.40 (hexane/EtOAc 7:3). Spectral data for **134**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.35 (m, 2H), 7.27 – 7.18 (m, 3H), 7.10 (s, 2H), 7.06 – 7.02 (m, 6H), 4.71 (s, 1H), 4.67 (s, 1H), 4.34 (s, 1H), 4.23 – 4.15 (m, 2H), 4.14 – 4.10 (m, 2H), 3.92 (ddd, *J* = 7.9, 5.2, 2.4 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.56 (s, 3H), 3.29 (s, 1H), 3.11 (s, 1H), 3.06 (td, *J* = 8.0, 3.4 Hz, 1H), 2.28 (s, 6H), 2.25 (s, 12H), 2.20 (s, 6H), 2.18-2.16 (m, 1H) 2.06 (s, 1H), 2.04 – 1.94 (m, 2H), 1.82 (td, *J* = 7.0, 3.6 Hz, 1H), 1.72 – 1.61 (m, 4H), 1.59 – 1.51 (m, 2H), 1.49 – 1.40 (m, 6H), 1.33 – 1.25 (m, 27H), 0.84 (s, 9H), -0.02 (s, 3H), -0.07 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.20, 156.20, 155.89, 155.73, 155.68, 140.40, 139.23, 138.66, 138.58, 138.55, 138.22, 130.58, 130.46, 130.44, 128.57, 128.54, 128.17, 128.04, 127.43, 127.09, 126.98, 85.34, 81.50, 80.77, 78.29, 74.54, 70.94, 70.91, 65.36, 64.01, 62.70, 61.83, 60.47, 59.63, 59.59, 59.46, 44.75, 38.26, 34.12, 33.36, 30.61, 29.92, 29.74, 29.65, 29.62, 29.35, 28.95, 28.88, 28.69, 28.63, 28.56, 28.53, 25.88, 25.79, 25.44, 25.29, 18.62, 17.99, 16.27, 16.25, 16.22, 14.34, -4.24, -5.03 (one sp^2 and one sp^3 carbon are not located). HRMS (ESI-TOF) *m/z* found 1305.8801 ($[M+H]^+$); calcd. 1305.8841 for $C_{82}H_{121}N_2O_9$.

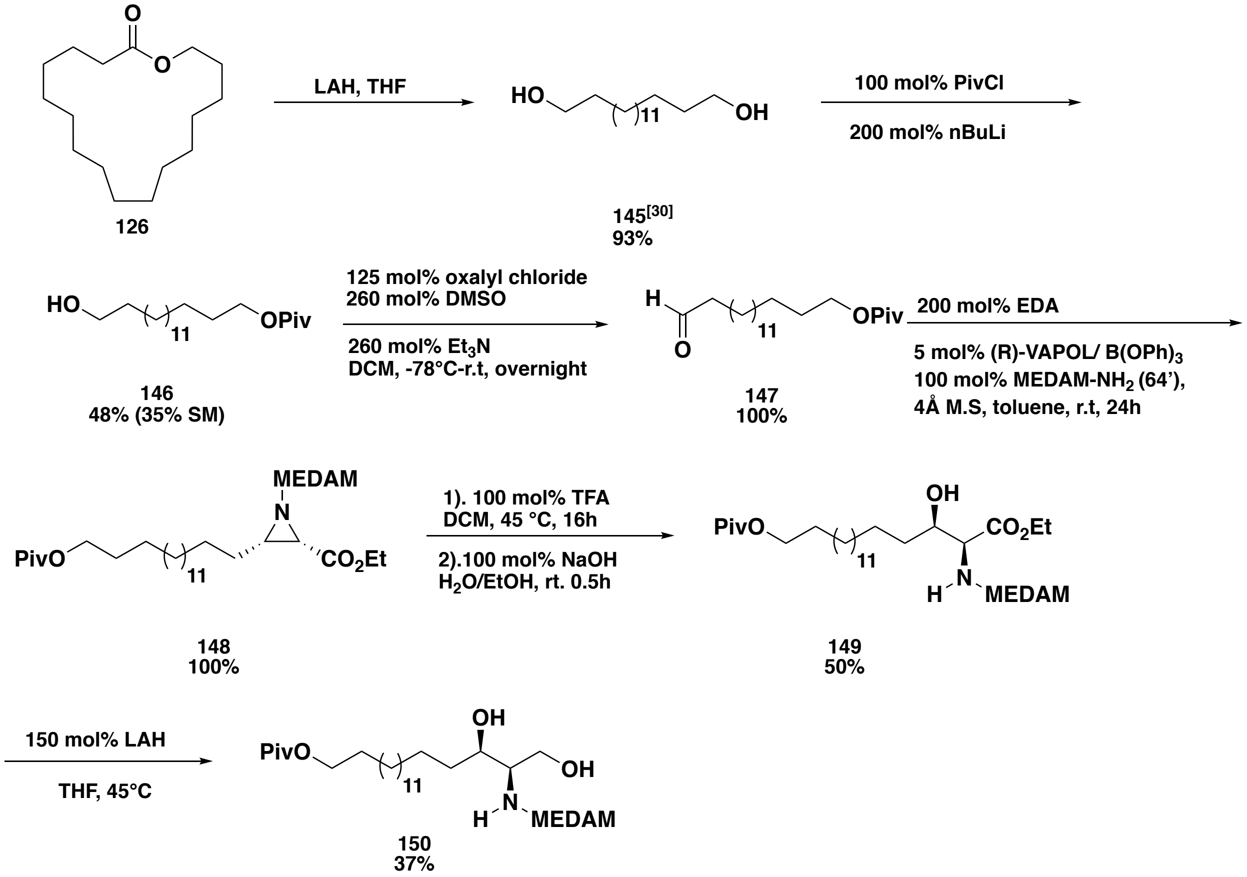


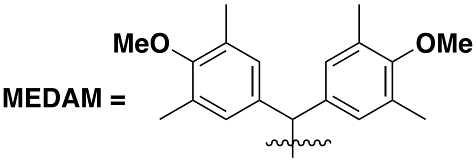


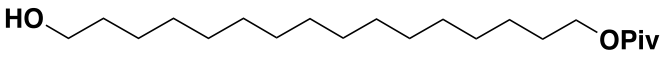
(2*S*,3*S*,27*R*)-27-(benzyloxy)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-27-((*R*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)aziridin-2-yl)-3-((*tert*-butyldimethylsilyl)oxy)heptacos-19-yne-1,18-diol **137**: To an oven-dried 50 mL round bottom flask filled with nitrogen were added **134** (0.13 g, 0.10 mmol, 1.00 equiv.) and THF (1.00 mL). After the solution was cool down to 0°C, $LiAlH_4$ (22.8 mg, 0.60 mmol, 6.0 equiv.) was slowly added. The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 1 hour. It was quenched by addition of H_2O (0.50 mL), followed by addition of aq. NaOH (15%, 0.10 mL) and then another two portions of H_2O (0.50 mL x

2). After the mixture was vigorously stirred at room temperature for 30 min, it became a white emulsion, which was filtered through a celite pad. The celite pad was washed with ethyl acetate several times until TLC indicated there was no product in the rinse. The combined organic solution was concentrated to give the crude product **137** (72.0 mg, 0.06 mmol, 63%) as an opaque oil, which could be directly used into the next step without further purification). R_f = 0.10 (hexane/EtOAc 7:3). Spectral data for **137**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.29 (m, 2H), 7.25 – 7.16 (m, 3H), 7.08 (s, 2H), 7.05 – 7.00 (m, 6H), 4.77 (s, 1H), 4.75 (s, 1H), 4.34 – 4.29 (m, 1H), 4.12 – 4.08 (m, 2H), 3.76 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 6H), 3.57 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.54 (s, 3H), 3.27 (s, 1H), 3.04 (dq, *J* = 8.1, 4.5 Hz, 1H), 2.49 – 2.44 (m, 2H), 2.26 (s, 6H), 2.25 (s, 12H), 2.18 (s, 6H), 2.04 (s, 1H), 1.98 (q, *J* = 7.3, 6.9 Hz, 1H), 1.81 (td, *J* = 7.0, 3.6 Hz, 1H), 1.71 – 1.60 (m, 3H), 1.57 – 1.49 (m, 3H), 1.49 – 1.38 (m, 6H), 1.33 – 1.18 (m, 25H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.18, 155.95, 155.66, 139.43, 139.19, 138.62, 138.38, 132.06, 130.82, 130.76, 130.57, 130.45, 129.72, 128.60, 128.52, 128.03, 127.68, 127.41, 127.08, 80.83, 80.73, 78.26, 73.45, 73.21, 70.91, 64.30, 63.91, 62.68, 62.14, 59.62, 59.45, 58.68, 44.74, 38.22, 37.35, 34.39, 33.34, 32.15, 30.59, 29.65, 29.30, 28.94, 28.54, 25.87, 25.54, 25.41, 25.25, 18.61, 16.28, 16.25, 16.20, 14.20 (one sp^2 and seven sp^3 carbons are not located).

6.4.5 Synthesis of new right head 140

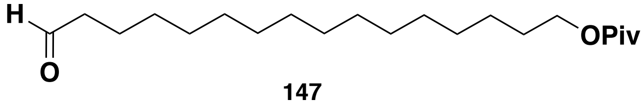






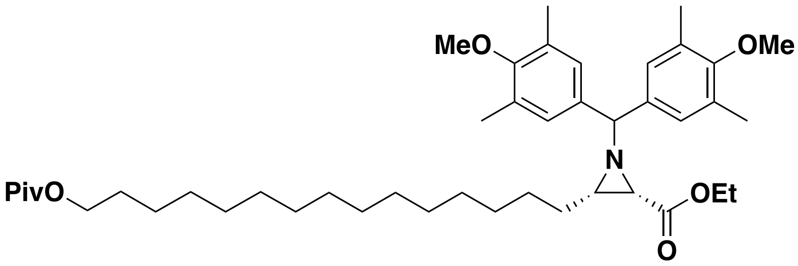
146

16-Hydroxyhexadecyl pivalate **146**: *n*BuLi (2.5 M, 1.1 mL, 2.67 mmol, 2.0 equiv.) was slowly added to the solution of **145**[120] (0.52 g, 2.00 mmol, 1.00 equiv.) in THF (20.0 mL) at 0°C under nitrogen. After the reaction was stirring for 30 minutes, it was added the solution of PivCl (0.16 mL, 2.0 mmol, 1.00 equiv.) in THF (8.00 mL). The mixture was then allowed to warm to the room temperature and was refluxing for 8 hours. The reaction was quenched by water (5.0 mL) and extracted by dichloromethane (10.0 mL x 2). The combined organic layer was washed with brine, dried over $NaSO_4$ and concentrated under rotary evaporation. Flash chromatography (silica gel, 20 mm x 160 mm, hexane/EtOAc 4:1) afforded the **146** (0.22 g, 0.96 mmol, 48%) as a colorless oil (35% of starting **145** was recovered after the column). R_f= 0.4 (7:3 hexane/EtOAc). Specific Rotation: $[\alpha]_D^{20}$= -35.8° (*c* 2.0, $CHCl_3$). Spectral data for **146**: ^1H NMR (500 MHz, Chloroform-*d*) δ 4.01 (t, *J* = 6.6 Hz, 2H), 3.59 (t, *J* = 6.7 Hz, 2H), 1.61 – 1.55 (dt, *J* = 8.2, 6.5 Hz, 2H), 1.52 (dt, *J* = 8.2, 6.5 Hz, 2H), 1.23 (d, *J* = 11.2 Hz, 22H), 1.16 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.69, 64.46, 62.97, 38.70, 32.77, 29.64, 29.60, 29.58, 29.53, 29.49, 29.43, 29.20, 28.57, 27.17, 25.88, 25.74 (four sp^3 carbons are not located); IR (thin film) 3300br, 2919vs, 2849vs, 1724vs, 1473s, 1286s, 1171s, 1076s cm^{-}1;HRMS (ESI-TOF) *m/z* found 343.3213 ($[M+H]^+$); calcd. 342.3212 for $C_{21}H_{43}NO_3$.



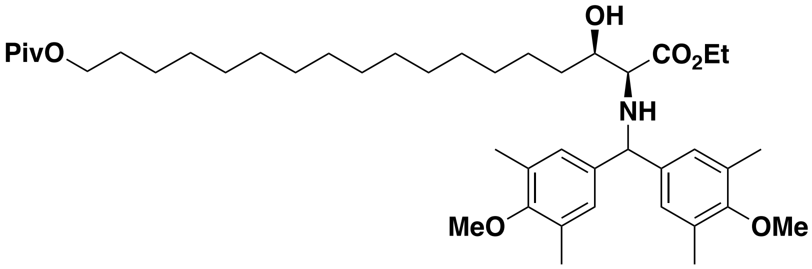
147

16-Oxohexadecyl pivalate **147**: Following the *General procedure for Swern oxidation of alcohol* (6.3.2), the reaction of **146** (0.32 g, 0.96 mmol, 1.00 equiv.), oxalyl chloride (0.1 mL, 1.2 mmol,1.25 equiv.), DMSO (0.17 mL, 2.50 mmol, 2.60 equiv.) and triethylamine (0.34 mL, 2.5 mmol, 2.60 equiv.) in dichloromethane (2.40 mL x 2) afford the product **147** (0.33 g, 0.96 mmol, 100%) as a light yellow oil. R_f= 0.6 (7:3 hexane/EtOAc). Spectral data for **147**: ^1H NMR (500 MHz, Chloroform-*d*) δ 9.76 (d, *J* = 2.0 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 2.42 (td, *J* = 7.4, 1.9 Hz, 2H), 1.66 – 1.57 (m, 4H), 1.34 – 1.22 (m, 22H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 203.01, 178.67, 64.46, 43.92, 38.72, 29.62, 29.56, 29.51, 29.42, 29.35, 29.22, 29.16, 28.60, 27.20, 25.90, 22.07 (three sp^3 carbons are not located); IR (thin film) 3435br, 2922vs, 2852s, 1728vs, 1480s, 1397s, 1284vs, 1158vs, 1034s cm-1; HRMS (ESI-TOF) *m/z* found 341.3052 [(M+H)$^+$; calcd. 341.3056 for $C_{21}H_{41}O_3$.



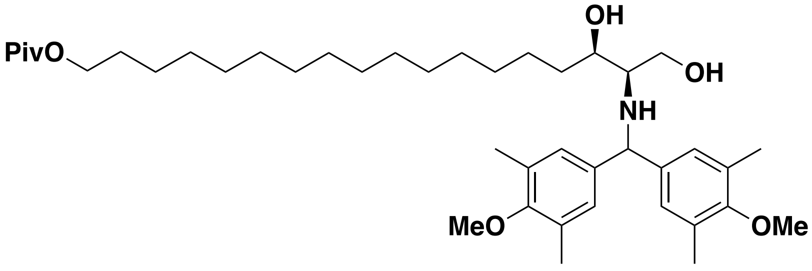
148

15-((2*S*,3*S*)-1-(Bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(2-ethoxy-2-oxoacetyl)aziridin-2-yl)pentadecyl pivalate **148**: To a flame-dried 50mL Schlenk flask equipped with a magnetic stir bar and filled with nitrogen gas was added (*R*)-VAPOL (97.5 mg, 0.18 mmol, 10 mol%), $B(OPh)_3$ (0.16 g, 0.54 mmol, 30 mol%) and MEDAM-NH_2 **64'** (0.54 g, 1.8 mmol, 1.00 equiv.) and 3.6 mL toluene. The flask was sealed. The resulting mixture was heated at 80°C for 1h. Then it was cooled to room temperature. A nitrogen flow was introduced to the neck of the flask to avoid absorption of moisture. The flask was opened, and 4Å (0.54 g) molecular sieve, aldehyde **147** (0.65 g, 1.90 mmol, 1.05 equiv.) and ethyl diazoacetate (0.76 mL, 7.20 mmol, 4.0 equiv.) was successively added at room temperature. The flask was sealed again. The resulting reaction mixture was stirred at -10°C for 16 hours. Then it was warmed up to room temperature and diluted with 5 mL hexane, filtered through celite pad in sintered glass funnel. The filtrate was concentrated under reduced pressure and followed by exposure to high vacuum for 1h. The crude oil was purified by silica gel column chromatography, 8:2 hexane/EtOAc as eluent (R_f = 0.4 in 7:3 hexane/EtOAc), affording the product (1.30 g, 1.80 mmol, 95%) as a yellow oil. Specific Rotation: $[\alpha]_D^{20}$= -31.6° (*c* 2.0, CH_3Cl). Spectral data for **148**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.11 (s, 2H), 7.02 (s, 2H), 4.27 – 4.13 (m, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.68 (d, *J* = 6.4 Hz, 6H), 3.41 (s, 1H), 2.24 (s, 12H), 2.22 (d, *J* = 6.8 Hz, 1H), 1.97 (td, *J* = 7.0, 5.9 Hz, 1H), 1.65 – 1.59 (m, 3H), 1.37 – 1.21 (m, 23H), 1.20 (s, 9H), 1.15 – 1.05 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.68, 169.71, 156.12, 155.78, 138.17, 137.76, 130.50, 130.44, 128.10, 127.39, 64.48, 60.69, 59.59, 53.44, 47.02, 43.57, 38.73, 29.68, 29.64, 29.58, 29.53, 29.25, 29.19, 28.61, 27.95, 27.26, 27.21, 25.92, 16.19, 16.14, 14.36 (three sp^3 carbons are not located); IR (thin film) 3020br, 1718s,1264s, 1214vs, 747vs cm$^-$1; HRMS (ESI-TOF) *m/z* found 708.5169 ([M+H]$^+$); calcd. 708.5203 for $C_{44}H_{70}NO_6$. The optical purity of **148** was determined to be 95% *ee* by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/2-propanol at 245 nm, flow-rate 0.7 mL/min); Retention times: R_t = 4.2 min as minor enantiomer] and R_t = 5.3 min as major enantiomer.



149

Ethyl (2*S*,3*R*)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxy-18-(pivaloyloxy)octadecanoate **149**: To a flame-dried 500 mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added the aziridine **148** (0.15 g 0.20 mmol, 1.00 equiv.), CH_2Cl_2 (2.00 mL, 0.1 M) and CF_3COOH (15.4 μL, 0.20 mmol, 1.00 equiv.). The flask was equipped with a condenser, sealed with a septum to which a nitrogen balloon was attached via a needle, and stirred overnight at room temperature. Then the volatile was removed under reduced pressure. 0.68 mL 15:2 EtOH/H_2O solution with NaOH (7.00 mg, 7.82 mmol, 1.00 equiv.) was added to the flask and stirred at room temperature for 0.5 hours. Thereafter, ethanol was removed under reduced pressure. The residue was extracted with ethyl acetate (1.0 mL x 3), the combined organic layers were dried over $NaSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, 4:1 hexane/EtOAc as eluent ($R_f = 0.2$), affording the product (72.5 mg, 0.10 mmol, 50%, 10:1 regioselectivity) as a colorless oil. Specific Rotation: $[\alpha]_D^{20}$=-15.5 (*c* 1.0, CH_2Cl_2). Spectral data for **149**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.00 (s, 2H), 6.96 (s, 2H), 4.58 (s, 1H), 4.25 – 4.14 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 3.69 (s, 3H), 3.67 (s, 3H), 3.63 (q, *J* = 6.0 Hz, 1H), 3.06 (d, *J* = 5.9 Hz, 1H), 2.25 (s, 6H), 2.24 (s, 6H), 1.65 – 1.58 (m, 2H), 1.52 – 1.46 (m, 2H), 1.44 – 1.39 (m, 1H), 1.36 – 1.22 (m, 26H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.68, 174.08, 156.06, 156.03, 139.20, 137.28, 130.83, 130.74, 127.84, 127.42, 72.41, 64.78, 64.47, 63.71, 60.94, 59.59, 38.73, 33.77, 29.67, 29.64, 29.59, 29.57, 29.52, 29.23, 28.60, 27.20, 25.91, 25.63, 16.28, 16.21, 14.33 (three sp^3 carbons are not located); IR (thin film) 3439br, 2925vs, 2853s, 1728vs, 1481s, 1152vs, 1019s, 750s cm$^-$1; HRMS (ESI-TOF) *m/z* found 726.5286 ($[M+H]^+$); calcd. 726.5309 for $C_{44}H_{72}NO_7$.



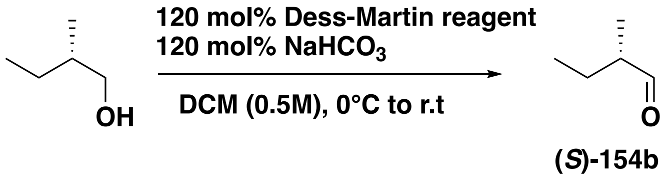
150

(16*R*,17*R*)-17-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-16,18-dihydroxyoctadecyl pivalate **150**: To an oven-dried 5 mL round bottom flask filled with nitrogen were added **149** (0.18 g, 0.24 mmol, 1.00 equiv.) and THF (2.40 mL). After the solution was cool down to 0°C, $LiAlH_4$ (14.0 mg, 0.37 mmol, 1.5 equiv.) was slowly added.

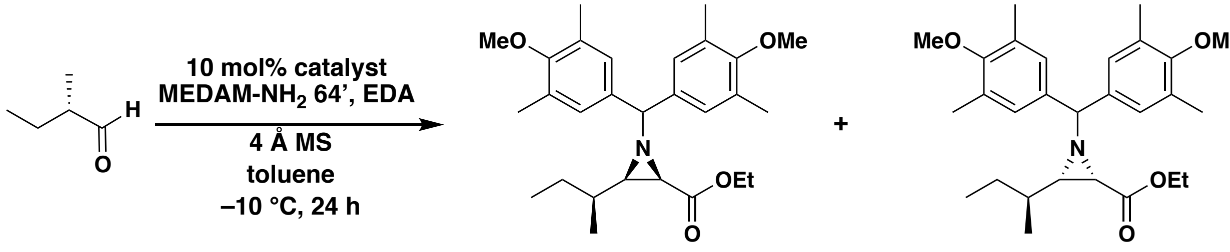
The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 1 hour. It was quenched by addition of H_2O (0.5 mL), followed by addition of aq. NaOH (15%, 0.1 mL) and then another two portions of H_2O (0.50 mL x 2). After the mixture was vigorously stirred at room temperature for 30 min, it became a white emulsion, which was filtered through a celite pad. The celite pad was washed with ethyl acetate several times until TLC indicated there was no product in the rinse. The combined organic solution was concentrated to give the crude product **150** (60.6 mg, 0.09 mmol, 37%) as an opaque oil, which could be directly used into the next step without further purification). R_f = 0.10 (hexane/EtOAc 7:3). Spectral data for **150**: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.03 (d, *J* = 7.2 Hz, 4H), 4.81 (s, 1H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.77 (dd, *J* = 12.1, 4.6 Hz, 1H), 3.68 (s, 6H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.69 (br, NH), 2.50 (q, *J* = 3.9 Hz, 1H), 2.25 (s, 12H), 1.59 (dt, *J* = 28.0, 7.0 Hz, 4H), 1.27 (m, 24H), 1.20 (s, 9H). (ESI-TOF) *m/z* found 684.5193 ($[M+H]^+$); calcd. 684.5203 for $C_{42}H_{70}NO_6$.

6.5 Experimental part for chapter Five

6.5.1 Asymmetric catalytic multi-component aziridination reaction of chiral aldehyde (*S*)-154b and 156



(*S*)-2-Methylbutanal **154b**: To a flame-dried 25 mL round bottom flask flashed with nitrogen and equipped with a stir bar was added the (*S*)-2-methylbutan-1-ol (5.40 mL, 50.0 mmol) and freshly distilled CH_2Cl_2 (100 mL). To the resulting clear solution was added Dess-Martin periodinane (25.5 g, 60.0 mmol, 1.2 equiv). The turbid reaction mixture was stirred for 30 min at 0°C under nitrogen atmosphere followed by adding $NaHCO_3$ (5.04 g, 1.2 equiv). The resulting mixture was allowed to warm to the room temperature and stirred for another 2 hours. The reaction was quenched by 1:1 mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$ solution. The organic layer was extract with DCM twice, washed by $NaHCO_3$ and dried over $MgSO_4$. The solvents were removed in *vacuo* under 0°C. Vacuum distillation the crude mixture provided the pure (*S*)-2-methylbutanal **5d** as a colorless liquid in 50% yield (2.15 g, 25.0 mmol). Spectral data for **(*S*)-154b**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.09 (d, *J* = 7.5 Hz, 3H), 1.39-1.47 (m, 1H), 1.71-1.77 (m, 1H), 2.25-2.29 (m, 1H), 9.64 (d, 1H). All spectroscopic properties matched those previously described.[121]

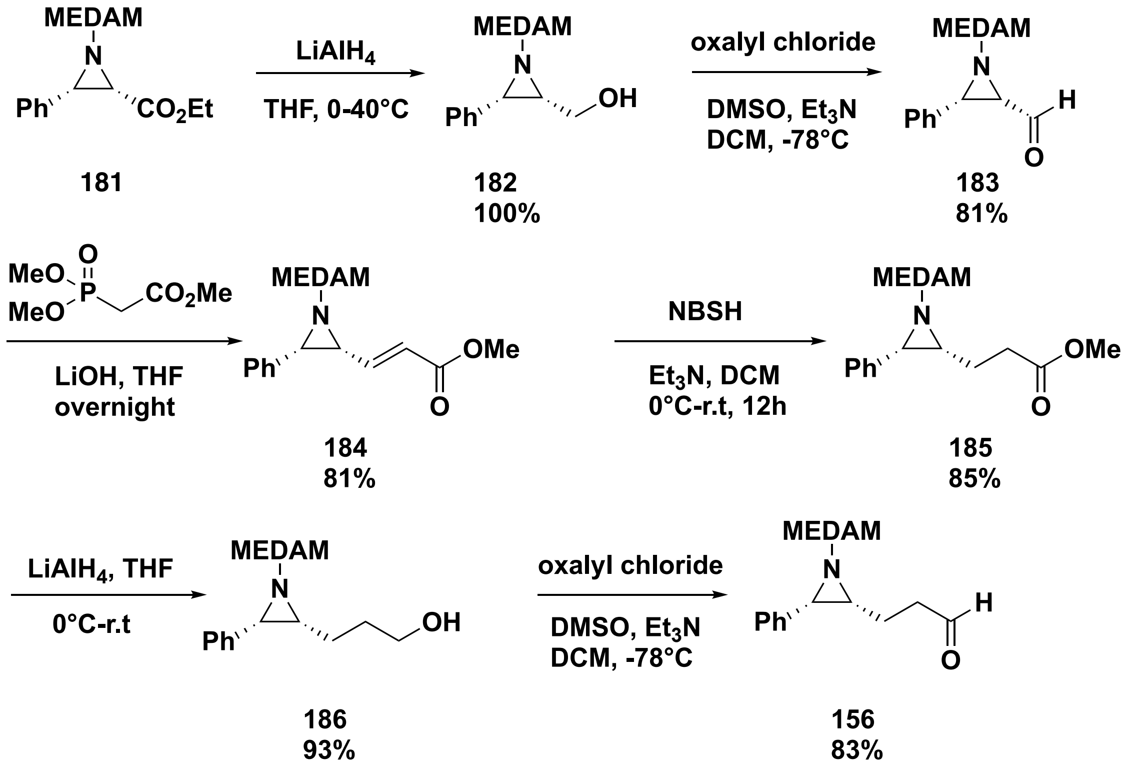


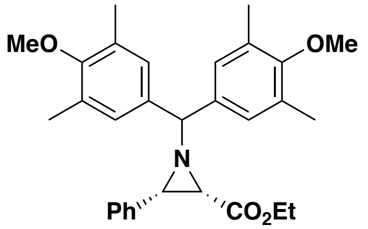
(*S*)-154b **(*2R, 4S*)-155b** **(*2S, 4S*)-155b'**

General Procedure for Multicomponent Aziridination - Illustrated for the Preparation of ethyl (2*R*,3*R*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-*sec*-butyl)aziridine-2-carboxylate **155b:** To a 50 mL flame-dried single-necked round bottom flask equipped with a stir bar and filled with nitrogen was added (*S*)-*t*Bu-VANOL (0.22 g, 0.40 mmol, 0.1 equiv.)， $B(OPh)_3$ (0.35 g, 1.20 mmol, 0.30 equiv.) and MEDAM amine **64'** (1.20 g, 4.00 mmol, 1.00 equiv.). Dry toluene (8.0 mL) was added under an nitrogen atmosphere to dissolve the reagents. The flask was fitted with a rubber septum and a nitrogen balloon. The reaction mixture was stirred at room temperature for 1 hour. Thereafter, 4Å molecular

Sieves (1.20 g, freshly flame-dried) was added followed by the addition of the **(*S*)-154** (2.40 mL in toluene, 4.80 mmol, 1.20 equiv.). To this solution was rapidly added ethyl diazoacetate (EDA) (1.93 mL, 16.0 mmol, 4.0 equiv.). The resulting mixture was stirred for 24 hours at -40°C. The reaction was diluted by addition of hexane (50 mL). The reaction mixture was then filtered through a Celite pad to a 250 mL round bottom flask. The reaction flask was rinsed with EtOAc (25.0 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as yellow oil. (*2R ,4S*)-**155b** and (*2S ,4S*)-**155b'** with a 96:4 diastereomeric ratio. Purification of the crude aziridines by neutral alumina chromatography (silica gel column, 10:1 hexanes/EtOAc as eluent, gravity column) afforded an inseparable mixture of aziridines **155b** and **155b'** as a viscous liquid in 95% isolated yield (1.72 g, 3.80 mmol). The diastereomeric ratio of (*2R ,4S*)-**155b** to (*2S ,4S*)-**155b'** was determined to be 96:4 by ^{1} H-NMR with Ph_3CH as the internal standard. R_f = 0.70 (3:1 hexanes/EtOAc); ^{1} H-NMR (500 MHz, $CDCl_3$) δ 0.48 (d, *J* = 5 Hz, 3H), 0.78 (t, J = 5.0 Hz, 3H), 1.11-1.14 (m, 1H), 1.25 (t, J = 5.0 Hz, 3H), 1.26 (m, 1H), 1.39-1.42 (m, 1H), 1.71 (dd, J = 10.0, 5.0 Hz, 1H), 2.20 (d, J = 5.0 Hz, 1H), 2.23 (s, 6H), 2.24 (s, 6H), 3.37 (s, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 4.16-4.24 (m, 2H), 6.91 (s, 2H), 7.11 (s, 2H); 13 C-NMR (125 MHz, CDCl3) δ 11.23, 14.34, 16.08, 16.19, 17.65, 27.46, 33.37, 44.14, 53.08, 59.61, 59.66, 60.66, 77.64, 127.30, 128.60, 130.37, 130.48, 137.66, 138.09, 155.70, 156.27, 169.91; IR (thin film) 2958vs, 1744s, 1438s, 1275vs, 1260vs, 1017s cm-1 ; HRMS (ESI-TOF) m/z 476.2769 [(M+Na+); calcd. for C28 H39 NO4 Na: 476.2777]; $[\alpha]^{20}$ +70.1 (c 1.0, CH_2Cl_2) on 96:4 dr material (NMR).

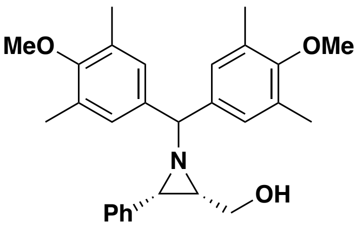
Ethyl (2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-*sec*-butyl)aziridine-2-carboxylate **155b'**: Aldehyde (*S*)-**154b** (1.62 mL, 2 M in toluene, 3.24 mmol, 1.20 equiv.), amine **64'** (814 mg, 2.70 mmol, 1.00 equiv.) and EDA (1.29 mL, 10.8 mmol, 4.0 equiv.) were reacted according to the general procedure E with (R)-*t*Bu-VANOL (145 mg, 0.270 mmol) as ligand and $B(OPh)_3$ (235 mg, 0.810 mmol) at –40 °C for 48 hours to afford aziridines (2*S* ,4*S*)-**155b'** and (2*R* ,4*S*)-**155b** with 96:4 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (silica gel, 10:1 hexanes/EtOAc as eluent, gravity column) afforded an inseparable mixture of aziridines **155b'** and **155b** as a viscous liquid in 90% isolated yield (1.10 g, 2.43 mmol). The diastereomeric ratio of (*2S ,4S*)-**155b'** and (*2R ,4S*)-**155b** was determined to be 96:4 by ^{1}H-NMR with Ph_3CH as the internal standard. R_f = 0.70 (3:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.56 (t, J = 5.0 Hz, 3H), 0.76 (d, J = 5.0 Hz, 3H), 1.03-1.09 (m, 1H), 1.25 (t, J = 5.0 Hz, 3H), 1.27 (m, 1H), 1.35-1.42 (m, 1H), 1.71 (dd, J = 10.0, 5.0 Hz, 1H), 2.20 (d, J = 5.0 Hz, 1H), 2.23 (s, 6H), 2.24 (s, 6H), 3.38 (s, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 4.14-4.27 (m, 2H), 6.98 (s, 2H), 7.11 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 10.09, 14.35, 15.78, 16.05, 16.18, 26.91, 33.15, 43.61, 52.65, 59.61, 59.65, 60.67, 77.53, 127.29, 128.57, 130.38, 130.47, 137.56, 138.10,155.69, 156.27, 169.76; IR (thin film) 2960vs, 1750s, 1442s, 1275vs, 1260vs, 1038s cm-1 ; HRMS (ESI-TOF) m/z 476.2770 [(M+Na+); calcd. for C28 H39 NO4 Na:476.2777]; $[\alpha]^{20}$ –99.5 (c 0.4, CH_2Cl_2) on 96:4 dr material (NMR).





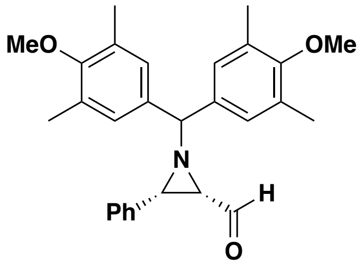
181

Ethyl (2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate **181**: Benzaldehyde **63a** (1.75 mL, 17.4 mmol, 1.05 equiv.) was reacted according to *the general procedure for multi-aziridination* by using (*S*)-VAPOL (0.45 g, 0.83 mmol, 0.05 equiv.) and EDA (2.10 mL, 20.4 mmol, 1.20 equiv.) at room temperature. Purification of the crude aziridine by silica gel chromatography (1:9 EtOAc/ hexanes as eluent, gravity column) afforded pure cis-aziridine **181** as a white solid (m.p 107-108 ºC on 98% *ee* material) in 92 % isolated yield (7.30 g, 15.4 mmol). The optical purity of **181** was determined to be 98 % *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow rate: 0.7 mL/min): retention times; Rt = 9.26 min (major enantiomer, 7) and Rt = 12.52 min (minor enantiomer **181**). These HPLC data match those previously reported for this compound. Spectral data for **181**: Rf = 0.42 (1:9 EtOAc/hexane); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.09 (t, J = 6.85 Hz), 2.32 (s, 6H), 2.39 (s, 6H), 2.75 (d, J = 6.85 Hz), 3.29 (d, J = 6.85 Hz), 3.71 (s, 3H), 3.78 (s, 3H), 3.85 (s, 1H), 4.06-4.02 (m, 2H), 7.29 (s, 3H), 7.36-7.33 (m, 3H), 7.38 (s, 3H), 7.54 (d, J = 7.34 Hz). ^{13}C (CDCl3, 126 MHz) δ 14.01, 16.16, 16.22, 46.26, 48.20, 59.52, 59.58, 60.47, 77.04, 127.21, 127.41, 127.70, 127.80, 127.85, 130.59, 130.60, 135.33, 137.79, 137.96, 155.95, 156.10, 168.01. Both spectral and HPLC data match those previously reported for this compound.[45]



182

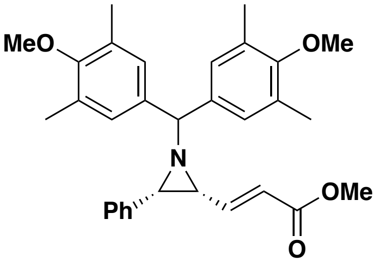
((2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl) methanol **182:** To a solution of **181** (7.40 g, 15.6 mmol, 1.00 equiv.) in 155 mL THF at 0 °C was added a solution LAH (0.94 g, 23.50 mmol, 1.5 equiv.) in 39 mL dry THF via cannula under N$_2$ atmosphere. The resulting reaction was allowed to stirred to room temperature and then at 40°C overnight. The reaction was quenched by the addition of sodium potassium tartrate 1.0 mL (Sat.) and stirred for 30 min. The aqueous layer was then extracted with Et$_2$O (3 x 10.0 mL). The combined organic layer was dried with NaSO$_4$, filtered, concentrated and purified by silica gel chromatography (1:4 EtOAc/Hexane as eluent, gravity column) afforded pure **182** (5.30 g, 11.9 mmol) as colorless oil with 79% yield. Spectral data for **182**: R_f = 0.4 (3:7 EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.16 (td, J1 = 6.36 Hz, J2 = 5.87 Hz, 1H), 2.16 (td, J1 = 6.36 Hz, J2 = 5.87 Hz, 1H), 2.21 (s, 6H), 2.29 (s, 6H), 2.94 (d, *J* = 6.36 Hz, 1H), 3.35-3.31 (m, 1H), 3.44-3.40 (m, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.76 (s, 1H), 7.13 (s, 4H), 7.24-7.21 (m, 1H), 7.30 (t, *J* = 7.83 Hz, 2H), 7.39 (d, *J* = 7.83 Hz, 2H); IR (thin film) 3250br, 2930vs, 1480s, 1221s, cm^{-1}; HRMS (ESI-TOF) *m/z* 432.2533 [(M+H$^+$); calcd. for $C_{28}H_{34}NO_3$: 432.2539]; $[\alpha]^{20}$ +106.0 (c 0.2, $CHCl_3$) on 98% *ee* material (HPLC).



183

(2S,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carbaldehyde **183**: To a stirred solution of oxalyl chloride (1.34 mL, 15.3 mmol, 1.25 equiv.) in dichlommethane (25.0 mL) at -78 ° under nitrongen was added DMSO (2.23 mL, 31.8 mmol, 2.60 equiv). After 15 rain, a solution of the corresponding **182** (5.27g, 12.2 mmol, 1.0 equiv) in dichloromethane (25.0 mL) was added. The mixture was stirred for 30 min and triethylamine (4.36 mL, 31.8 mmol, 2.60 equiv.) was added and the resulting mixture was then separated between dichloromethane and saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$), concentrated and purified by by silica gel chromatography (3:17 EtOAc/Hexane as eluent, gravity column) afforded pure **183** (4.24 g, 9.88 mmol) as white foam (mp 49 ºC) with 81% yield. Spectral data for **183**: R*f* = 0.4

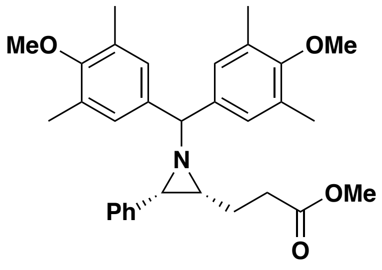
(3:7 EtOAc/Hexane); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.25 (s, 6H), 2.27 (s, 6H), 2.46-2.44 (m, 1H), 3.67 (s, 3H), 3.32 (d, *J* = 6.36, 1H), 3.70 (s, 3H), 3.75 (s, 1H), 7.11 (s, 3H), 7.17 (s, 3H), 7.25-7.24 (m, 1H), 7.30 (t, *J* =6.85, 2H), 7.44 (d, *J* = 6.85 Hz, 2H), 9.05 (s, H). ^{13}C (CDCl$_3$, 126 MHz) 16.26, 16.29, 45.76, 49.43, 51.18, 59.60, 76.84, 127.29, 127.30, 127.49, 127.63, 128.39, 130.82, 130.90, 135.04, 137.40, 137.75, 165.15, 165.17, 201.05; IR (thin film) 3320br, 2945vs, 1716s, 1483s, 1221vs, 1143s, 1012s cm^{-1}; HRMS (ESI-TOF) *m/z* 430.2379 [(M+H$^+$); calcd. for $C_{28}H_{32}NO_3$: 432.2382]; [α]^{20} -35.2 (c 1.0, CH_2Cl_2) on 98% ee material (HPLC).



184

((2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)acrylate **184:** A suspension of **183** (3.00 g, 7.00 mmol, 1.00 equiv.), phosphonoacetate (1.24 mL, 7.70 mmol, 1.10 equiv.) and lithium hydroxide monohydrate (0.32 g, 7.70 mmol, 1.10 equiv.) in dry THF (70.0 ml) was stirred at room temperature under argon atmosphere until disappearance of starting material. The resulting reaction mixture was washed by brine, dried over NaSO$_4$, concentrated and purified by by silica gel chromatography (3:17 EtOAc/Hexane as eluent, gravity column) afforded pure **184** (3.00 g, 6.16 mmol) as a white foam (m.p 55 ºC) with 88% yield. Spectral data for **184**: R$_f$ = 0.4 (3:7 EtOAc/Hexane); ^{1}H-NMR (500 MHz, CDCl$_3$): δ 2.20 (s, 6H), 2.25 (s, 6H), 2.51 (m, 1H), 3.11 (d, *J* = 6.87 Hz, 1H), 3.63 (s, 3H), 3.64 (s, 3H), 3.69 (s, 3H), 3.71 (s, 1H), 5.96 (d, *J* = 15.65, 1H), 6.53 (dd, *J$_1$* = 15.65 Hz, *J$_2$* = 7.83 Hz, 1H), 7.07 (s, 2H), 7.08 (s, 2H), 7.28-7.19 (m, 3H), 7.32

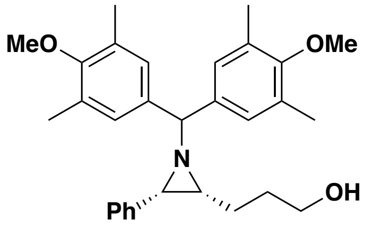
(d, *J* = 6.85 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 16.20, 16.20, 16.27, 49.84, 47.11, 51.40, 59.54, 59.60, 77.73, 123.15, 127.01, 127.46, 127.69, 127.72, 128.02, 130.55, 130.57, 136.04, 138.01, 138.22, 145.02, 155.88, 155.94, 166.30; IR (thin film) 2932vs, 1780s, 1620s, cm^{-1}; HRMS (ESI-TOF) *m/z* 486. 2647 [(M+H$^+$); calcd. for $C_{31}H_{36}NO_4$: 486.2644]; [α]^{20} -17.0 (c 0.3, CH_2Cl_2) on 98% ee material (HPLC).



185

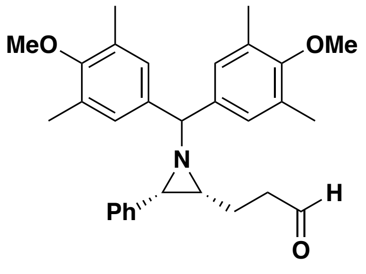
Ethyl 3-((2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)propanoate **185:** To a solution of **184** (3.00 g, 6.20 mmol, 1.00 equiv.) in dry CH_2Cl_2 (20.3 mL) were added NBSH (5.40 g, 24.8 mmol, 4.00 equiv.) and triethylamine (6.90 mL, 49.6 mmol, 8.00 equiv.) at 0 °C. The reaction mixture was stirred from 0 °C to RT for 12 h. The mixture became homogenous after 4h, and the reaction mixture was stirred for another 8 h. The reaction was quenched with aqueous saturated sodium bicarbonate (60 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 60.0 mL). The combined organic layers were dried over $NaSO_4$, concentrated and purified by silica gel chromatography (3:17 EtOAc/Hexane as eluent, gravity column) afforded pure **185** (2.56 g, 5.27 mmol) as colorless oil with 85% yield. Spectral data for **185**: R_f = 0.4 (3:7 EtOAc/Hexane); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.50 (m, 1H), 1.51 (m, 1H), 1.95- 1.91 (m, 2H), 2.07- 1.95 (m, 1H), 2.20 (s, 3H), 2.30 (s, 3H), 2.76 (d, *J* = 6.36 Hz, 1H), 3.51 (s, 3H), 3.55 (s, 1H), 3.65 (s, 3H), 3.72 (s, 3H), 7.10 (s, 2H), 7.13 (s, 2H), 7.22 (t, *J* = 7.34 Hz, 1H), 7.31 (t, *J* = 7.34, 2H), 7.41 (d, *J* = 7.34 Hz, 2H); ^{13}C-NMR (126

MHz, $CDCl_3$): δ 16.22, 16.25, 22.91, 31.26, 45.73, 47.03, 51.33, 59.55, 59.64, 78.16, 126.51, 127.54, 127.80, 127.84, 127.99, 130.33, 130.51, 137.36, 138.50, 139.12, 155.68, 156.02, 173.68; IR (thin film) 2924s, 1736vs, 1485s, 1221s, 1016s cm^{-1}; $[\alpha]^{20}$ +72.8 (c 1.0, CH_2Cl_2) on 98% ee material (HPLC).



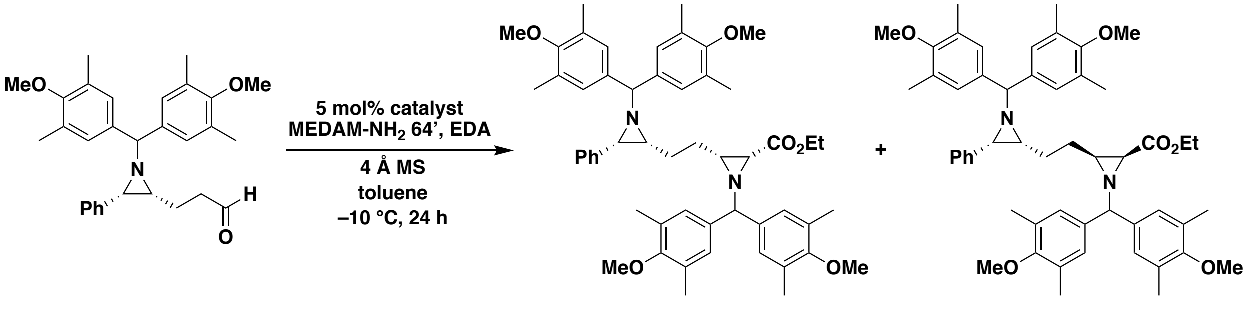
186

3-((2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)propan-1-ol **186:** To a solution of **185** (2.80 g, 5.74 mmol, 1.00 equiv.) in 57.0 mL THF at 0 °C was added a solution LAH (0.34 g, 8.60 mmol, 1.50 equiv.) in 14 mL dry THF via cannula under N_2 atmosphere. The resulting reaction was allowed to stirred to room temperature and then at 40°C overnight. The reaction was quenched by the addition of sodium potassium tatrate 1 mL (Sat.) and stirred for 30 min. The aqueous layer was then extracted with Et_2O (3 x 10 mL). The combined organic layer was dried with $NaSO_4$, filtered, concentrated and purified by silica gel chromatography (1:4 EtOAc/Hexane as eluent, gravity column) afforded pure **186** (1.93 g**,** 4.19 mmol) as a white foam (mp 45 ºC) with 73% yield. Spectral data for **12**: R_f = 0.4 (3:7 EtOAc/Hexane); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.27-1.24 (m, 2H), 1.35-1.29 (m, 2H), 1.89 (d, $J_1 = J_2$ = 6.36 Hz, 1H), 2.21 (s, 6H), 2.31 (s, 6H), 2.75 (d, J = 6.36 Hz, 1H), 3.27 (t, J = 5.87 Hz, 2H), 3.59 (s, 1H), 3.65 (s, 3H), 3.72 (s, 3H), 7.14 (s, 2H), 7.15 (s, 2H), 7.22 (t, J = 7.34 Hz, 1H), 7.31 (t, J = 7.34, 2H), 7.42 (d, J = 7.34, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 16.24, 16.27, 23.54, 30.01, 46.55, 46.96, 59.56, 59.68, 62.09, 78.26, 126.46, 127.61, 127.82, 127.82, 128.04, 130.34, 130.48, 138.60, 137.62, 139.16, 155.68, 155.97; IR (thin film) 3148br, 2932vs, 1483s, 1221s, 1138s cm^{-1}; HRMS (ESI-TOF) *m/z* 460.2855 [(M+H$^+$); calcd. for $C_{30}H_{38}NO_3$: 460.2852]; [α]^{20} +78.5 (c 1.0, CH_2Cl_2) on 98% ee material (HPLC).



156

3-((2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)propanal **156**: Alcohol **186** (1.93 g, 4.19 mmol) was reacted according to the general Procedure C described above. Purification of 13 by silica gel chromatography (3:17 EtOAc/Hexane as eluent, gravity column) afforded pure **156** (1.70 g, 3.71 mmol**)** as colorless oil (not stable, should be directly used in next step) with 89% yield. Spectral data for **156**: R_f = 0.4 (3:7 EtOAc/Hexane); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.45-1.38 (m, 1H), 1.64-1.59 (m, 1H), 2.10-2.04 (m, 2H), 2.20-2.11 (m, 1H), 2.28 (s, 6H), 2.39 (s, 6H), 2.86 (d, *J* = 6.36 Hz), 3.65 (s, 1H), 3.70 (s, 3H), 3.77 (s, 3H), 7.18 (s, 2H), 7.23 (s, 2H), 7.27 (t, *J* = 7.34, 1H), 7.37 (t, *J* = 7.83, 2H), 7.50 (d, *J* = 7.34, 2H), 9.38 (s, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 16.23, 16.45, 20.07, 41.48, 45.56, 47.27, 59.69, 59.56, 78.15, 126.59, 127.77, 127.87, 128.18, 130.35, 130.59, 137.21, 138.26, 139.13, 155.69, 156.10, 201.96;

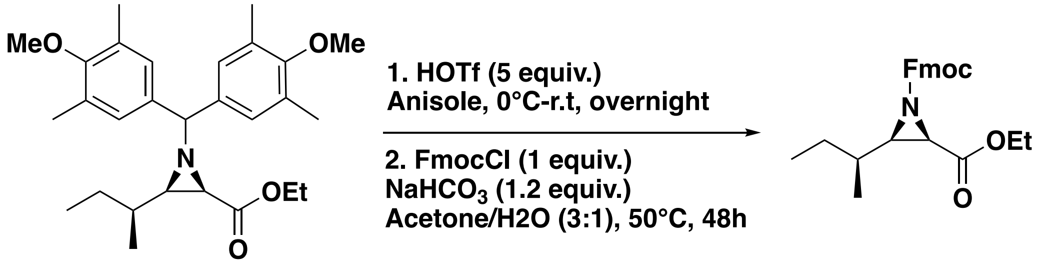


156 **155c** **155c'**

Ethyl (2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(2-((2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)ethyl)aziridine-2-carboxylate **155c** :Aldehyde **156** (95.0 mg, 0.20 mmol) was reacted according to *the general procedure for multi-aziridination* by using (*S*)-VAPOL (5.40 mg, 0.01 mmol) described above except that the addition of aldehyde **156** was carried out at –10 °C followed by the addition of EDA (0.10 mL, 0.80 mmol, 4.00 equiv.) at the same temperature. The reaction was stirred at –10 °C for 24h. Purification of **155c** by silica gel chromatography (3:17 EtOAc/Hexane as eluent, gravity column) afforded pure **155c and 155c'** (0.14 g, 0.17 mmol) as a white foam (m.p 72 ºC) with 78% yield with 95:5 ratios. The ratio of **155c** and **155c'** was determined by comparing the ^{1}H NMR integration of methine protons on the MEDAM group on the nitrogen in the crude reaction mixture. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.86-0.92 (m, 1H), 0.99-1.03 (m, 1H), 1.13-1.19 (m, 1H), 1.20 (t, *J* = 7.5 Hz, 3H), 1.26-1.29 (m, 2H), 1.58 (s, 1H), 1.89 (d, *J* = 10 Hz, 1H), 2.16 (s, 6H), 2.21 (s, 6H), 2.26 (s, 6H), 2.30 (s, 6H), 2.47 (d, *J* = 5 Hz, 1H), 3.08 (s, 1H), 3.32 (s, 1H), 3.62 (s, 3H), 3.67 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 4.12-4.03 (m, 2H), 6.94 (s, 2H), 7.03 (s, 2H), 7.06 (s, 2H), 7.08 (s, 2H), 7.15-7.18 (m, 1H), 7.22-7.26 (m, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.32, 16.17, 16.18, 16.23, 16.31, 24.38, 25.06, 44.14, 45.10, 47.38, 59.52, 59.59, 59.67,59.71, 60.53, 77.49, 78.75, 126.28, 127.17, 127.37, 127.64, 127.79, 128.12, 128.24, 130.27, 130.45, 130.46, 130.52, 137.55, 137.68, 138.30, 138.65, 139.28, 155.58, 155.71, 156.07, 156.25, 169.38; IR (thin film) 2988w, 1601s, 1482s, 1275vs, 1260vs, 764vs cm^{-1}; HRMS (ESI-TOF) *m/z* 825.4849 [(M+H$^+$); calcd. for $C_{53}H_{65}N_2O_6$: 825.4843]; $[\alpha]^{20}$ +91.4 (c 1.0, CH_2Cl_2) on 98% ee material (HPLC).

Ethyl (2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(2-((2*R*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridin-2-yl)ethyl)aziridine-2-carboxylate **155c':** Aldehyde **156** (1.70 g, 3.72 mmol) was reacted according to *the general procedure for multi-aziridination* described above except that the addition of aldehyde **156** was carried out at –10 °C followed by the addition of EDA (1.54 mL, 14.88 mmol, 4.00 equiv.) at the same temperature. The reaction was stirred at –10 °C for 24h. Purification of **14** by silica gel chromatography (3:17 EtOAc/Hexane as eluent, gravity column) afforded pure **155c'** and **155c** (2.65 g, 3.20 mmol) as a white foam (m.p 72 ºC) with 90% yield with 96:4 ratio. The ratio of **155c'** and **155c** was determined by comparing the ^{1}H NMR integration of methine protons on the MEDAM group on the nitrogen in the crude reaction mixture. Spectral data for **155c'**: R*f* = 0.4 (3:7 EtOAc/Hexane); ^{1}H-NMR (500 MHz, CDCl$_3$): δ 1.00-0.91 (m, 1H), 1.10-1.01 (m, 1H), 1.20 (t, J = 7.34 Hz, 3H), 1.34-1.26 (m, 2H), 1.64 (td, J_1 = 6.86, J_2 = 6.36, 1H), 1.71 (td, J_1 = J_2 = 6.36 Hz, 1H), 1.95 (d, J = 6.86 Hz, 1H), 2.16 (s, 6H), 2.18 (s, 6H), 2.22 (s, 6H), 2.27 (s, 6H), 2.57 (d, J = 6.36 Hz, 1H), 3.25 (s, 1H), 3.47 (s, 1H), 3.62 (s, 3H), 3.64 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 4.15-4.07 (m, 2H), 6.87 (s, 2H), 7.02 (s, 2H), 7.05 (s, 2H), 7.06 (s, 2H), 7.19-7.15 (m, 1H), 7.27 (s, 4H). ^{13}C-NMR (126 MHz, CDCl$_3$): δ 14.29, 16.09, 16.18, 16.23, 16.31, 25.24, 25.80, 43.01, 46.59, 46.70, 46.83, 59.54, 59.56, 59.59 (2C), 60.61, 76.91, 78.20, 127.41, 127.63, 127.63, 127.77, 127.86, 127.90, 130.24, 130.35, 130.36, 130.44, 137.53, 137.71, 137.97, 137.97, 139.01, 155.60, 155.73, 155.85, 156.00, 169.46; IR (thin film) 2926vs, 1743s, 1483s, 1221s, 1016s cm^{-1}; HRMS (ESI-TOF) *m/z* 825.4819 [(M+H$^+$); calcd. for $C_{53}H_{65}N_2O_6$: 825.4843]; [α]^{20} +4.2 (c 1.0, CH_2Cl_2) on 98% ee material (HPLC).

6.5.2 Synthesis of β^3-homo-D-allosisoleucine 157 and β^3-L-isoleucine 158

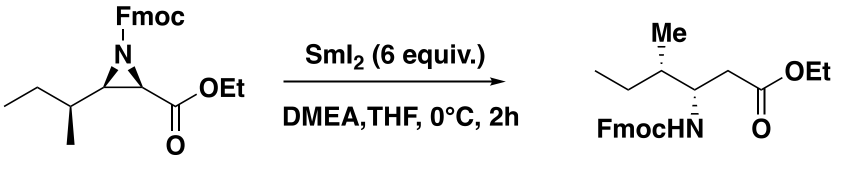


155b **187**

1-((9*H*-fluoren-9-yl)methyl) 2-ethyl (2*R*,3*R*)-3-((*S*)-*sec*-butyl)aziridine-1,2-dicarboxylate **187:** To a flame-dried round-bottom flask were added aziridine **155b** (0.47 g, 1.00 mmol) and anisole (20.0 mL). The resulting mixture was stirred at 0°C for 5 min and followed by adding HOTf (0.50 mL, 5.0 equiv.) dropwisely. After stirring 1 hour under 0°C, the reaction was allowed to stir at room temperature overnight. Sat. $NaHCO_3$ (20.0 mL) was added to quench the reaction and the organic layer was extracted by diethyl ether twice, washed with brine and dried with $NaSO_4$. No further purification was needed after remove all solvents in *vacuo*.

To a 100 mL round-bottomed flask were added crude deprotected aziridine **155b** (0.17g, 1.00 mmol, 1.00 equiv.), $NaHCO_3$ (0.252 g, 2.00 mmol, 2.00 equiv), 20.0 mL of a mixture of acetone, and H_2O (3:1). The mixture was stirred at room temperature for 5 min, and then 9-fluorenylmethylchloroformate (0.26 g, 1.00 mmol, 1.00 equiv) was added. The reaction mixture was then stirred at 50°C for 48 hours. The acetone was removed by rotary evaporation, and the aqueous residue was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with sat aq NaCl, dried over MgSO4, and concentrated by rotary evaporation to afford a yellow oil. Purification by silica-gel chromatography (15 mm Å~ 250 mm, 10:1 hexanes/EtOAc as eluent) afforded **187** as a colorless oil in 66% isolated yield. Spectral data for **187**: R_f = 0.7 (1:3 EtOAc/hexanes)

^{1}H-NMR (500 MHz, CDCl$_3$) δ 0.81 (t, *J* = 5 Hz, 3H), 1.01 (d, *J* = 10 Hz, 3H), 1.17-1.27 (m, 1H), 1.30 (t, *J* = 5 Hz, 3H), 1.40-1.44 (m, 1H), 2.12 (dd, J_1 = 10 Hz, J_2 = 5 Hz, 1H), 3.09 (d, *J* = 5 Hz, 1H), 4.22-4.27 (m, 3H), 4.44-4.48 (m, 1H), 4.52-4.57 (m, 1H), 7.30-7.34 (m, 2H), 7.39-7.42 (m, 2H), 7.58-7.60 (m, 2H), 7.76 (d, *J* = 5 Hz, 2H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ11.08, 14.22, 17.94, 26.86, 33.15, 40.54, 47.01, 49.30, 61.50, 68.10, 119.95, 119.99, 124.90, 125.02, 127.06, 127.14, 127.81, 127.82, 141.34, 141.47, 143.33, 143.50, 161.92, 167.40; [α]^{20} +50.1 (c 1.0, CH$_2$Cl$_2$); IR (thin film) 3583 (s), 2963 (s), 2924 (s), 1731 (vs), 1451 (s), 1340 (s), 1276 (vs), 1261 (vs), 1199 (s), 1040 (vs) cm^{-}1; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C24H28NO4^{+}, 394.2018; found, 394.2020.

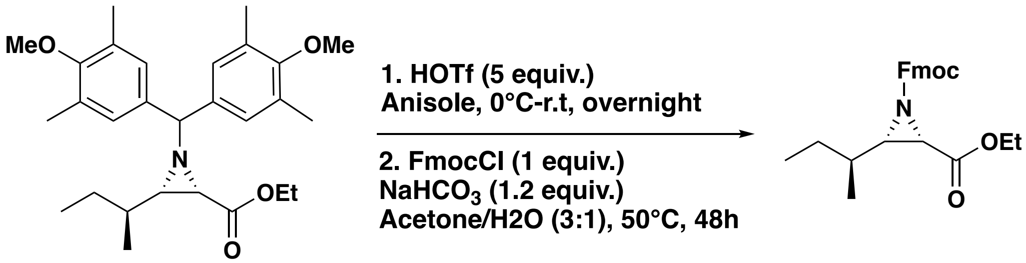


187

157

***N*-Fmoc-β^{3}–homo-D-alloisoleucine ethyl ester**

Ethyl (3R,4S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-methylhexanoate **157:** A 100 mL Schlenk tube equipped with a Teflon-coated magnetic stir bar and a septum was flame-dried under vacuum. The tube was allowed to cool to room temperature and evacuated/backfilled with nitrogen three times. 0.165 g (1.1 0mmol) of “inactive” samarium metal was added, the tube was sealed with a septum and subjected to three evacuation/backfilling cycles. After the final cycle, the tube was left under a positive pressure of nitrogen, and stirring was started at medium to high speed. After the mixture was stirred for 24 hours, 4.5 mL of THF was added, followed by 0.14 g (0.55 mmol) of iodine dissolved in 1mL of THF under nitrogen. The reaction flask was sealed and heated at 60 °C for 18 h resulting in a dark-blue slurry. The slurry was then precooled to 0 °C in an ice bath. Subsequently, to a flame-dried 5 mL round-bottomed flask filled with nitrogen were added **187** (28.0 mg, 0.07 mmol, 1.0 equiv), dry THF (0.70 mL, freshly distilled), and N,N-dimethylethanolamine (0.40 mL, 0.84 mmol, 12.0 equiv). The solution was purged with nitrogen under the surface of the solution for 2 min and transferred to the flask containing the SmI_2 slurry (2.00 mL) dropwise via cannula. Vigorous stirring was maintained during the addition of the aziridine to the SmI_2 slurry. The 5 mL flask was washed with 0.20 mL of degassed THF, and the rinse was also transferred to the reaction flask containing SmI_2. The reaction mixture was stirred at 0 °C for 40 min to 1 h and then quenched by the addition of sat aq $NaHCO_3$ (5.00 mL) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5.00 mL). The combined organic layer was dried with Na_2SO_4 and filtered. The solvent was removed by rotary evaporation to give light-yellow oil. Purification by silica-gel chromatography (18 Å~ 250 mm, 1: 20 ethyl acetate/hexanes as eluent) afforded **157** as colorless oil in 68% isolated yield (19.0 mg, 0.05 mmol). Spectral data for **157**: R_f = 0.6 (1:3 EtOAc/hexanes) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.90-0.94 (m, 6H), 1.11-1.19 (m, 1H), 1.25 (t, *J* = 5 Hz, 3H), 1.42-1.50 (m, 1H), 1.59-1.65 (m, 1H), 2.52 (d, *J* = 5 Hz, 2H), 3.99-4.04 (m, 1H), 4.14 (q, *J* = 5 Hz, 2H), 4.23 (t, *J* = 5 Hz , 1H), 4.36-4.43 (m, 2H), 5.06 (d, 1H, NH), 7.32 (t, *J* = 5 Hz, 2H), 7.41 (t, *J* = 5 Hz, 2H), 7.60 (d, *J* = 5 Hz, 2H), 7.77 (d, *J* = 5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) 11.40, 14.19, 14.60, 26.07, 37.56, 38.11, 47.31, 51.83, 60.64, 66.57, 119.94, 125.07， 127.01, 127.64, 141.30, 143.93, 155.97, 171.68; $[\alpha]^{20}$ +8.0 (c 1.0, CH_2Cl_2); IR (thin film) 3340 (w), 3005 (s), 2981 (s), 1731 (vs), 1538 (s), 1451 (s), 1275 (vs), 1260 (vs), 750 (vs) cm$^-$1; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C24H30NO4$^+$, 396.2175; found, 396.2177.



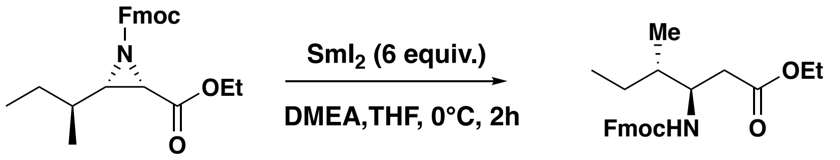
155b’

188

1-((9*H*-fluoren-9-yl)methyl) 2-ethyl (2*S*,3*S*)-3-((*S*)-*sec*-butyl)aziridine-1,2-dicarboxylate **188:** To a flame-dried round-bottom flask were added aziridine **155b’** (0.22 g, 0.50 mmol) and anisole (10.0 mL). The resulting mixture was stirred at 0°C for 5 min and followed by adding HOTf (0.50 mL, 5.00 equiv.) dropwisely. After stirring 1 hour under 0°C, the reaction was allowed to stir at room temperature overnight. Sat. $NaHCO_3$ (20.0 mL) was added to quench the reaction and the organic layer was extracted by diethyl ether twice, washed with brine and dried with $NaSO_4$. No further purification was needed after remove all solvents in *vacuo*.

To a 100 mL round-bottomed flask were added crude deprotected aziridine **155b’** (0.18 g, 1.00 mmol, 1.00 equiv.), $NaHCO_3$ (0.08g, 2.00 mmol, 2.00 equiv.), 20 mL of a mixture of acetone, and H_2O (3:1). The mixture was stirred at room temperature for 5 min, and then 9-fluorenylmethylchloroformate (0.12 g, 1.00 mmol, 1.00 equiv.) was added. The reaction mixture was then stirred at 50°C for 48 h. The acetone was removed by rotary evaporation, and the aqueous residue was extracted with ethyl acetate (10.0 mL x 3). The combined organic layer was washed with sat aq NaCl, dried over MgSO4, and concentrated by rotary evaporation to afford a yellow oil. Purification by silica-gel chromatography ((15 mm Å~ 250 mm, 10:1 hexanes/EtOAc as eluent) afforded **188** as a colorless oil in 50% isolated yield. Spectral data for **188**: R_f = 0.7 (1:3 EtOAc/hexanes) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.81 (d, *J* = 5 Hz, 3H), 0.88 (t, *J* = 5 Hz, 3H), 1.30 (t, *J* = 5

Hz, 3H), 1.35-1.39 (m, 2H), 1.58-1.62 (dd, J_1 = 10 Hz, J_2 = 5 Hz, 1H), 3.06 (d, J = 5 Hz, 1H), 4.21-4.27 (m, 3H), 4.44-4.48 (m, 1H), 4.52-4.57 (m, 1H), 7.29-7.34 (m, 2H), 7.39-7.41 (m, 2H), 7.58-7.60 (m, 2H), 7.76 (d, J = 5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ10.87, 14.23, 15.82, 27.82, 33.44, 39.61, 46.98, 49.07, 61.51, 68.11, 119.94, 119.98, 124.88, 124.98, 127.06, 127.14, 127.81, 127.82, 141.35, 141.47, 143.35, 143.46, 161.77, 167.34; $[\alpha]^{20}$ -15.8 (c 0.35, CH_2Cl_2); IR (thin film) 3005 (s), 2989 (s), 1680 (s), 1462 (s), 1275 (s), 1260 (vs), 750 (vs) $cm^{-}1$; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C24H28NO4^+$, 394.2018; found, 394.2018.



188

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***N*-Fmoc-β³–homo-L-isoleucine ethyl ester**

Ethyl (3*S*,4*S*)-3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-methylhexanoate **158**: A Schlenk tube equipped with a Teflon-coated magnetic stir bar and a septum was flame-dried under vacuum. The tube was allowed to cool to room temperature and evacuated/backfilled with nitrogen three times. 0.17 g (1.1 mmol) of “inactive” samarium metal was added, the tube was sealed with a septum and subjected to three evacuation/backfilling cycles. After the final cycle, the tube was left under a positive pressure of nitrogen, and stirring was started at medium to high speed. After the mixture was stirred for 24 hours, 4.5 mL of THF was added, followed by 0.14 g (0.55 mmol) of iodine dissolved in 1mL of THF under nitrogen. The reaction flask was sealed and heated at 60 °C for 18 h resulting in a dark-blue slurry. The slurry was then precooled to 0 °C in an ice bath. Subsequently, to a flame-dried 5 mL round-bottomed flask filled with nitrogen were added **188** (35.0 mg, 0.08 mmol, 1.00 equiv.), dry THF (0.75 mL, freshly distilled), and N, N-dimethylethanolamine (0.50 mL, 0.96 mmol, 12.0 equiv). The solution was purged with nitrogen under the surface of the solution for 2 min and transferred to the flask containing the SmI_2 slurry (2.10 mL) dropwise via cannula. Vigorous stirring was maintained during the addition of the aziridine to the SmI_2 slurry. The 5 mL flask was washed with 1 mL of degassed THF, and the rinse was also transferred to the reaction flask containing SmI_2. The reaction mixture was stirred at 0 °C for 40 min to 1 h and then quenched by the addition of sat aq $NaHCO_3$ (5.0 mL) at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5.00 mL). The combined organic layer was dried with Na_2SO_4 and filtered. The solvent was removed by rotary evaporation to give light-yellow oil. Purification by silica-gel chromatography (18 x 250 mm, 1: 20 ethyl acetate/hexanes as eluent) afforded **158** as a colorless oil in 70% isolated yield (25.0 mg, 0.06 mmol) and 20% starting material **158** was recovered. Spectral data for **158**: R_f = 0.6 (1:3 EtOAc/hexanes) ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89-0.94 (m, 6H), 1.10-1.15 (m, 1H), 1.26 (t, *J* = 5 Hz, 3H), 1.50-1.56 (m, 1H), 1.59-1.65 (m, 1H), 2.47-2.57 (m, 2H), 3.88-3.91 (m, 1H), 4.13 (q, *J* = 5 Hz, 2H), 4.23 (t, *J* = 5 Hz, 1H), 4.38-4.41 (m, 2H), 5.21 (d, 1H, NH), 7.32 (t, *J* = 5 Hz, 2H), 7.41 (t, *J* = 5 Hz, 2H), 7.60 (d, *J* = 5 Hz, 2H), 7.77 (d, *J* = 5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) 11.41, 14.18, 15.28, 25.51, 36.47, 38.14, 47.30, 52.48, 60.65, 66.55, 119.94, 125.08， 127.00, 127.62, 141.29, 143.92; $[\alpha]^{20}$ -12.0 (c 0.25, CH_2Cl_2 IR (thin film) 3583 (w), 3005 (s), 1731 (vs), 1275 (vs), 1260 (vs), 764 (vs), 50 (vs) $cm^{-}1$; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C24H30NO4$^+$, 396.2175; found, 396.2176.

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