CATALYTIC ASYMMETRIC α-IMINOL REARRANGEMENT BY VANOL ZIRCONIUM COMPLEX

By

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A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Chemistry – Doctor of Philosophy

2014

ABSTRACT

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Catalytic asymmetric α-iminol rearrangement to the corresponding α-amino ketone is developed that is based on a chiral zirconium complex generated from the vaulted biaryl ligand VANOL. As many as 19 different asymmetric catalysts were examined to identify the first chiral catalyst for the asymmetric α-iminol rearrangement. Aluminate complexes of VANOL, VAPOL and 7,7'-*t*Bu_2VANOL were found very effective for this reaction giving up to 88% ee. The ne plus ultra catalyst for this reaction was discovered to be the VANOL zirconium complex, and for the majority of the substrates it gave 97% to >99% ee. An X-ray analysis of the crystal that was grown from the catalyst solution revealed that the zirconium has bonded to three VANOL molecules and this is also the first structure reported for zirconium with three bis-phenol ligands.

ACKNOWLEDGEMENTS

These 5 and half years I spent in MSU are definitely most precious time in my life, thanks to the offer for graduate study from MSU, I was able to learn organic chemistry, teach undergraduate courses, do research, make friends as well as experience and understand a lot more things out there. I feel so lucky to have the opportunity to meet all kind people around me, without their help, I would not be able to complete my PhD study.

I would like to thank my advisor Professor Wulff, who allows me the full freedom to explore my research ideas. Without his support and suggestions, I would never have the opportunity to discover the methodology of catalytic asymmetric α-iminol rearrangement and VANOL aluminate and VANOL zirconium complex chiral catalysts. I feel so lucky to be one student in Professor Wulff's group.

I also would like to thank my PhD committee members Prof. Maleczka, Prof. Jackson, and Prof. Odom for their lectures in CEM 850, 851 and 852, and also their time and insightful suggestions for my research. I also would like to thank them for the support to my postdoc application.

Members of the Wulff group are the best colleagues. In no particular order, I would like to thank Dr. Li Huang, Dr. Hong Ren, Dr. Yong Guan, Dr. Aman Desai, Dr. Anil Gupta, Dr. Dima Bervasov, Dr. Victor Prutyanov, Dr. Munmun Mukherjee, Dr. Nilanjana Majumdar, Dr. Wynter Osminski, Dr. Wenjun Zhao and Dr. Mathew

Vetticatt, for their generous help and suggestions when I encountered difficulties in the experiments. Also thank them for many happy hours outside the lab. Yijing Dai, Yubai Zhou and Xiaopeng Yin are also active and creative soldiers in the lab.

I also would like to express my grateful thanks to my best buddies in MSU, Greg Spahlinger, Dillon Cogan, Miles Kamaloski, Bob Philange and Jason Lam, et al, they added so many spices to my life in the past few years, best memories in my life.

Last but not the least, I grew up with the priceless love from my parents, thanks mom and dad for their unconditional love and support for the last 28 years.

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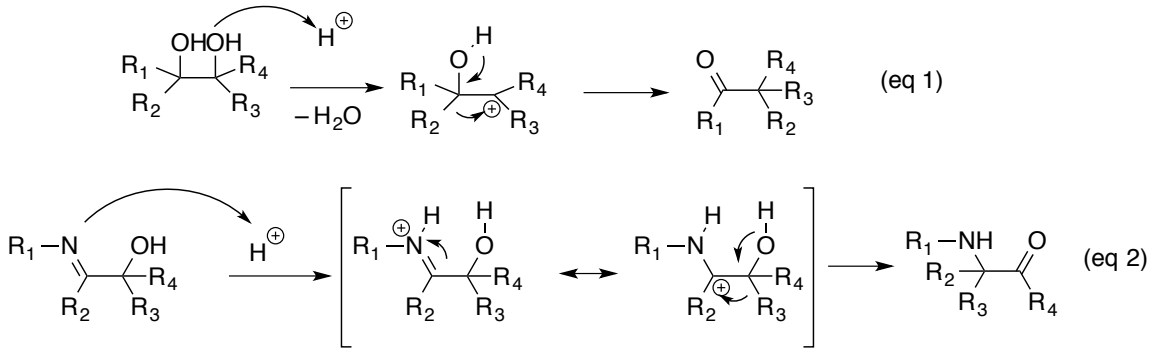
CHAPTER ONE
α-IMINOL REARRANGEMENT IN THE LITERATURE

1.1 Introduction

The Pinacol rearrangement was first described by Fittig in 1860.[1] In the course of this reaction, protonation of one of the two OH groups occurs followed by loss of water, forming a carbocation. Rearrangement is initiated by this carbocation (Scheme 1.1, eq 1). If the substituents on the two alcohol carbons are not identical, the more stable carbocation forms to participate in the reaction.

Scheme 1.1 Pinacol and α-iminol rearrangement

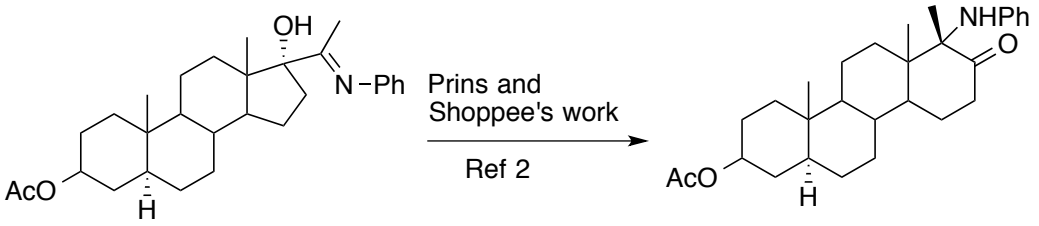


Compounds containing vicinal imine and hydroxyl functional groups are known as α-iminols, and they can undergo a rearrangement reaction to yield the corresponding α-amino ketones through a mechanism related to that of the Pinacol rearrangement (Scheme 1.1, eq 2). Protonation of the imine is expected due to the greater basicity of the nitrogen atom relative to OH, and the positive charge is then delocalized to the imine carbon through resonance. Migration can then be initiated by both the push of the electron pair on oxygen and the pull of the positive charge on the carbocation. In this case, if R_3=R_4, the migration from the Si face or Re face will result in two enantiomers; if R_3≠R_4, it will result in two

regioisomers, each of which has two enantiomers.

The α-iminol rearrangement is in fact a known process and was first reported by Prins and Shoppee in 1943 (Scheme 1.2).[2] A comprehensive review of this type of reaction appeared in 2003 that summarized the subsequent research progress since Prins and Shoppee.[3]

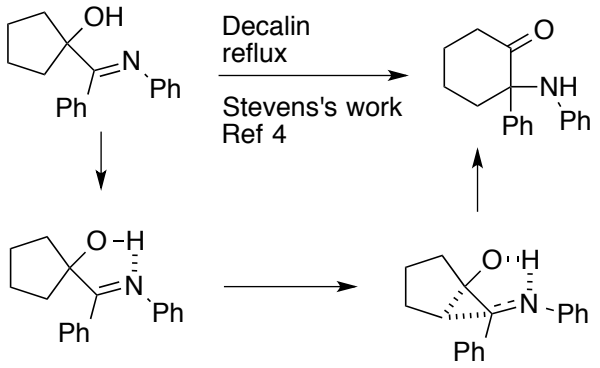
Scheme 1.2 α-Iminol rearrangement by Prins and Schoppee



1.2 Methods developed for the α-iminol rearrangement in the literature

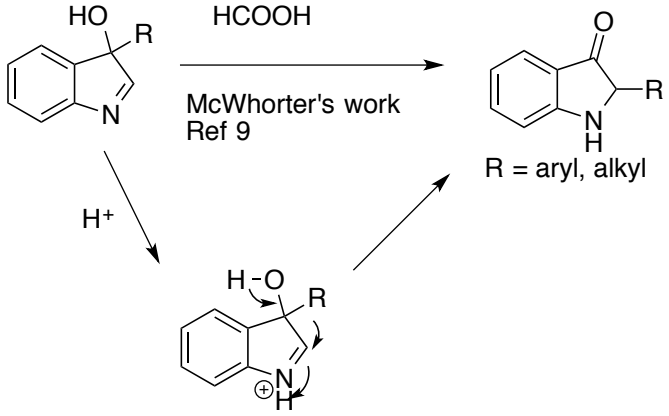
Various methods to conduct the α-iminol rearrangement have been reported in the literature. One is to utilize heat as the promoter;[4-8] usually a temperature higher than 150 °C is necessary to overcome the activation barrier and initiate the reaction (Scheme 1.3).[4] The transition state of this reaction under heat has been proposed to proceed in a concerted manner where the C-C, O-H and C=N bonds are partially broken and the new C-C and N-H bonds are partially formed.[4]

Scheme 1.3 α-Iminol rearrangement promoted by heat



Another approach is to employ a catalyst to effect the reaction. There are three commonly used catalysts in the literature: 1. Brønsted acids: HCOOH,[9-12] HCl, H_2SO_4, TsOH, CH_3COOH, CF_3CH_2OH,[13] etc. 2. Lewis acids: $Sc(OTf)_3$,[14,15] $Cu(OTf)_2$, $Zn(OTf)_2$, etc. 3. Brønsted base: Sodium methoxide,[16] DBU,[17] TBAF,[18] etc.

Scheme 1.4 α-Iminol rearrangement promoted by Brønsted acid

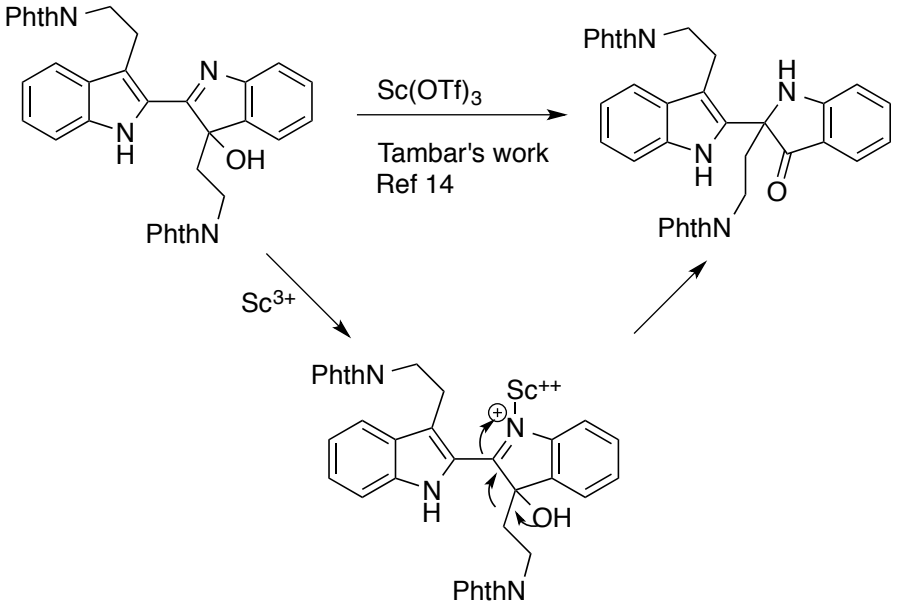


In the case of the Brønsted acid catalyzed rearrangement (Scheme 1.4),[9] protonation of the imine was proposed to be the initial step. Next, the hydroxyl group provided an electron pair triggering the R group to migrate to the imine carbon, and deprotonation from the carbonyl completed the reaction.

The Brønsted acid catalyzed reaction proceeded at a faster rate compared to the uncatalyzed reaction.[3]

In the case of the Lewis acid catalyzed rearrangement (Scheme 1.5),[14] the mechanism was proposed to be similar to the Brønsted acid promoted reaction. The coordination of the Lewis acid to the imine was the first step.

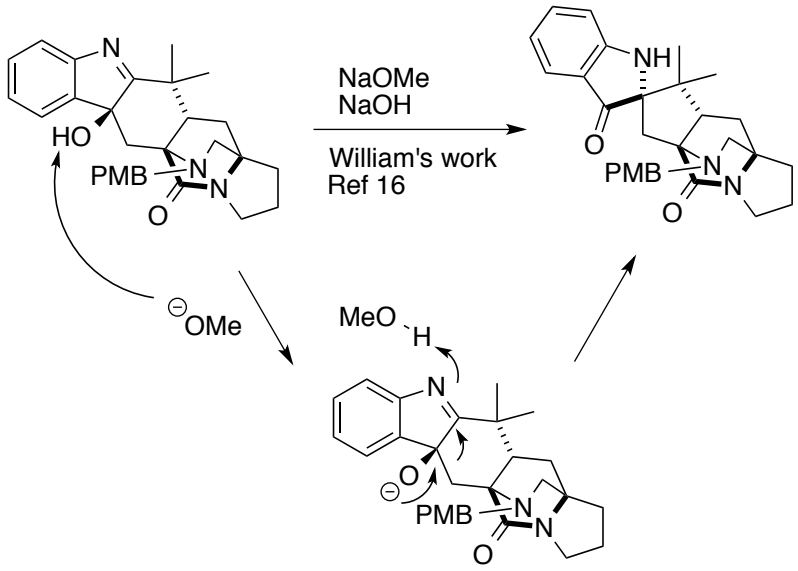
Scheme 1.5 α-Iminol rearrangement promoted by Lewis acid



In the case of Brønsted base catalyzed rearrangement (Scheme 1.6),[16] the deprotonation on the hydroxyl occurred with the aid of the base. Next, the electron pair on the negatively charged oxygen donated to the carbon forming a C=O double bond while the R group migrated to the imine carbon.

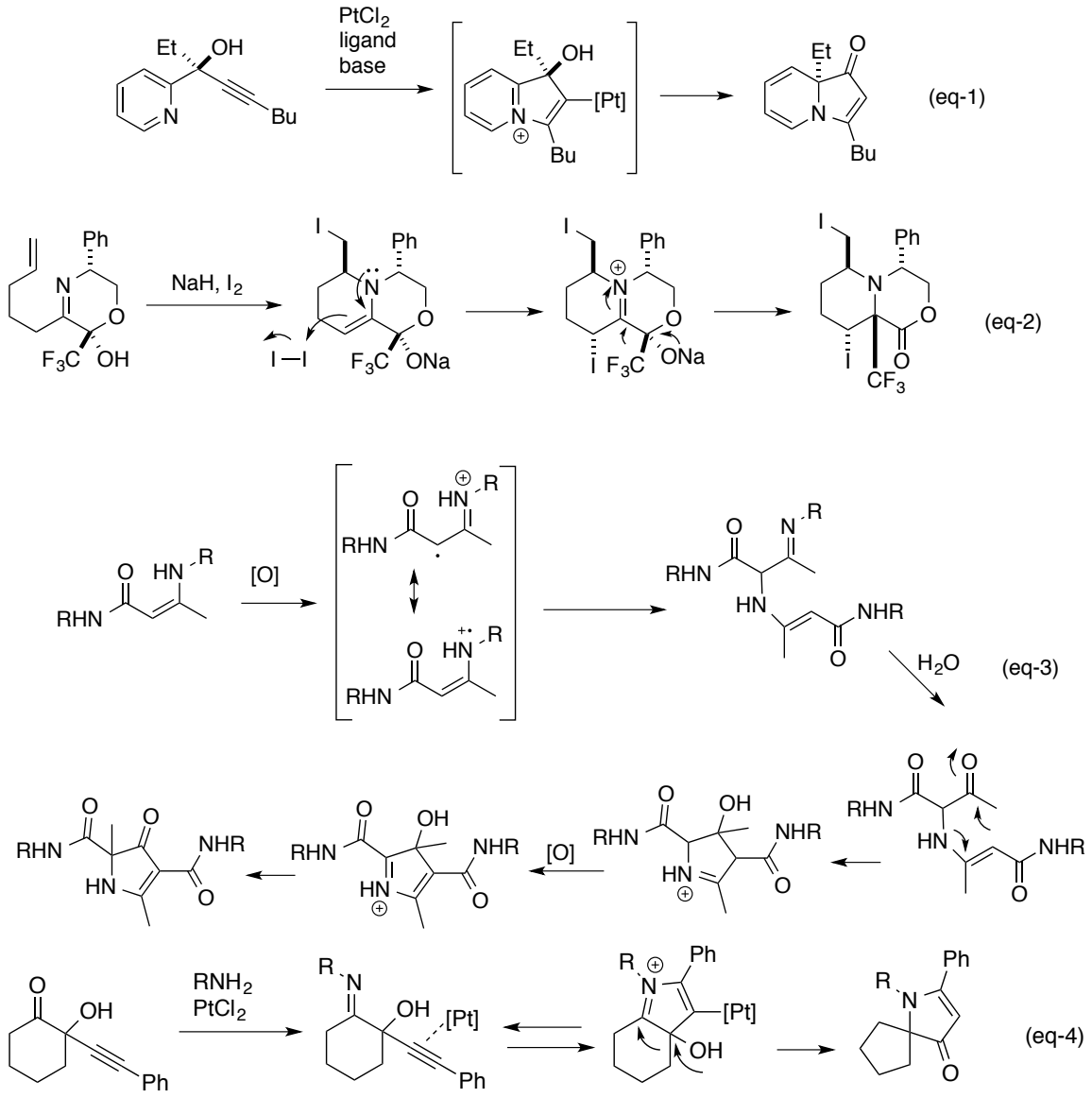
The Brønsted base catalyzed reaction proceeded at a faster rate compared to the uncatalyzed reaction.[3]

Scheme 1.6 α-Iminol rearrangement promoted by Brønsted base



There are four examples of an α-Iminol rearrangement occurring with an iminium cation intermediate forming in the course of another reaction. The first one is a platinum catalyzed indolizinone synthesis (scheme 1.7, eq 1),[19] the second involves the iodination of olefin (scheme 1.7, eq 2),[20] the third one is copper catalyzed oxidative tandem cyclization (scheme 1.7, eq 3).[21] and the last one is synthesis of heterocyclic systems (scheme 1.7, eq 4).[22]

Scheme 1.7 α-Iminol rearrangement through iminium intermediate



The α-iminol rearrangement has also served as an important step in the total synthesis of complicated natural products and drugs, such as Trigonoliimine C[14], Brevianamide B[16], and (*S*)-Ketamine[23]. The reaction usually requires either high temperature, or strong acid/base catalysts, or both as described above. These harsh conditions mean that many sensitive compounds will not survive during the course of this reaction. Thus the development of milder conditions that do not

involve high temperatures, or strong acid/bases are worthy of serious investigation.

All of the reported α-iminol rearrangement examples involve non-enantioselective reactions. One report does describe an attempt to enantioselectively conduct this reaction by using chiral nickel or lanthanum complexes.[24] While all of the chiral complexes examined were able to form the products, unfortunately all were racemic. An efficient catalytic asymmetric α-iminol rearrangement protocol that offers excellent enantioselectivity thus remains an unsolved challenging problem that would be a worthy undertaking.

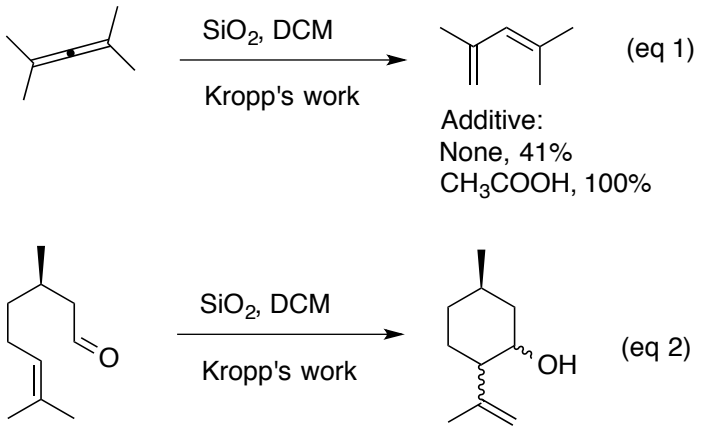
Chapters two and three will address these issues and try to provide some plausible solutions.

CHAPTER TWO
α-IMINOL REARRANGEMENT CATALYZED BY SILICA GEL AND MONTMORILLONITE K 10

2.1 Introduction

Silica gel is silicon dioxide in a granular and porous form. Usually it is used in organic synthesis as a stationary phase for column chromatography for the purpose of purification. Due to its acidity it is also used in acid-catalyzed reactions, such as the isomerization of allene and nucleophilic addition to aldehyde by Kropp and coworkers (Scheme 2.1).[25] Some modifications may also be made to silica gel to enhance its catalytic ability. Based on its acidity, silica gel is expected to catalyze the α-iminol rearrangement reaction as well.

Scheme 2.1 Silica gel catalyzed reactions

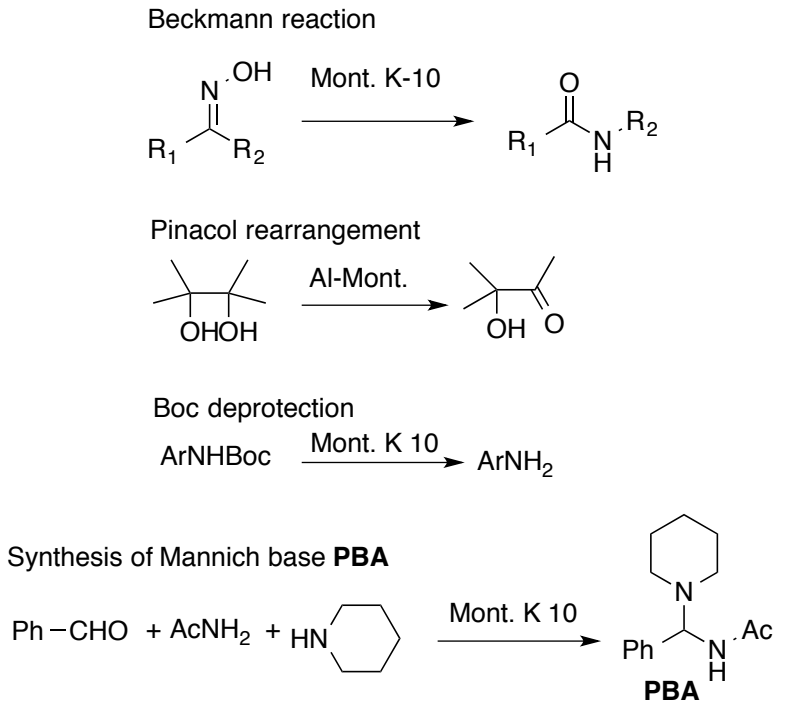


Montmorillonite is a clay formed from phyllosilicate minerals. It was named after the commune Montmorillon in France. It has an empirical formula of $Na_{0.3}Ca_{0.3}Al_2Mg_2Si_4O_{10}(OH)_2 \cdot nH_2O$,[26] but since potassium, iron and other metals are common substitutes for the metal ions above, the exact ratio can vary widely.

Montmorillonite is an efficient, heterogeneous and green catalyst in organic

synthesis and has been explored intensively; a comprehensive review on this subject appeared in 2012.[27] Some selected examples are listed in Scheme 2.2.

Scheme 2.2 Montmorillonite clay catalyzed reactions

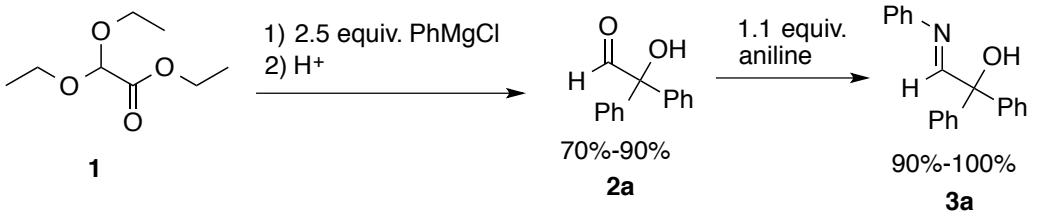


Based on these results, Montmorillonite clay was also investigated as a catalyst for the α-iminol rearrangement reaction.

2.2 Initial results of the rearrangement by silica gel and other catalysts

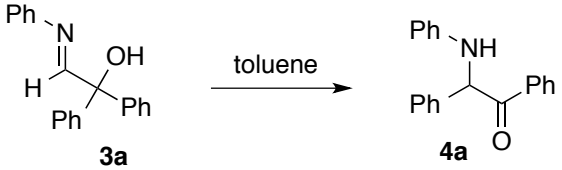
A model iminol **3a** was prepared as shown in Scheme 2.3. Ethyl diethoxyacetate was treated with 2.5 equivalent of PhMgCl and following acid hydrolysis, yields the aldehyde **2a** in 70% to 90% over two steps. The aldehyde **2a** was converted to iminol **3a** with aniline in 90% to 100% yield.

Scheme 2.3 Preparation of model iminol **3a**

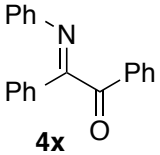


A summary of the rearrangement is provided in Table 2.1. In entries 1 and 2, the reaction was conducted with no catalyst by heating. It was discovered that at 80 °C the reaction was not proceeding after a prolonged 42 h. When the temperature was raised to 150 °C, the rearranged product **4a** was observed in 20% yield, with a 30% recovery of **3a** and the formation of a byproduct **4x** in 50% that was tentatively assigned as an imine resulting from the oxidation of **4a**. This result is consistent with the literature data that high temperatures are necessary to drive the reaction.[3]

Table 2.1 Rearrangement of α-iminol **3a** with heat, silica gel and Montmorillonite



Entry	Catalyst	Temp	Time	Yield
1	none	80 °C	42 h	0%
2[b]	none	150 °C	2 h	20%
3	silica gel	60 °C	2 h	30%
4	silica gel	80 °C	1 h	95%
5	Mont. K 10	60 °C	1.5 h	100%

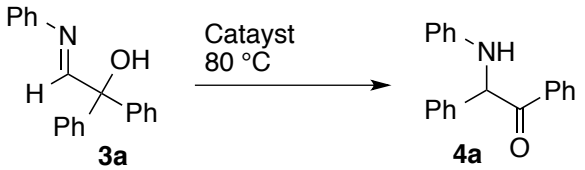

4x

[a.] Unless otherwise specified, the reaction was carried out on 0.1 mmol scale with no catalyst or 100 wt% silica gel or 100 wt% Montmorillonite K 10 in toluene

in the presence of air. [b.] The solvent was mesitylene, and yield was determined by NMR.

Entries 3 and 4 involve the rearrangement in the presence of silica gel. The temperature could be significantly decreased to as low as 60 °C with the rearrangement still proceeding to give a 30% yield in **4a**. At 80 °C, the reaction was complete in only 1 h, giving 95% yield. In the presence of Montmorillonite K 10 clay, this reaction went to completion with 100% yield in 1.5 h at 60 °C, which means the clay was a better catalyst than silica gel in this case.

Table 2.2 Screen of the rearrangement



3a **4a**

Entry	Catalyst	Solvent	Time	Yield[b]
1	1 equiv. HOAc	Toluene	10 h	no conversion
2	10 equiv. HOAc	Toluene	15 h	40% S. M. 60% byproduct
3	1 equiv. H_2SO_4	DMF	1 h	90%
4[c]	1 equiv. H_2SO_4 on silica gel	Toluene	1.5 h	13%
5[d]	1 equiv. $TsOH{\cdot}H_2O$	DMF	1 h	56%
6	1 equiv. $Zn(OTf)_2$	DMF	2 h	9%
7	1 equiv. NaOEt	EtOH	1 h	No desired product

[a.] Unless otherwise specified, the reaction was done on a 0.1 mmol scale at 80 °C in presence of air. [b.] yield was determined by NMR. [c.] Reaction was done at 60 °C. [d.] 44% aldehyde **2a** was observed.

For comparison, a summary of the rearrangement with different catalysts is listed in Table 2.2. In entry 1, 1 equivalent acetic acid seemed not acidic enough to initiate the reaction. In entry 2, 10 equivalent acetic acid was added, but it produced the oxidized imine byproduct **4x**, and no desired product **4a** was observed. In entry 3, sulfuric acid was examined, and the result indicated that it was a good catalyst for this reaction, although it is much more acidic than silica gel. In entry 4, the reaction was done with 1 equivalent sulfuric acid absorbed in the silica gel. The combination of the two was not as good as silica gel alone (Table 2.1 entry 4). In entry 5, p-toluenesulfonic acid monohydrate was tested. The water present in the monohydrate partially hydrolyzed the iminol, resulting in a low yield. Zinc triflate was examined in entry 6, and the poor result indicated that this Lewis acid is not efficient in this reaction. In entry 7 the base sodium ethoxide gave a complex mixture perhaps because the base abstracted the α-proton in the product **4a** leading to an Aldol reaction.

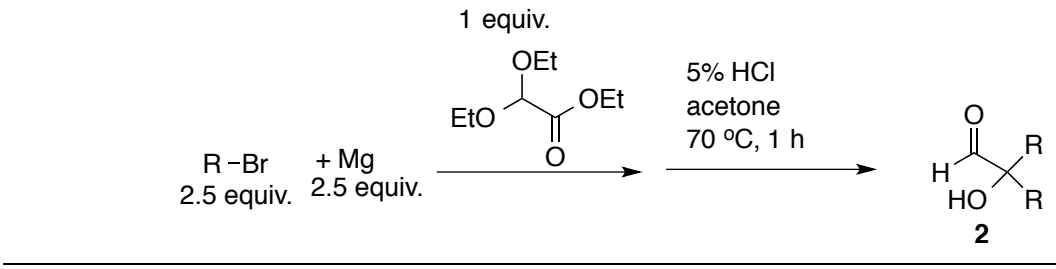
In summary, the Brønsted acid sulfuric acid was a good catalyst in the α-iminol rearrangement, while the Lewis acid zinc triflate or the Brønsted base sodium ethoxide proved not to be a good choice. However, some acid sensitive compounds may not survive in the presence of sulfuric acid and thus mild catalysts, such as silica gel and Montmorillonite K 10 would be the preferred catalysts.

2.3 Iminol rearrangement catalyzed by silica gel and Montmorillonite

2.3.1 Synthesis of substrates: aldehydes and iminols

The aldehydes in the series **2** were prepared via the Grignard reaction, followed by acid hydrolysis. The results are summarized in Table 2.3. All substrates were synthesized via the Grignard reaction except **2m**, which was made by using the corresponding lithium reagent.

Table 2.3 Synthesis of aldehydes **2**



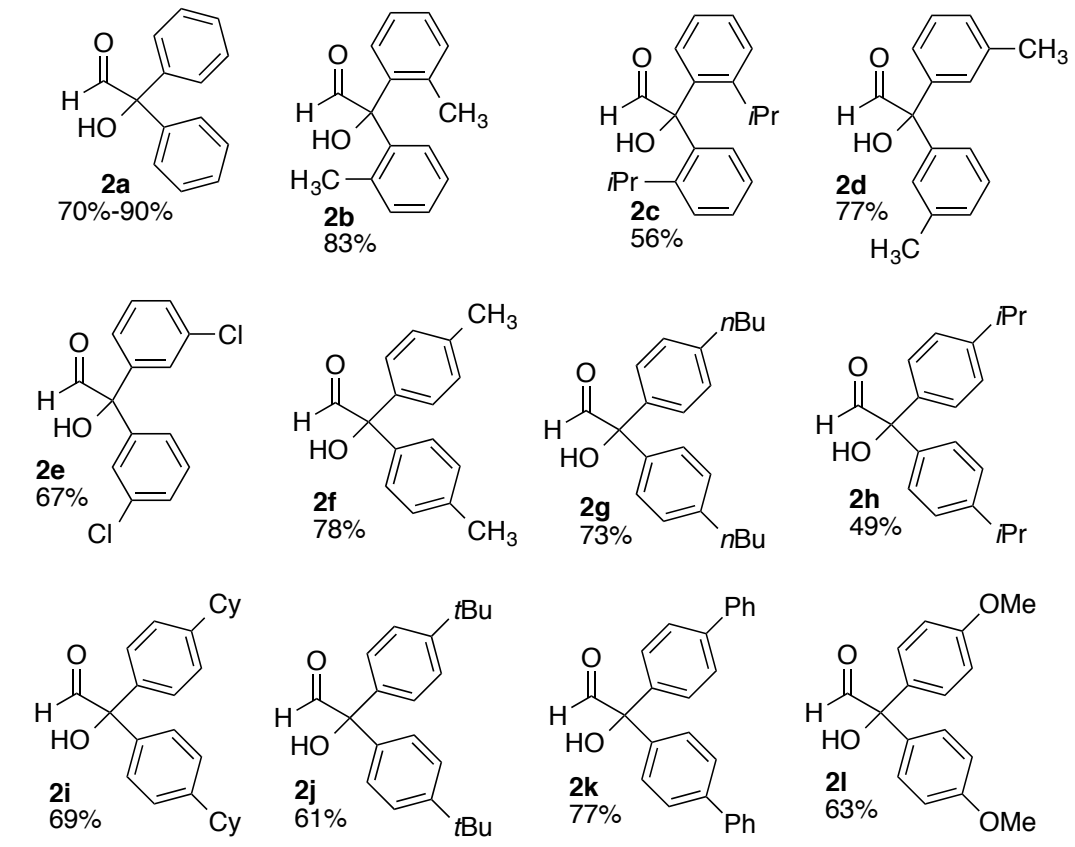
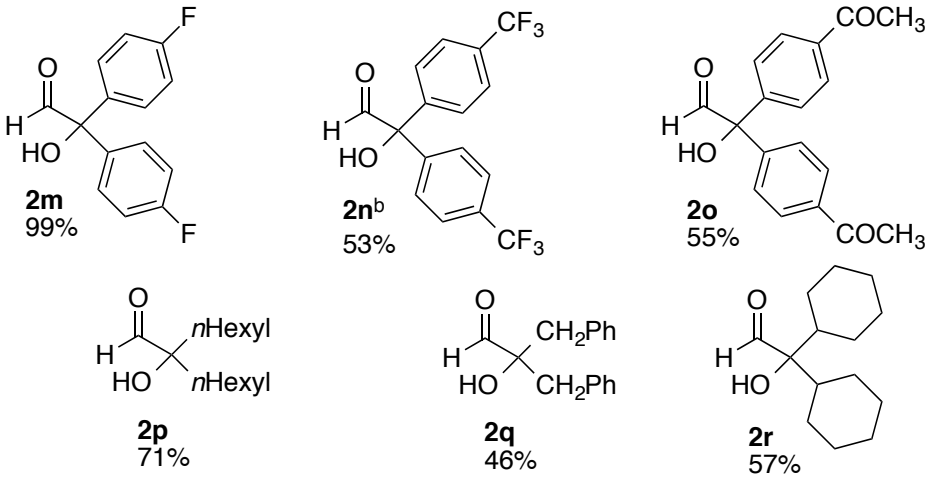


Table 2.3 (cont'd)

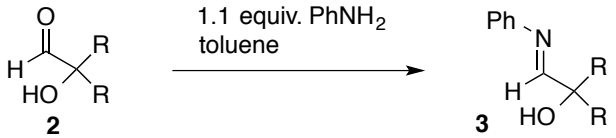


[a.] Unless otherwise specified, the Grignard reagent was prepared from the corresponding bromide and magnesium metal in THF, and 5% HCl = 1.7 M HCl. [b.] **2m** was prepared by an organolithium reagent at –78 °C.

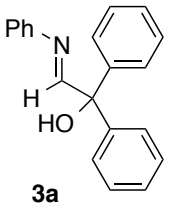
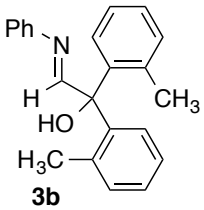
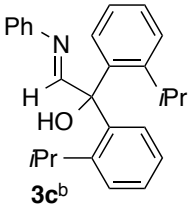
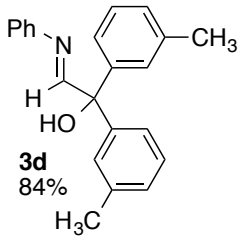
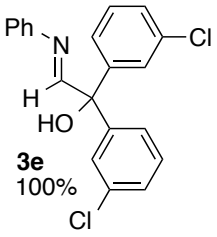
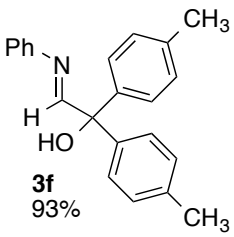
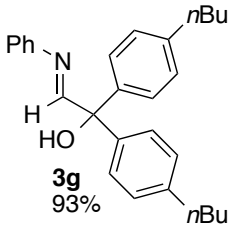
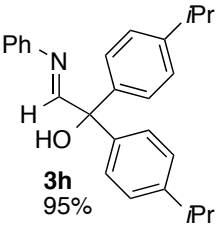
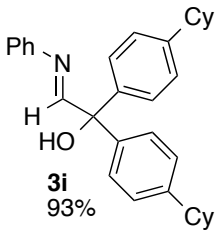
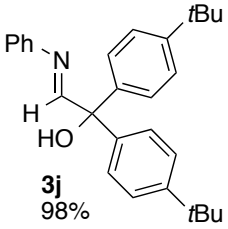
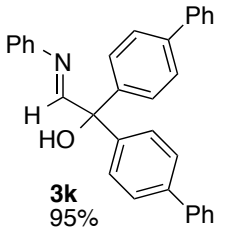
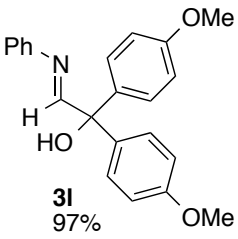
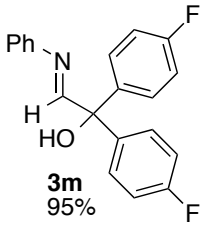
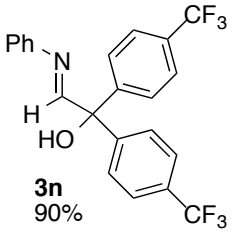
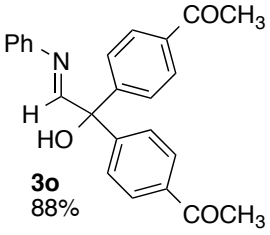
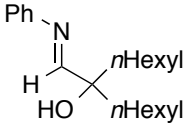
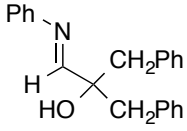
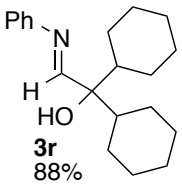
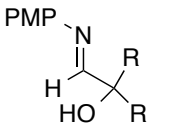
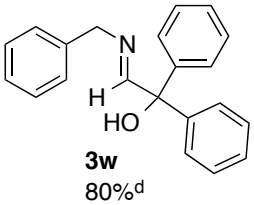
The yields of aldehydes were moderate because the acetal hydrolysis step produced some unknown byproducts that stayed at the origin on TLC. Lowering the temperature or using a milder acid may help to improve the yield, but this has not been tried.

Iminols in the series **3** were prepared with the corresponding aldehyde **2** and aniline. The results are summarized in Table 2.4.

Table 2.4 Synthesis of iminols **3**



2 **3**

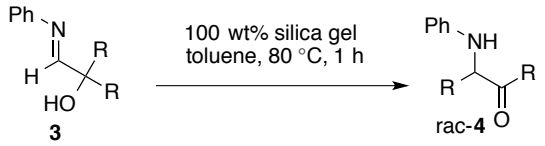
 **3a** 78%-100%	 **3b** 88%	 **3c**[b] –	 **3d** 84%
 **3e** 100%	 **3f** 93%	 **3g** 93%	 **3h** 95%
 **3i** 93%	 **3j** 98%	 **3k** 95%	 **3l** 97%
 **3m** 95%	 **3n** 90%	 **3o** 88%	 **3p** 88%
 **3q** 100%	 **3r** 88%	 **3s** R=Ph, 99%[c] **3t** R=Cy, 81%[c]	 **3w** 80%[d]

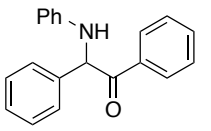
[a.] Unless otherwise specified, the reaction was done with 1 equivalent of aldehyde **2** and 1.1 equivalent aniline in toluene at room temperature for 30 min. [b.] The reaction for substrate **3c** did not go to completion, and gave a mixture of aldehyde **2c** : imine **3c** = 1 : 3.2. [c.] The starting amine for **3s** and **3t** was 4-anisidine. [d.] The starting amine for **3w** was benzyl amine.

2.3.2 Iminol rearrangement catalyzed by silica gel and Montmorillonite

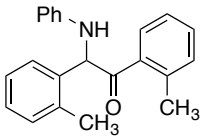
The next step is to test the substrates with silica gel. The results are summarized in Table 2.5. All substrates gave good to excellent yields of the iminol rearranged product **4** except for **3m**.

Table 2.5 Iminol rearrangement catalyzed by silica gel[a]

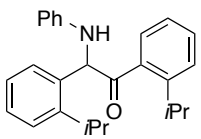




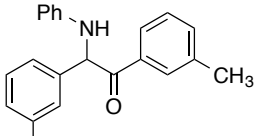
rac-**4a**
95%



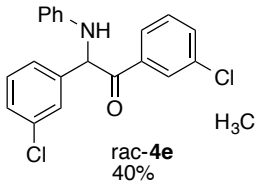
rac-**4b**
92%



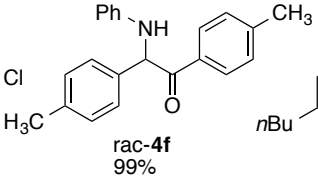
rac-**4c**
90%



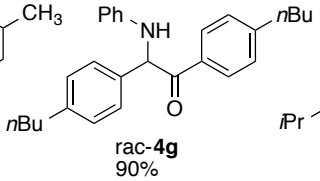
rac-**4d**
90%



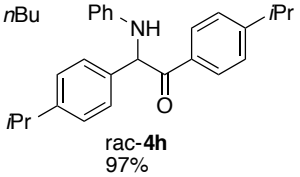
rac-**4e**
40%



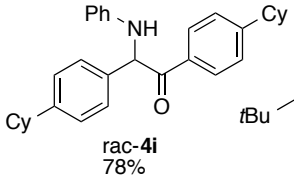
rac-**4f**
99%



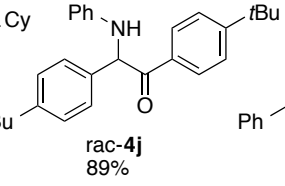
rac-**4g**
90%



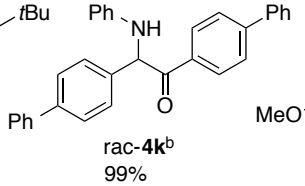
rac-**4h**
97%



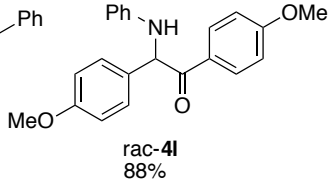
rac-**4i**
78%



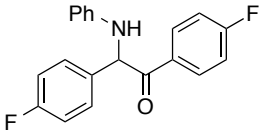
rac-**4j**
89%



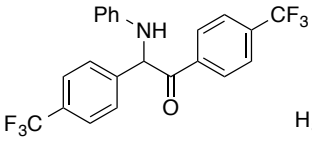
rac-**4k**[b]
99%



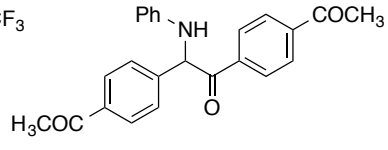
rac-**4l**
88%



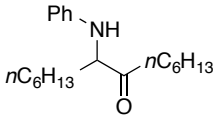
rac-**4m**
85%



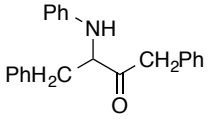
rac-**4n**
0%[c], (27%[d])



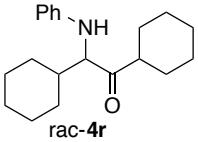
rac-**4o**
N/A



rac-**4p**
62%[e], (85%[f])



rac-**4q**
85%



rac-**4r**
83%

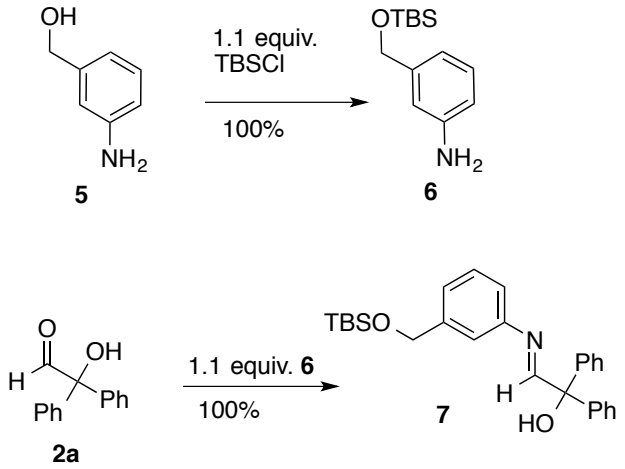
[a.] Unless otherwise specified, the reaction was done on 0.1 mmol scale with 100 wt% silica gel in 0.3 mL toluene at 80 °C for 1 h, in presence of air. Yield in parenthesis was with Montmorillonite K 10. [b.] The reaction time was 3 h. [c.] The reaction time was 24 h. This substrate rac-**4m** was oxidized to imine under air, and no desired product was observed, see details in experimental section. [d.] The reaction was done with 100 wt% Montmorillonite K 10 under a nitrogen atmosphere for 38 h. Yield determined by NMR, 43% **3m** and 29% byproduct was also identified. [e.] The reaction temperature was 90 °C. [f.] Reaction was run with Montmorillonite K 10, at 60 °C for 10 h. [g.] Reaction was run under N_2.

The substrate **4m** was oxidized to an imine byproduct by air under the conditions of the reaction.

2.3.3 Comparison of sulfuric acid, silica gel and Montmorillonite K 10 with an acid sensitive substrate

Iminol **7** was synthesized from **5**. The alcohol was protected by a TBS group, and condensed with aldehyde **2a**. Compound **7** has an acid sensitive TBS group and was designed to examine the stability toward the α-iminol rearrangement conditions with sulfuric acid, silica gel and Montmorillonite (Scheme 2.4).

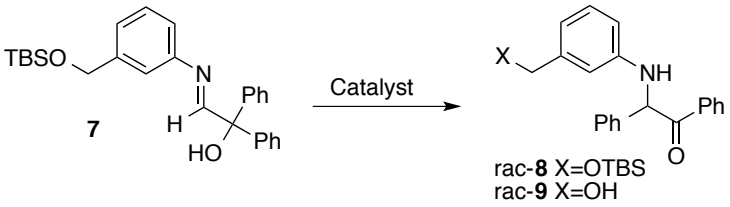
Scheme 2.4 Synthesis of iminol substrate **7**



Iminol **7** was subjected to the rearrangement conditions indicated in Table 2.6.

In entry 1, the reaction was run with sulfuric acid and this led to compound **9** instead of desired product **8** as a result of loss of TBS group. In entries 2 and 3, silica gel and Montmorillonite K 10 were used respectively. Both catalysts gave the desired product **8**, with no cleavage of TBS; however, the clay catalyst gave a higher yield than silica gel. Therefore, Montmorillonite K 10 is a better catalyst for this acid sensitive substrate.

Table 2.6 Synthesis of rac-**8**



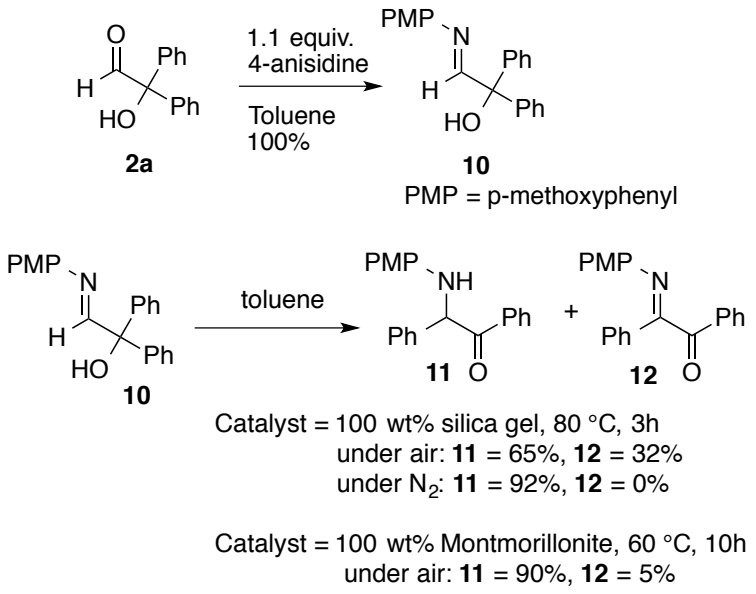
Entry	Catalyst	Sovent	Temp,Time	Yield **8**, **9**
1	1 equiv. H_2SO_4	DMF	80 °C, 1h	0%, 56%
2	100 wt% silica gel	toluene	80 °C, 1h	70%, 0%
3	100 wt% Montmorillonite K 10	toluene	70 °C, 2 h	96%, 0%

[a.] Unless otherwise specified, reactions were run on 0.1 mmol scale in 0.3 mL solvent under the indicated conditions.

2.3.4 Rearrangement of a PMP protected iminol catalyzed by silica gel and Montmorillonite K 10

The protecting group on the nitrogen atom of the iminol could be changed to a removable p-methoxylphenyl (PMP) group if the aldehyde **2a** was treated with p-anisidine instead of aniline. In this case, **10** was prepared in 100% yield (Scheme 2.5).

Scheme 2.5 Rearrangement with a removable PMP group on the iminol



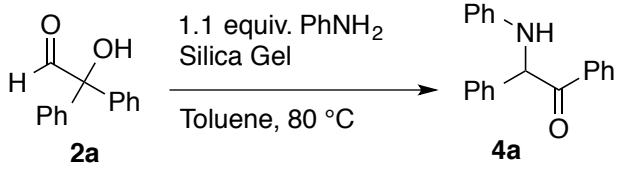
The rearrangement of **10** was carried out with silica gel, but something different was observed. First, the reaction rate was slower than the phenyl protected iminol **3a**; second, the rearranged product **11** was partially oxidized to an imine byproduct **12** under air. A second run under N_2 atmosphere eliminated the formation of byproduct **12**. With Montmorillonite K 10 under air, the reaction temperature was lowered to 60 °C, and although the reaction time was longer, the formation of byproduct **12** was much less than with silica gel catalysis.

2.3.5 Tandem imine formation and rearrangement catalyzed by silica gel and Montmorillonite

As previously described, the synthesis of amino ketone **4a** was achieved from the iminol **3a**. However, if **4a** could be accessed directly from the aldehyde **2a** this would shorten the synthesis by one step, namely the formation of iminol **3a**

(Scheme 2.6). The progress of the reaction starting from **2a** was monitored by NMR and the results are summarized in Table 2.7. In entry 1, the ratio of aldehyde:iminol:product was 1:2.7:3.3 at 1 h. This means that the formation of iminol **3a** and its rearrangement were occurring at the same time in the reaction mixture. After 2.5 h, the aldehyde disappeared completely but the iminol **3a** was still present. After 3.5 h some iminol was still present in the reaction mixture. This is to be contrasted to complete reaction in 1 h starting from iminol **3a** (Table 2.5). This reaction rate difference may be related to the presence of water, which is formed by the condensation between aldehyde and aniline, and which might somehow decrease the catalytic activity of silica gel.

Table 2.7 Reaction progress for the tandem synthesis of **4a**



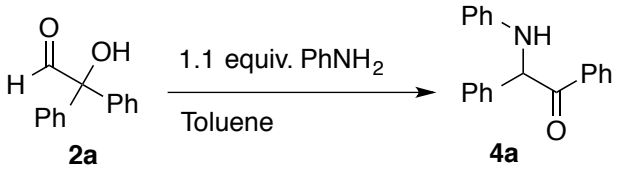
2a **4a**

Entry	Time	aldehyde:iminol:product **2a:3a:4a**
1	1 h	1:2.7:3.3
2	2.5 h	0:1:3.4
3	3 h	0:1:4
4	3.5 h	0:1:5

[a.] Unless otherwise specified, the reaction was done on 0.2 mmol scale, 100 wt% silica gel was used, the progress was monitored by NMR.

However, with Montmorillonite K 10 clay, the reaction was complete at 70 °C in 3 h. Again, the clay is a more efficient catalyst compared to silica gel in this case.

Scheme 2.6 One-pot synthesis of **4a** from aldehyde **2a**



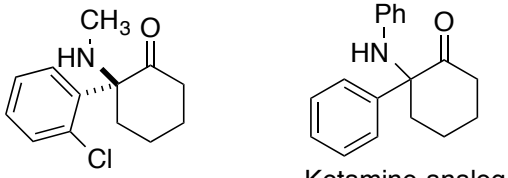
Catalyst = 100 wt% silica gel,
80 °C, 3.5 h, 80%

Catalyst = 100 wt% Montmorillonite K 10,
70 °C, 3 h, 95%

2.3.6 Synthesis of Ketamine analog by silica gel

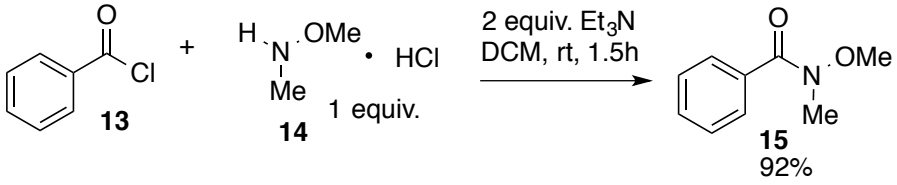
Ketamine is a drug used in general anesthesia to put a patient to sleep for surgery,[28] and it is also a candidate as an antidepressant.[29] Studies have shown that the main side effect of Ketamine is that it causes hallucinations in some cases.[30]

Figure 2.1 Ketamine and its analog

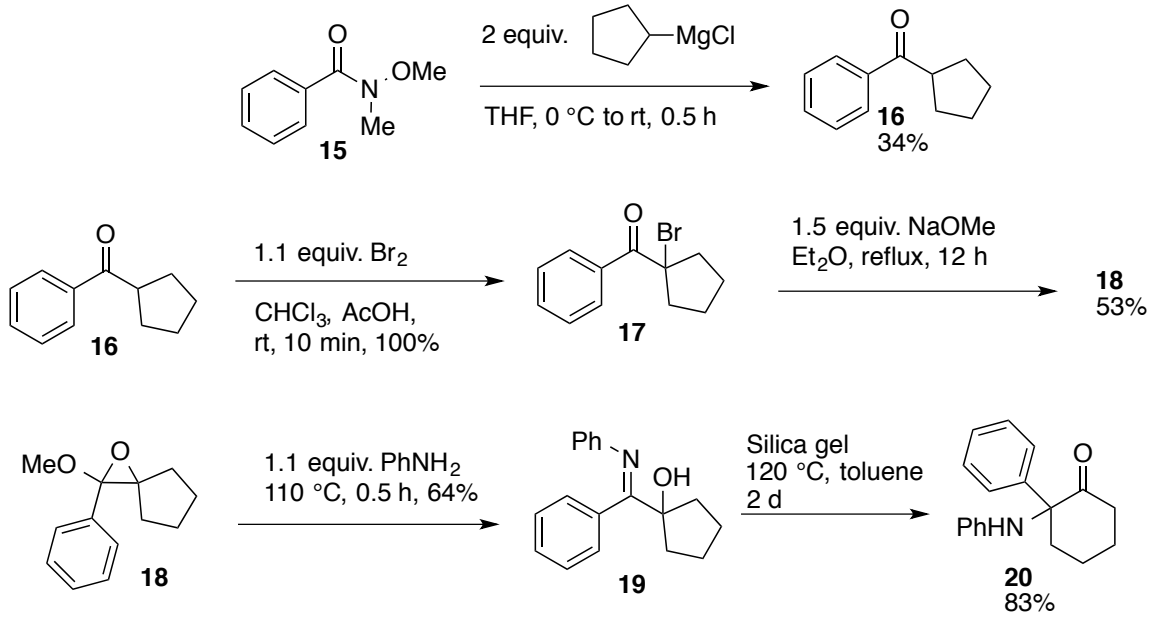


The synthesis of Ketamine has been described in some patents.[31] Synthesis of Ketamine analog **20** was pursued as an initial evaluation of a potential synthesis of Ketamine.

Scheme 2.7 Synthesis of Ketamine Analog **20**



Scheme 2.7 (cont'd)



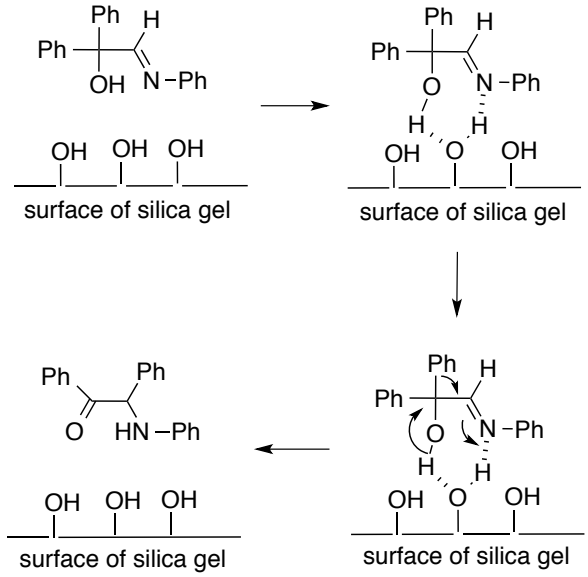
The synthesis started from benzoyl chloride and N,O-dimethylhydroxylamine, forming the Weinreb amide **15** in 92%. Then **15** was reacted with cyclopentyl Grignard reagent to form the ketone **16** in 34%. The yield was low because a substantial amount of byproduct benzaldehyde was observed in this step. Bromination and epoxidation giving the epoxide **18** in 53% yield. The iminol **19** was synthesized in 64% yield from epoxide **18** by heating with aniline.[4]

The rearrangement of **19** has been reported by refluxing in decalin (b. p. 189-191 °C) without catalyst (Scheme 1.3).[4] In this work, with the addition of silica gel, the reaction temperature could be significantly reduced to 120 °C, affording product **20** in 83% yield; however, the reaction took two days to go to completion.

2.3.7 Proposed mechanism for the rearrangement catalyzed by silica gel

A proposed mechanism for the silica gel catalyzed rearrangement is shown in Figure 2.2. The OH groups on the surface of silica gel may serve two purposes: one is to provide a proton to form a hydrogen bond with the imine nitrogen, which increased the positive charge density on the imine; the other is to provide an oxygen that accepts the proton from the OH in the substrate, which increases the negative charge density on the oxygen. Both effects favor the migration, thus this reaction proceeded smoothly even at much lower temperatures (i. e. 60 °C, Table 2.1 entry 3).

Figure 2.2 Proposed rearrangement mechanism on the surface of silica gel



2.4 Conclusion

Silica gel and Montmorillonite K 10 clay were both very good catalysts for effectively promoting the iminol rearrangement. In many cases, the clay was superior to silica gel in terms of reaction rate and yield of the desired product.

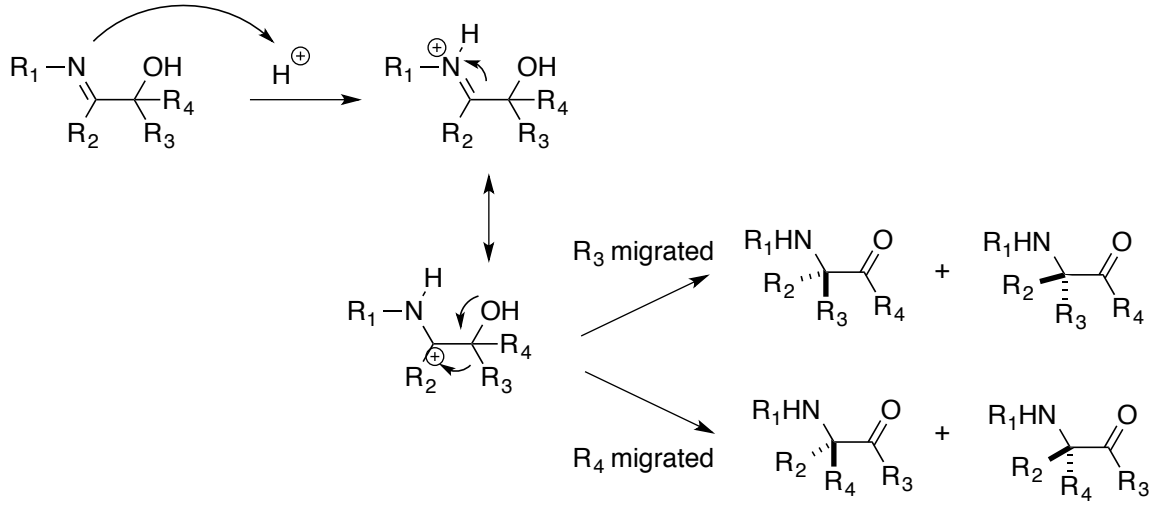
CHAPTER THREE

CATALYTIC ASYMMETRIC α-IMINOL REARRANGEMENT CATALYZED BY A VANOL ZIRCONIUM COMPLEX

3.1 Introduction

An α-Iminol has a Re face and a Si face with respect to the C=N imine bond. The rearrangement may occur on the Re face, or Si face, and if R_3=R_4 this will afford two enantiomers (Scheme 3.1, assuming it was activated by a proton). When R_3≠R_4, the two migrating groups are not identical, and there will be two regioisomers in the product, each of which can have two enantiomers.

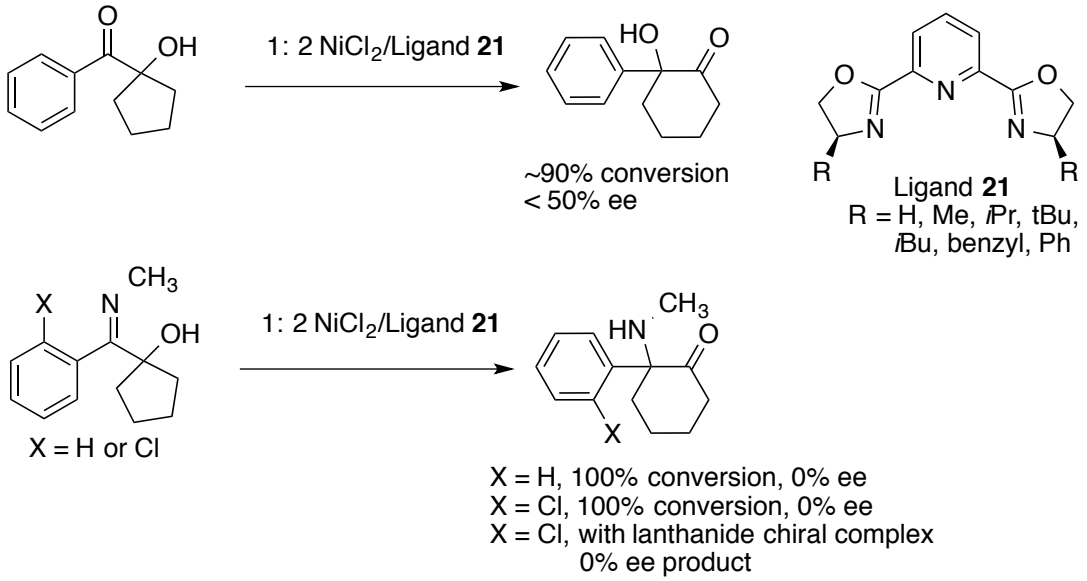
Scheme 3.1 α-iminol rearrangement catalyzed by proton



A review of catalytic asymmetric Pinacol-type rearrangements appeared in 2014.[32] In 2003, Brunner and his coworkers reported the first attempt at a catalytic asymmetric α-iminol rearrangement, which is the only example reported in the literature to date.[24] Besides α-iminols, they examined α-ketols as well (Scheme 3.2). The catalysts they screened were several different nickel and

lanthanium complexes as well as $Pr(tfc)_3$ and $Eu(tfc)_3$.

Scheme 3.2 Asymmetric α-ketol and α-iminol rearrangements by Brunner



In the case of the α-ketol rearrangement, the conversion was very high but the ee could not be improved to greater than 50% after screening 34 different ligands. In the case of the α-iminol rearrangement, they screened ligand **21** with chiral nickel and lanthanide salts when R = isopropyl, but only obtained the racemic product with partial decomposition as well. Other chiral catalysts including $La(acac)_3$/(**21** R=*i*Pr), $LaCl_3$/(**21** R=*i*Pr), $Pr(tfc)_3$ and $Eu(tfc)_3$ were only able to give racemic products. Therefore, there is no example of an effective catalytic asymmetric α-iminol rearrangement in the literature.

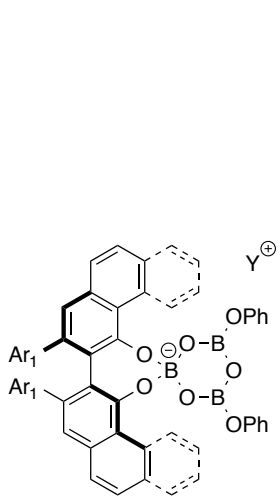
3.2 Initial results of the rearrangement by other chiral catalysts

3.2.1 α-iminol rearrangement by VANOL/VAPOL-B3 complex

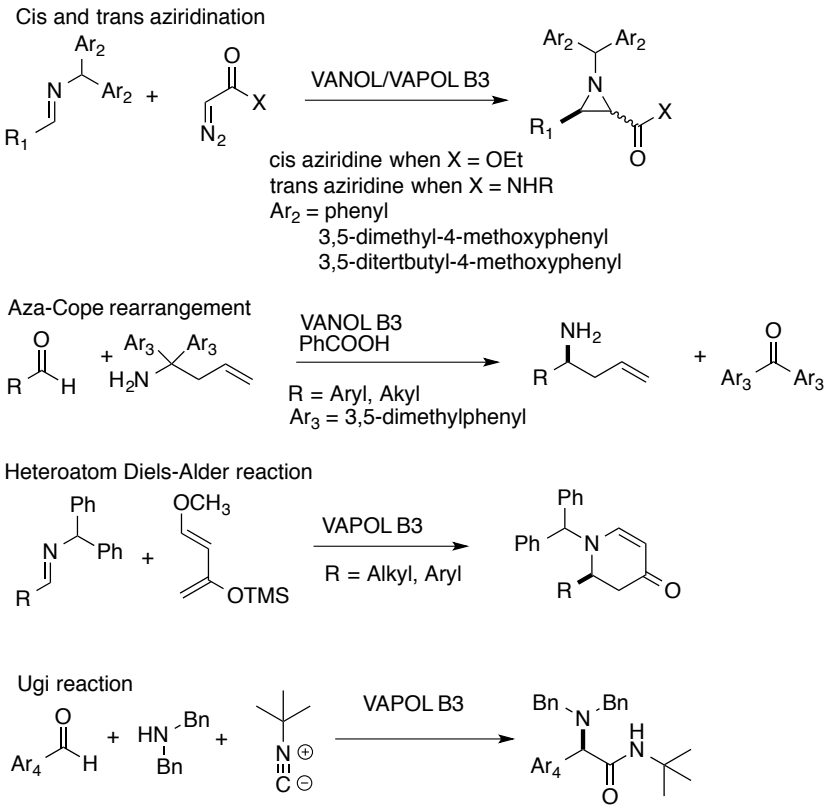
VANOL/VAPOL-B3 complexes **22**[33] are chiral Brønsted acids that have played an important role in asymmetric catalytic cis aziridinations,[34,35,36,37] trans

aziridinations,[38] aza-Cope rearrangements,[39,40] heteroatom Diels-Alder reactions[41] and Ugi reactions[42] (Scheme 3.3).

Scheme 3.3 VANOL/VAPOL-B3 complex as chiral catalyst in various reactions



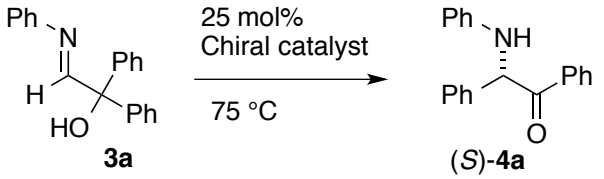
(*S*)-VANOL/VAPOL-B3 complex **22**



The proton in these complexes activates the imine substrate (Y^+ = H-imine$^+$) and hence subsequent asymmetric nucleophilic addition to the iminium occurred. It is also expected that these catalysts should catalyze the α-iminol rearrangement via protonation of the imine of the α-iminol, hopefully in good yield and enantioselectivity. However, VANOL/VAPOL-B3 complexes did not exhibit effective catalytic ability in this reaction (Table 3.1). VANOL-B3 **22** gave 17% ee while VAPOL-B3 **22** gave 0% ee in entries 1 and 4. In entry 2, one equivalent of benzoic acid (relative to the catalyst) was added during the preparation of the

catalyst, and presumably coordinates to one of the three-coordinate borons forming a second tetra-coordinated boron.[39,40] This catalyst proved to be optimal for the Aza-Cope rearrangement,[39] but ineffective in this reaction, giving only 2% ee.

Table 3.1 Rearrangement of **3a** by VANOL and VAPOL-B3 complex **22**



3a (*S*)-**4a**

Entry	Catalyst **22**	Solvent	Time (h)	Yield	Ee
1	(S)-VANOL-B3	Toluene	42	60%	–17%
2[b]	(S)-VANOL-B3	Toluene	25	75%	–2%
3[c]	(S)-VANOL-B3	Toluene	50	22%	–62%
4	(S)-VAPOL-B3	Toluene	20	73%	0%
5	(S)-VANOL-B3	Acetonitrile	45	73%	–18%
6	(S)-VANOL-B3	THF	48	72%	–9%
7	(S)-VANOL-B3	DCE	48	67%	–2%
8[d]	1:2 (S)-VANOL/$B(OPh)_3$	Toluene	63	56%	–17%
9[e]	1:1 (S)-VANOL/$B(OPh)_3$	Toluene	63	33%	–30%

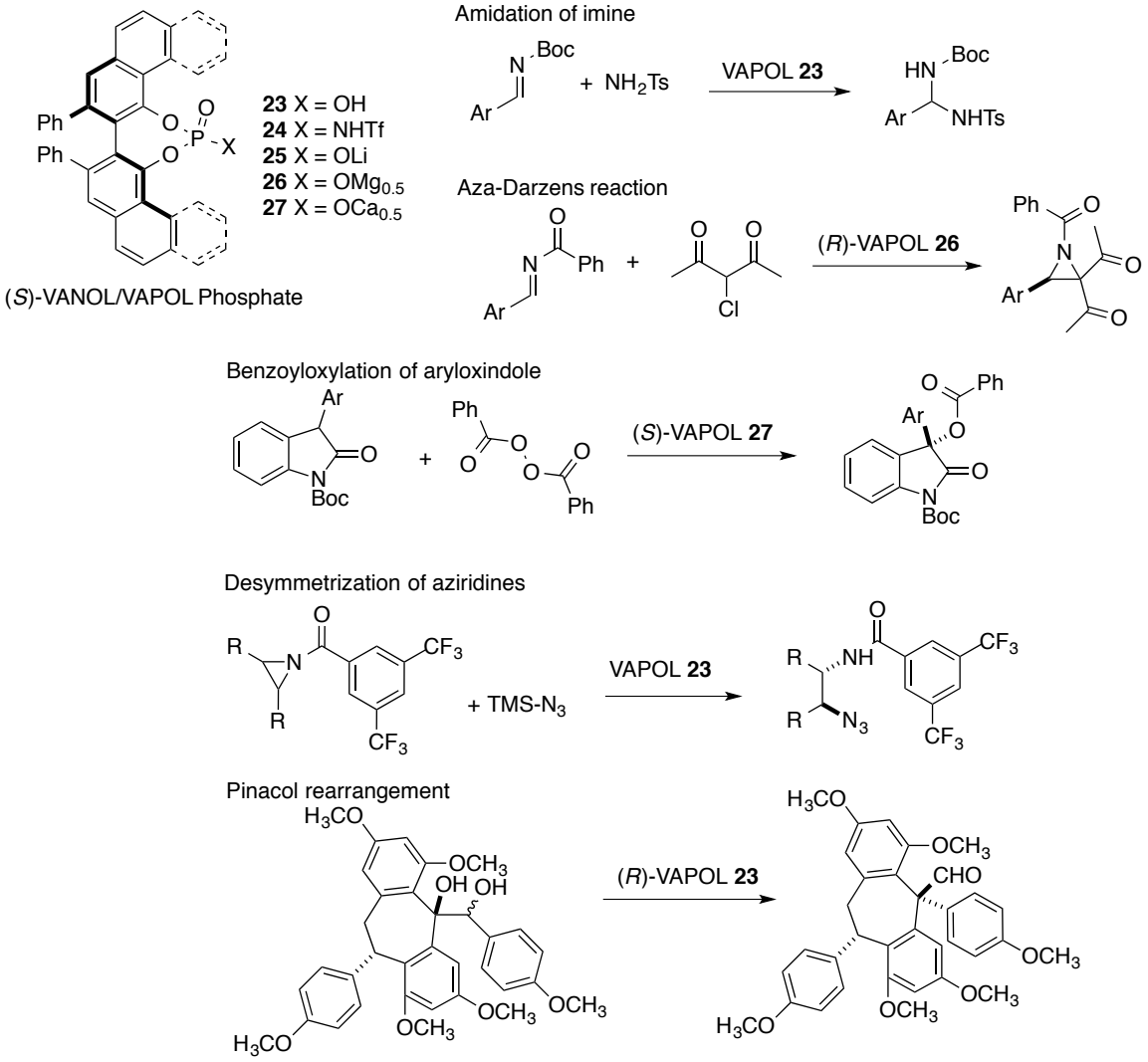
[a.] Unless otherwise specified, all reactions were done on 0.1 mmol scale at 75 °C with 25 mol% catalyst **22** in 0.3 mL solvent in a Schlenk flask. The catalyst was prepared from the ligand and 3 equivalent of $B(OPh)_3$. [b.] 1 equivalent benzoic acid (relative to the ligand) was added during preparation of the catalyst. [c.] The catalyst was prepared from a 1:3:2 mixture of ligand:$BH_3 \cdot SMe_2$:2,4,6-tri-*tert*-butylphenol. [d.] The catalyst was prepared from a 1:2 mixture of ligand:$B(OPh)_3$. [e.] The catalyst was prepared from a 1:1 mixture of ligand:$B(OPh)_3$.

In entry 3, a bulkier phenol, 2,4,6-tri-*tert*-butylphenol was used to prepare the catalyst. The *t*-butyl groups on the phenol were expected to create a more sterically demanding environment near the VANOL ligand, which may improve the enantioselectivity. In fact, it did improve the ee to 62%, but the reaction rate was greatly compromised; only 22% of **4a** was observed after 50 h. In the following entries some different solvents, acetonitrile, THF and DCE were examined, but the results were not encouraging. Finally, the ratio between the ligand and $B(OPh)_3$ was adjusted because it may form a different catalyst, but no significant improvement were observed (entries 8 and 9 in Table 3.1). To sum up, VANOL/VAPOL-B3 were not good catalysts for the α-iminol rearrangement.

3.2.2 α-iminol rearrangement by VANOL hydrogen phosphate its derivatives

VANOL and VAPOL hydrogen phosphate[43] and their derivatives[44] were used as very effective chiral Brønsted acid catalysts in many catalytic asymmetric reactions, including amidation of imines,[45] aza-Darzen reaction,[46] benzoyloxylation of aryloxindoles,[47] desymmetrization of aziridines,[48] and Pinacol rearrangement,[49] (Scheme 3.4). With these observations that VANOL/VAPOL phosphoric acid and their derivatives were able to catalyze a wide range of reactions, these catalysts were also tested for the α-iminol rearrangement in the hope of observing excellent yield and enantioselectivity.

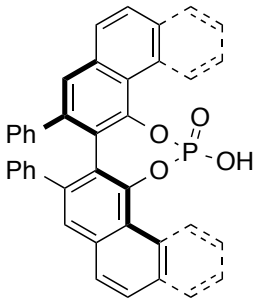
Scheme 3.4 Reactions catalyzed by VANOL/VAPOL hydrogen phosphates and derivatives



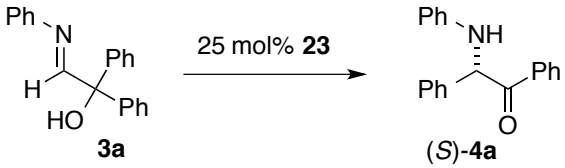
The first catalyst tested was (*S*)-VANOL hydrogen phosphate **23** (Table 3.2 entry 1). The reaction did not proceed at 45 °C, so a higher temperature 75 °C was tested. In this case, the reaction went to completion after half a day, but disappointingly, it only gave 2% ee. Next, (*S*)-VAPOL hydrogen phosphate **23** was examined, with a little improvement to 10% ee. These results indicated that the VANOL/VAPOL hydrogen phosphates are not good catalysts for the α-iminol

rearrangement.

Table 3.2 α-Iminol rearrangement with VANOL/VAPOL hydrogen phosphates **23**



(*S*)-VANOL/VAPOL hydrogen phosphate **23**



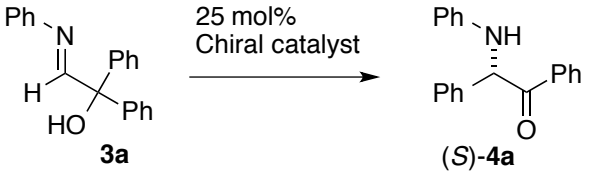
3a (*S*)-**4a**

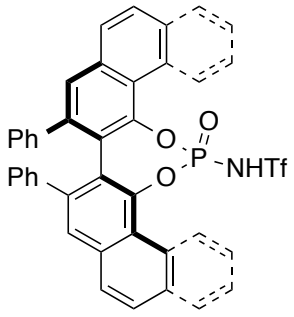
Entry	Catalyst	Temp (°C)	Solvent	Time (h)	Yield	Ee
1	(*S*)-VANOL **23**	45	CH_2Cl_2	24	trace	–
2	(*S*)-VANOL **23**	75	CH_2Cl_2/MeCN	14	89%	–2%
3	(*S*)-VAPOL **23**	75	CH_2Cl_2/MeCN	48	60%	–10%

[a.] All reactions were done on 0.1 mmol scale with 25 mol% catalyst **23** in 0.3 mL solvent in a Schlenk flask.

The next catalyst examined was VANOL and VAPOL N-triflyl phosphoramide **24** in Table 3.3. The results of rearrangement with VANOL and VAPOL N-triflyl phosphoramide gave essentially the same asymmetric induction, 24% ee, but yield was doubled with VANOL (entries 1 and 2). Solvents other than CCl_4 were examined but led to reduced induction (entries 3-5). Entries 1, 6 and 7 list results from different temperatures, but lower temperatures did not lead to improved results and there was no reaction at room temperature. From these results, one can conclude that VANOL/VAPOL N-triflyl phosphoramides are not effective in the α-Iminol rearrangement.

Table 3.3 α-Iminol rearrangement with VANOL/VAPOL N-triflyl phosphoramides





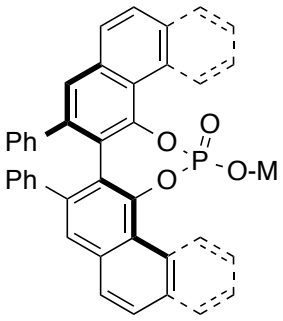
(*S*)-VANOL/VAPOL
N-trifyl phosphoramides **24**

Entry	Catalyst	Temp (°C)	Solvent	Time (h)	Yield	Ee
1	(*S*)-VANOL **24**	60	CCl_4	36	100%	–24%
2	(*S*)-VAPOL **24**	60	CCl_4	41	45%	–24%
3	(*S*)-VANOL **24**	60	hexane	41	54%	–14%
4	(*S*)-VANOL **24**	60	benzene	41	58%	–12%
5	(*S*)-VANOL **24**	70	DCE	20	78%	–12%
6	(*S*)-VANOL **24**	40	CCl_4	48	complex mixture	
7	(*S*)-VANOL **24**	25	CCl_4	48	No Reaction	

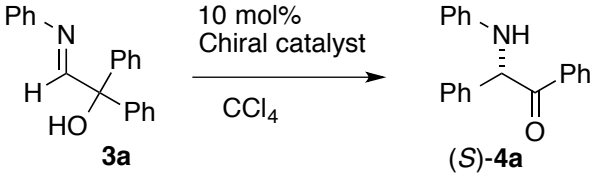
[a.] All reactions were done on 0.1 mmol scale with 25 mol% catalyst **24** in 0.3 mL solvent in a Schlenk flask.

The next catalyst candidate to be examined was the VANOL/VAPOL hydrogen phosphate salts **25** and **26**. With salts **25** and **26**, the rearrangement did not occur at 75 °C, but did at 100 °C. However, the yields and ees were extremely poor, probably because the high temperature favored dissociation of the metal cation, and the more the metal was separated from the ligand chiral environment, the less asymmetric induction it would provide. All chiral catalysts tested thus far failed to provide high yield and high enantioselectivity in the α-Iminol rearrangement.

Table 3.4 α-Iminol rearrangement with VANOL/VAPOL hydrogen phosphate salts



(*S*)-VANOL/VAPOL
Hydrogen phosphate salts **25**/**26**
25 M = Li
26 M = $Mg_{0.5}$



3a (*S*)-**4a**

Entry	Catalyst	Temp (°C)	Time (h)	Yield	Ee
1	(*S*)-VANOL **25**	75	14	trace	–
2	(*S*)-VANOL **26**	75	14	trace	–
3	(*S*)-VANOL **25**	100	24	30%	–2%
4	(*S*)-VANOL **26**	100	24	36%	–8%

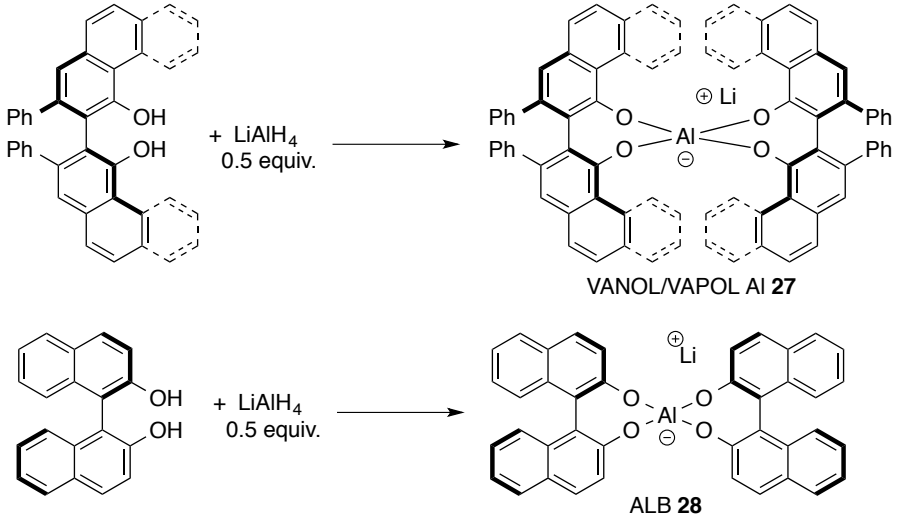
[a.] Reactions were done in 0.1 mmol scale with 10 mol% catalyst in 0.3 mL solvent in a Schlenk flask.

3.3 Rearrangement by VANOL aluminum complex 27

3.3.1 Initial results

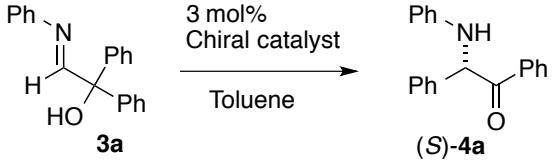
The VANOL aluminum complex **27** is a new catalyst that has not been previously reported in literature. The idea of this new catalyst originated from the utility of the known BINOL aluminum complex **28**,[50] a very effective catalyst for asymmetric Michael addition reactions developed by Shibasaki and coworkers.[15,50] The addition was proposed to occur when the aluminum in **28** activates the carbonyl substrate and the lithium phenoxide deprotonates the Michael donor. Based on the proposed mechanism for this bi-functional catalyst in the Michael reaction, it was wondered if the bi-functional mode of action could also induce an α-Iminol rearrangement.

Figure 3.1 VANOL/VAPOL aluminum complex and BINOL aluminum complex



Initial results with aluminum complexes **27** and **28** are listed in Table 3.5. the VANOL and VAPOL aluminum complexes both gave excellent yield and identical enantioselectivity, 68% ee. The corresponding BINOL catalyst **28** behaved very poorly, giving only 11% yield with 28% ee after a prolonged reaction time.

Table 3.5 α-Iminol rearrangement with VANOL/VAPOL/BINOL Al complexes



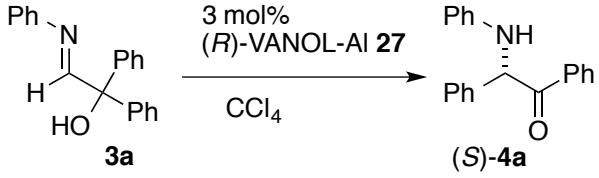
Entry	Catalyst	Temp (°C)	Time (h)	Yield	Ee
1	(*R*)-VANOL-Al **27**	70	19	100%	68%
2	(*S*)-VAPOL-Al **27**	70	23	88%	–68%
3	(*S*)-BINOL-Al **28**	80	1	No Reaction	
4[b]	(*S*)-BINOL-Al **28**	80	15	11%	–28%

[a.] Unless otherwise specified, all reactions were run on 0.1 mmol scale in toluene wth 3 mol% catalyst in a Schlenk flask under N_2. [b.] The catalyst loading was 10 mol%.

3.3.2 Optimization with the VANOL ligand

VANOL was chosen to be the ligand for further studies because it was as good as VAPOL and has a smaller molecular weight than VAPOL. The next step in the optimization was temperature screen in Table 3.6. At 70 °C, catalyst **27** gave 100% yield and 68% ee in 19 hours. At 60 °C, the reaction seemed to slow down dramatically, and at 45 °C, there was no reaction at all. The minimal temperature for this reaction was determined to be 70 °C.

Table 3.6 Temperature screen with VANOL-Al complex **27**

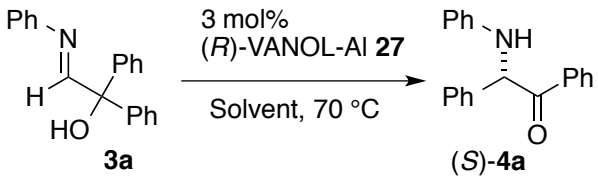


Entry	Temp (°C)	Time (h)	Yield	Ee
1	70	19	100%	68%
2	60	48	trace	
3	45	6	No Reaction	

[a.] Unless otherwise specified, reaction were run in 0.1 mmol scale with 3 mol% catalyst in CCl_4 in a Schlenk flask under N_2.

It was found the enantioselectivity was not affected greatly in different solvents, except for chloroform and DMF (Table 3.7). Nonpolar solvents including CCl_4, toluene, benzene, m-xylene all gave excellent yield and good induction. More polar solvents, including DCE, THF, MeCN, and EtOAc all also gave the same excellent yield and good induction. Toluene was chosen to be the solvent in further studies.

Table 3.7 Solvent screen with VANOL-Al complex **27**

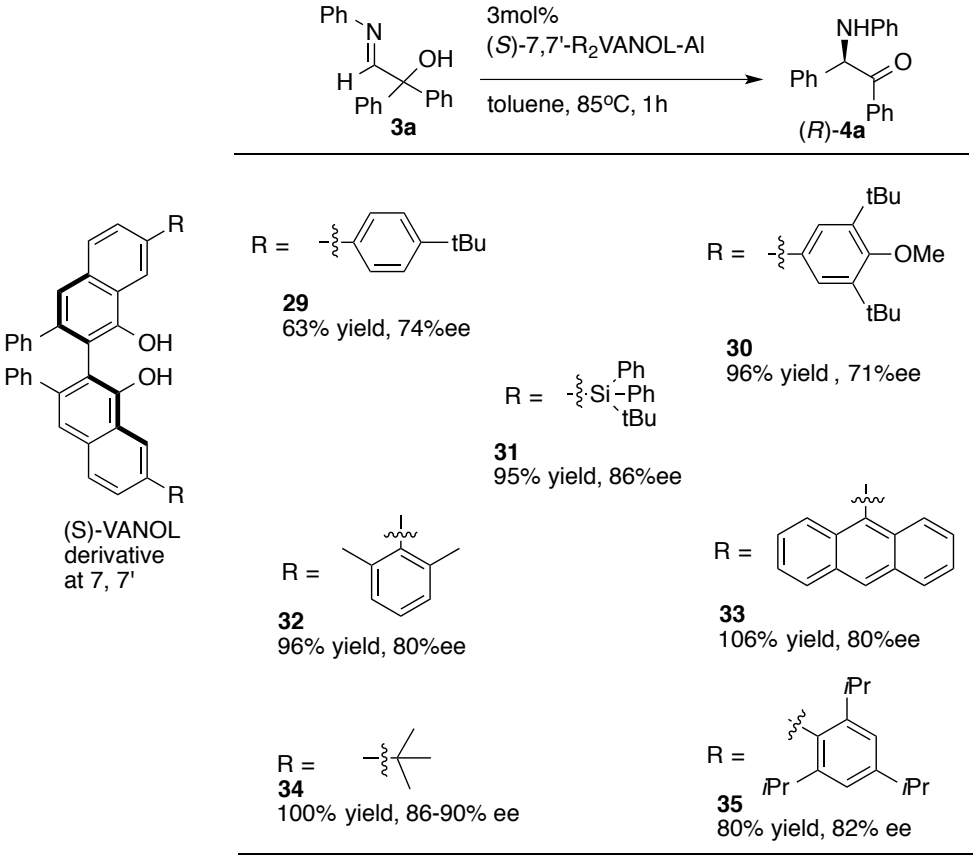


Entry	Solvent	Time (h)	Yield	Ee	Entry	Solvent	Time (h)	Yield	Ee
1	CCl_4	19	100%	68%	6	THF	5	100%	68%
2	toluene	8	100%	68%	7	acetonitrile	14	100%	60%
3	benzene	14	96%	66%	8	EtOAc	14	99%	70%
4	m-xylene	6.5	100%	70%	9	chloroform	4	No Reaction	
5	1,2-DCE	9.5	100%	66%	10	DMF	4	No Reaction	

[a.] Unless otherwise specified, all reaction were run on 0.1 mmol scale with 3 mol% catalyst at 70 °C in 0.3 mL solvent in a Schlenk flask under N_2.

Dr. Yong Guan suggested that derivatives of the VANOL ligand might provide better asymmetric induction. He observed improved enantioselectivity with VANOL derivatives in the aziridination reactions,[51] especially ligand **34** bearing *tert*-butyl groups at 7 and 7' positions on VANOL which gave the best result. Therefore an evaluation of various VANOL derivatives was initiated. It was found that aryl substitutions at the 7 and 7' positions on VANOL ligand, including **29**, **30**, **32**, **33** and **35** improved the ee of the product from 68% to 82% (ligand **35**). Ligand **31** has silyl groups at the 7 and 7' positions, which enhanced the ee to 86%. Ligand **34**, with *tert*-butyl groups at 7 and 7' positions, gave 86%-90% ee over several trials. Thus, ligand **34** was chosen to be the optimal ligand for further studies.

Scheme 3.5 Ligand screen with VANOL derivatives

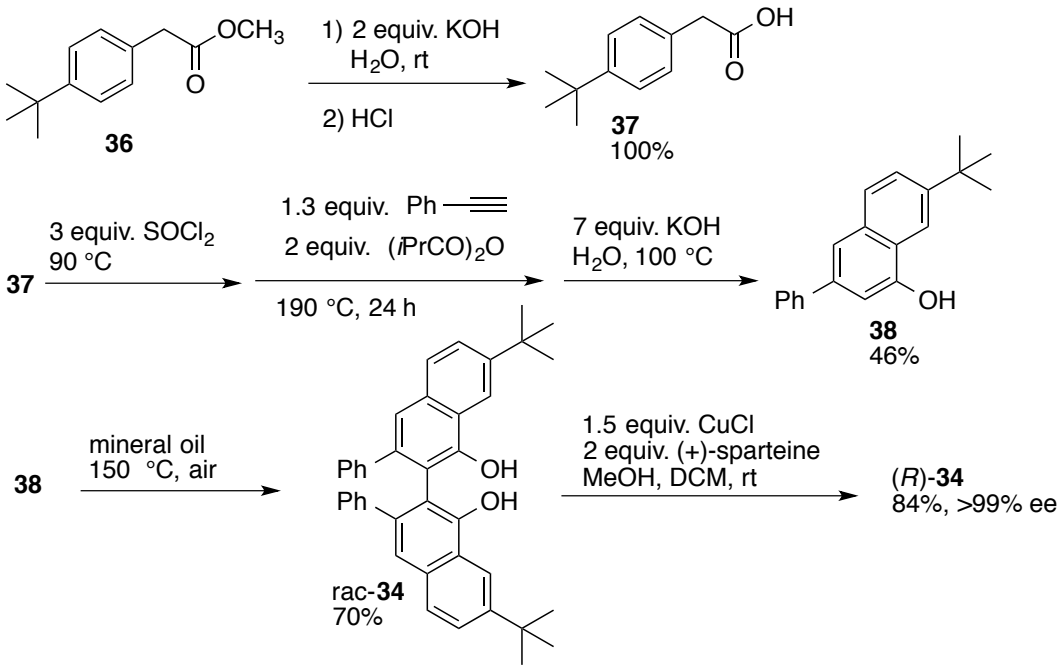


[a.] Unless otherwise specified, reactions were run on 0.1 mmol scale with 3 mol% catalyst, at 85 °C for 1 h in 0.3 mL toluene in a Schlenk flask under N_2.

3.3.3 Synthesis of 7,7'-*t*Bu$_2$VANOL ligand 34

A synthesis of ligand **34** was carried out on gram scale according to the procedure developed by Dr. Yong Guan.[51] The synthesis started from commercially available ester **36**. Hydrolysis of the ester gave the corresponding acid **37** in 100% yield, and the acid was then cyclized with phenyl acetylene through a ketene intermediate to afford the monomer **38** in 46% yield. Dimerization under heat in the presence of air in 70% and deracemization with (+)-sparteine gave the enantiopure ligand (*R*)-**34** in 84% yield (1.5 gram).

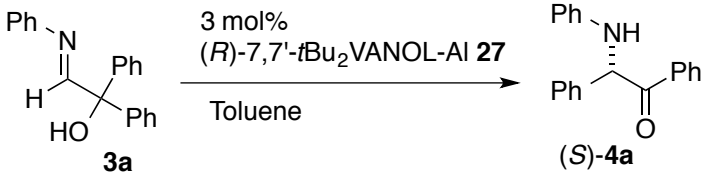
Scheme 3.6 Synthesis of ligand (*R*)-**34**



3.3.4 Optimization with 7,7'-*t*Bu$_2$VANOL ligand 34 in complex 27

The aluminum catalyst **27** formed from the 7,7'-*t*-butyl-VANOL ligand **34** was examined for the α-iminol rearrangement of **3a** at different temperatures and the results are presented in Table 3.8. The maximal enantioselectivity was observed at 80 °C and 90 °C, but it seemed the ee of the product could not be improved to more than 88% with catalyst **27**. A more efficient catalyst was sought and the results of this search are presented below.

Table 3.8 Temperature screen with ligand **34** in aluminum complex **27**



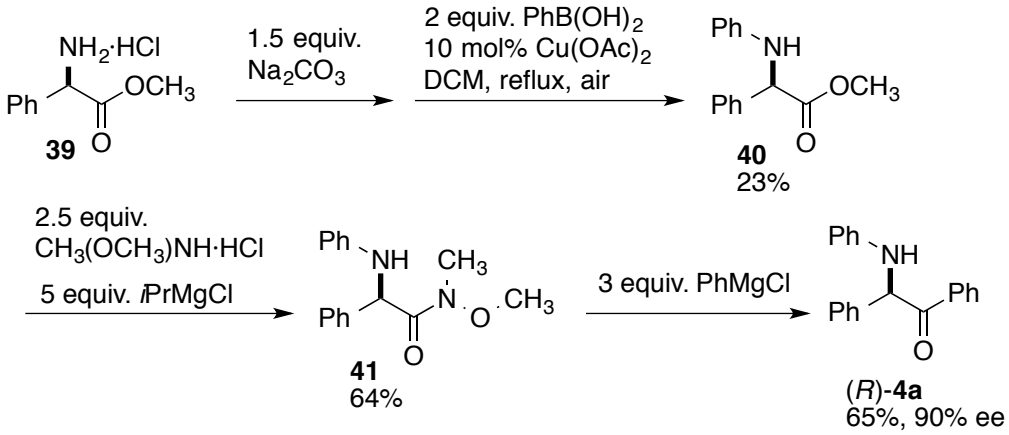
Entry	Temp (°C)	Time (h)	Yield	Ee
1	60	48	32% conversion	
2	70	8	100%	82%
3	80	1.5	94%	88%
4	90	1	85%	88%
5	100	0.5	100%	84%
6	110	0.25	100%	84%

[a.] Unless otherwise specified, all reactions were run in 0.1 mmol scale in 0.3 mL toluene in a Schlenk flask under N_2 with 3 mol% catalyst (*R*)-7,7'-*t*Bu_2VANOL-Al **27** derived from ligand (*R*)-**34**.

3.3.5 Determination of the absolute stereochemistry of 4a

The absolute stereochemistry of **4a** was determined by an independent synthesis of **4a** starting from commercially available enantiopure amino ester **39**. The first step was to neutralize the salt with sodium carbonate, and then couple the free amine with phenylboronic acid, to give the N-phenyl amino ester **40**. Compound **40** was converted to the Weinreb amide and further converted to (*R*)-**4a** with phenyl Grignard reagent. Optical rotation and chiral HPLC both suggested this product (*R*)-**4a** is identical to the iminol rearrangement product **4a** observed with (*S*)-VANOL-Al **27** as the catalyst.

Scheme 3.7 Synthesis of (*R*)-**4a** from **39**

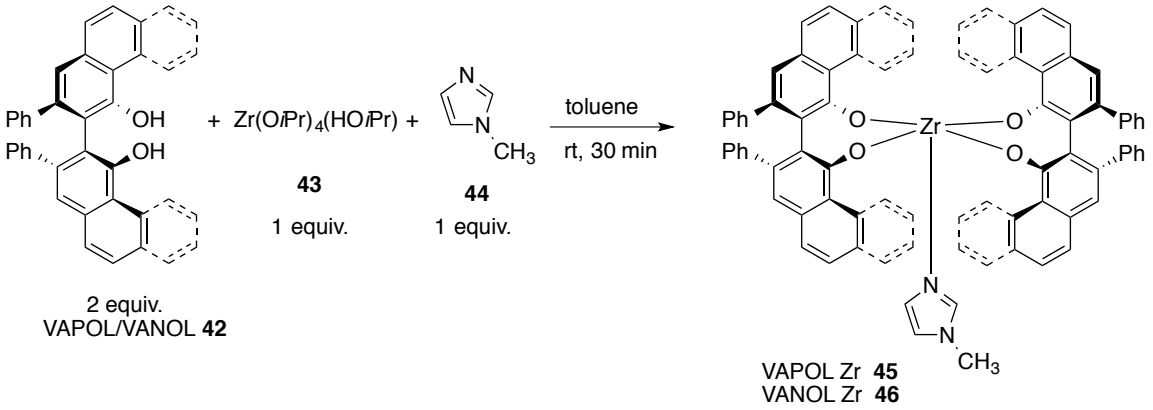


3.4 Rearrangement by VANOL zirconium complex

3.4.1 The Mannich type reaction with VAPOL zirconium complex

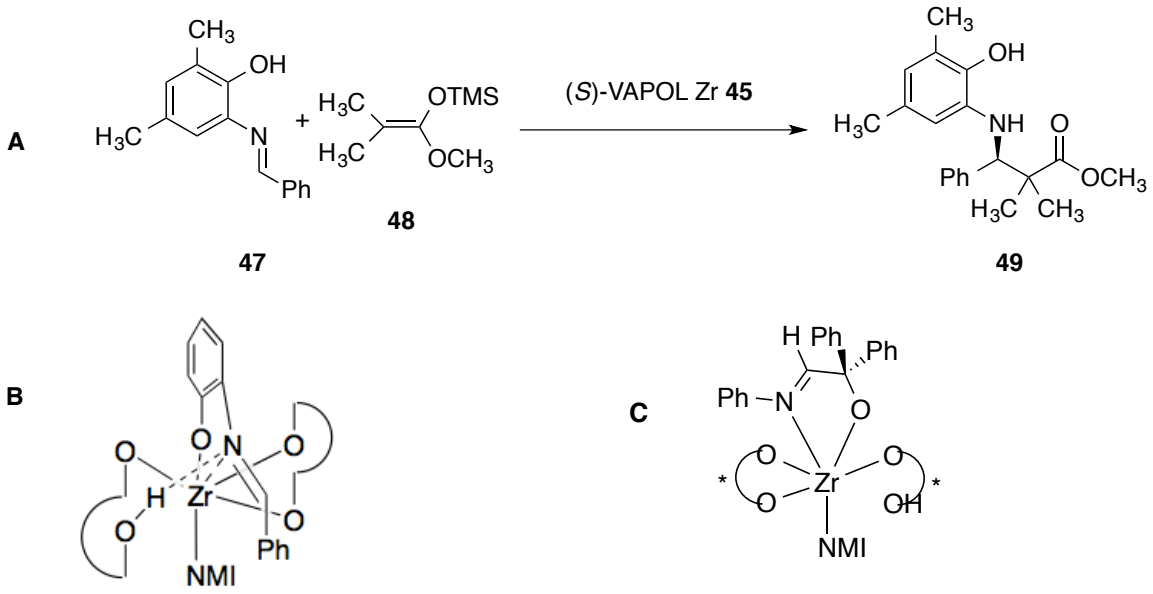
Zirconium VANOL/VAPOL catalysts **45** were first used in Mannich type reactions by Dr. Wulff in 2001.[52] In this reaction, Dr. Wulff and colleagues synthesized the VAPOL zirconium complex **45** with a 2:1:1 mixture of (*S*)-VAPOL **42**, zirconium(IV) isopropoxide isopropanol adduct **43** and N-methylimidazole **44** (Scheme 3.8). This catalyst did an excellent job in the Mannich type reaction between imine **47** and ketene acetal **48** to give the beta-amino ester **49** with excellent yield and ee (Scheme 3.9 A).

Scheme 3.8 Synthesis of VAPOL Zr catalyst **45** and VANOL Zr catalyst **46**



The origin of the excellent enantioselectivity was proposed to be that the vicinal N and O atoms in imine **47** chelated to zirconium center in the catalyst **45** (Scheme 3.9 B), and the chiral ligand VAPOL on the zirconium atom hindered one side of the imine while leaving the other side open for attack by the ketene acetal.

Scheme 3.9 Synthesis of chiral amino ester **49** and chelation between **45** and **47**



3.4.2 The iminol rearrangement with VANOL and VAPOL zirconium complex

The fact that α-Iminol **3a** also has vicinal N and O atoms was the reason that

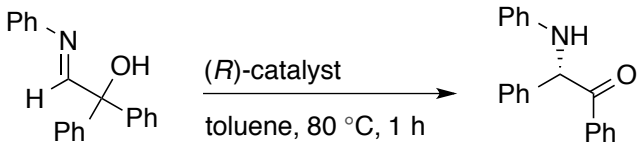
this catalyst was examined for the α-Iminol rearrangement, because similar chelation may also occur between catalyst and substrate (Scheme 3.9 C). Catalyst **45** and **46** were prepared according to a literature procedure[52] (Scheme 3.8). Specifically, this involved mixing 2 equivalent of ligand (VAPOL for **45**, VANOL for **46**), 1 equivalent of zirconium(IV) isopropoxide isopropanol adduct **43** and 1 equivalent of N-methylimidazole **44** in toluene in a screw capped vial under air at room temperature for 30 min. The catalyst **45** gave a light yellow solution while **46** gave a white slurry. The appearance of white precipitate was taken as an indication of the successful formation of catalyst **46**. Catalyst **45** did in fact effect the α-Iminol rearrangement, but the product **4a** was only obtained with 28% ee. If the ligand VAPOL in catalyst **45** was replaced with VANOL (catalyst **46**), the yield and ee of product **4a** in the iminol rearrangement reaction dramatically improved to 94% and 97% respectively, with only 2.5 mol% catalyst loading (Table 3.9 entries 1 and 2).

3.4.3 Optimization of reaction conditions with VANOL Zr complex 46

With the encouraging result shown in entry 2 of table 3.9 in hand, various reaction conditions were probed with the VANOL Zr catalyst **46**. Catalyst loading was examined first (Table 3.9). Initially, 5 mol% catalyst was used, but it was found that 2.5 mol% and also 1 mol% were as effective in terms of yield and asymmetric induction. The catalyst loading could be even as low as 0.5 mol% with nearly the same yield and ee of product **4a**. However, with 0.1 mol% **46** very poor

results were observed. To obtain the highest asymmetric induction, 2.5 mol% catalyst was used for further reactions.

Table 3.9 Catalyst loading screen with catalyst **45** and **46**



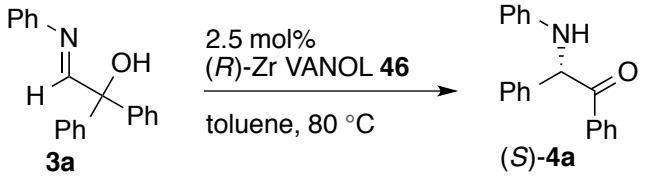
3a (*S*)-**4a**

entry	catalyst	catalyst loading (mol%)	%yield **4a**	%ee **4a**
1	VAPOL Zr **45**	5	86	28
2	VANOL Zr **46**	5	96	97
3	VANOL Zr **46**	2.5	97	97
4	VANOL Zr **46**	1	98	96
5	VANOL Zr **46**	0.5	96	95
6	VANOL Zr **46**	0.1	23	23

All reactions were run with 0.1 mmol substrate, indicated loading of catalyst **46** in 0.3 mL toluene under air in a screw capped vial at 80 °C for 1 h. All were isolated yield except entry 6, which was an NMR yield. Ee were determined with chiral HPLC.

The effect of the concentration of the iminol substrate on the reaction was studied and summarized in Table 3.10. The experiment results suggest that the reaction concentration only slightly effects the performance of the catalyst in terms of yield and ee of product **4a**. For example, when the concentration is varied from 1 M to 0.03 M, the ee for **4a** improved from 95% to 97%. To achieve the highest asymmetric induction and lowest volume of solvent, 0.3 M was chosen for the further reactions.

Table 3.10 Concentration screen with catalyst **46**



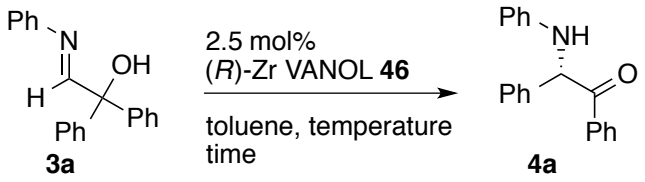
entry	Concentration of **3a** [M]	Time (h)	%yield **4a**	%ee **4a**
1	1	0.17	100	95
2	0.5	0.25	100	95
3	0.3	1	97	97
4	0.1	1	96	97
5	0.03	1	100	97

All reactions were run with 0.1 mmol substrate, 2.5 mol% catalyst **46**, at the indicated concentration of **3a** and reaction time in 0.3 mL toluene under air in a screw capped vial at 80 °C. All yields were isolated yield. The %ee was determined by HPLC.

The effect of temperature on the rearrangement of **3a** with VANOL Zr catalyst **46** was examined and the results are presented in Table 3.11. It was remarkable that the reaction with catalyst **46** was very temperature independent. When the reaction temperature was varied from 25 °C to 120 °C, the yield and enantioselectivity stayed essentially the same except that at 25 °C the reaction was not complete in two days. Even at 160 °C, the reaction was complete in only 30 seconds with surprisingly little loss in ee. For the reaction at 160 °C in mesitylene, the catalyst solution was pre-heated to 160 °C before the addition of the substrate, this is because it was found the reaction proceeded fast at 100 °C and 120 °C, the reaction may have completed at a lower temperature if it was not

pre-heated to 160 °C. To obtain the highest ee in shortest time period at the lowest temperature, 60 °C was found to be the optimal temperature and was used for further reactions.

Table 3.11 Temperature screen with catalyst **46**[a]



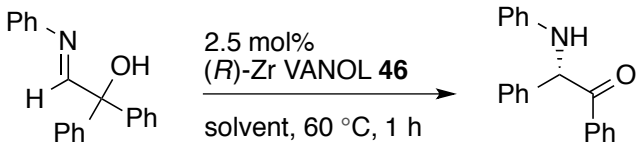
entry	temp (°C)	Time (h)	%yield **4a**	%ee **4a**
1	25	48	55	97
2	40	8	98	98
3	50	2.5	95	97.5
4	60	1	94	97
5	70	1	95	97
6	80	0.5	97	97
7	100	0.17	100	95
8	120	0.08	96	95
9[b]	160	0.008	95	89

[a.] Unless otherwise specified, all reactions were run with 0.1 mmol substrate, 2.5 mol% catalyst in 0.3 mL toluene under air in a screw capped vial and under the indicated temperature and time. All yields were isolated yield. The %ee was determined by HPLC. [b.] The catalyst solution was preheated to the indicated temperature before adding **3a**, and the solvent was mesitylene.

The effect of solvent on the rearrangement of **3a** with VANOL Zr catalyst **46** was examined and the results are presented in Table 3.12. Aromatic solvents were very good for this reaction, including benzene, toluene and mesitylene. However, when a polar/coordinating solvent was used, the reaction rate was

greatly reduced, and the asymmetric induction was reduced slightly as well. The reason for the slower reaction rate and lower ee with polar/coordinating solvent is not clear at this point. This study identified toluene as the optimal solvent.

Table 3.12 Solvent screen with catalyst **46**



3a **4a**

entry	solvent	%yield **4a**	%ee **4a**
1	Benzene	100	97
2	Toluene	94	97
3	Mesitylene	96	95
4	THF	6	95
5	Ethyl acetate	15	92
6	Acetonitrile	9	71
7	1,2-dichloroethane	20	90
8	Chloroform	56	94

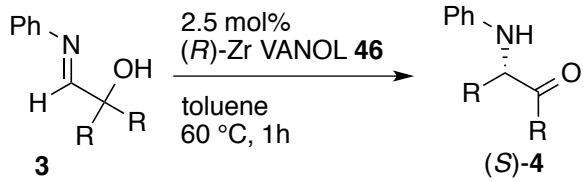
All reactions were run with 0.1 mmol substrate, 2.5 mol% catalyst in 0.3 mL indicated solvent under air in a screw capped vial at 60 °C and stopped at 1 h. Yields in entry 1, 2 and 3 were isolated yields, the rest were determined with NMR. The %ee were determined by HPLC.

3.4.4 Scope of the α-iminol rearrangement of aldimines

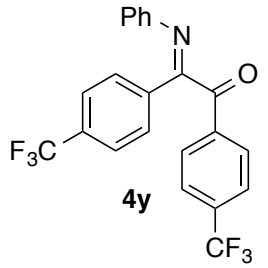
After optimization of the reaction conditions, the scope of the α-iminol rearrangement reaction was studied with both aryl and alkyl aldimines of the general type **3**. A broad range of substrates was examined as shown in Table 3.13. Most of the substrates gave excellent yield and ee (>97%) except those with

ortho substitutions and para CF_3 group on the migrating phenyl ring. In entries 2 and 3, the bulkier isopropyl group at the ortho position resulted in a lower ee than a smaller methyl group. Aryl aldimines with a methyl group on the meta position and para position gave excellent yield and induction (entries 4 and 5). Several substrates with substitutions in the para position were examined including F, Cy, *i*Pr, *n*Bu, Ph, *t*Bu groups all of which gave excellent yield and ee, as well as the electron donating para methoxyl groups (entries 6-12). However, the electron withdrawing CF_3 group in the para position rearranged with a sluggish reaction rate, and only the side product **4y** could be observed. Deoxygenation of the reaction mixture by the freeze-pump-thaw method improved the results and good yield and moderate ee of the desired product **4m** could be realized (entries 13 and 14). Despite the moderate asymmetric induction of the para CF_3 substituted substrate **3m**, the electron withdrawing para acetyl substituted substrate **3n** underwent the rearrangement to give **4n** with 97% ee. For aliphatic migrating groups, hexyl, benzyl, cyclohexyl were examined and all gave excellent yield and induction except a slight drop in ee with hexyl group (entries 16-18).

Table 3.13 Scope of the α-iminol rearrangement of aldimines



Entry	Series	R	% yield[b] **4**	% ee[c] **4**
1	a	Ph	94	97
2	b	2-$CH_3C_6H_4$	88	84
3	c	2-*i*PrC_6H_4	95	–54[d]
4	d	3-$CH_3C_6H_4$	96	98
5	e	3-ClC_6H_4	92	–93[d,e]
6	f	4-$CH_3C_6H_4$	92	98
7	g	4-*n*BuC_6H_4	95	99
8	h	4-*i*PrC_6H_4	98	99
9	i	4-CyC_6H_4	97	94
10	j	4-*t*BuC_6H_4	100	> 99
11	k	4-PhC_6H_4	100	> 99
12	l	4-(CH_3O)C_6H_4	90	98
13	m	4-FC_6H_4	97	> –99[d]
14	n	4-$CF_3C_6H_4$	<5[f]	–
15	n	4-$CF_3C_6H_4$	74	73[g]
16	o	4-AcC_6H_4	100	97
17	p	*n*-hexyl	95	89
18	q	benzyl	98	99
19	r	cyclohexyl	97	98



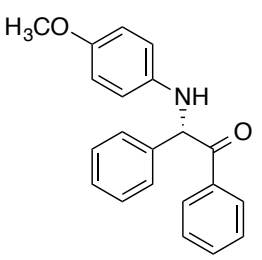
4y

Table 3.13 (cont'd)

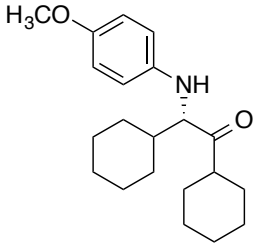
[a.] Unless otherwise specified, all reactions were run with 0.1 mmol **3**, 2.5 mol% (*R*)-catalyst **46** in 0.3 mL toluene under air in a screw capped vial at 60 °C for 1 h. [b.] Isolated yield. [c.] The %ee was determined by HPLC. [d.] (*S*)-catalyst **46** was used, thus (*R*)-product formed. [e.] Reaction was done under N_2 atmosphere in Schlenk flask. [f.] This reaction gave 18% byproduct **4y** and 70% starting **3m**. [g.] Reaction was done under N_2 on a reaction mixture that was deoxygenated by the freeze-pump-thaw method in a Schlenk flask.

Imines bearing substituted arenes as well as a benzyl group on the nitrogen were also examined in this reaction (Scheme 3.10). For aniline derivatives, the p-methoxyl derivatives **4s** and **4t**, the p-ethyl ester **4u**, and the 3-TBS protected methanol derivative **4v**, all were formed in excellent yield and ee. When the aliphatic protecting group benzyl was used, the reaction required significantly higher temperature (120 °C) and the asymmetric induction dropped to 10% ee in the rearranged α-amino ketone **4w**. The reaction scale in Scheme 3.10 was 0.1 mmol for all substrates. For **4s**, the reaction could be conducted on a 40-fold larger scale (1.22 gram) than that for the reactions in Scheme 3.10, with only 1 mol% catalyst loading and still gave 94% yield and 95% ee.

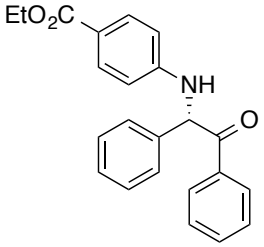
Scheme 3.10 Substituted anilines in α-iminol rearrangement



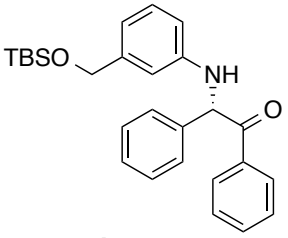
4s
80 °C, 1 h
98% yield, 98% ee



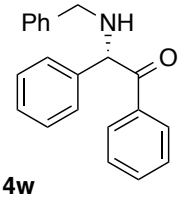
4t
80 °C, 2 h
97% yield, 94% ee



4u
60 °C, 0.5 h
88% yield, 96% ee



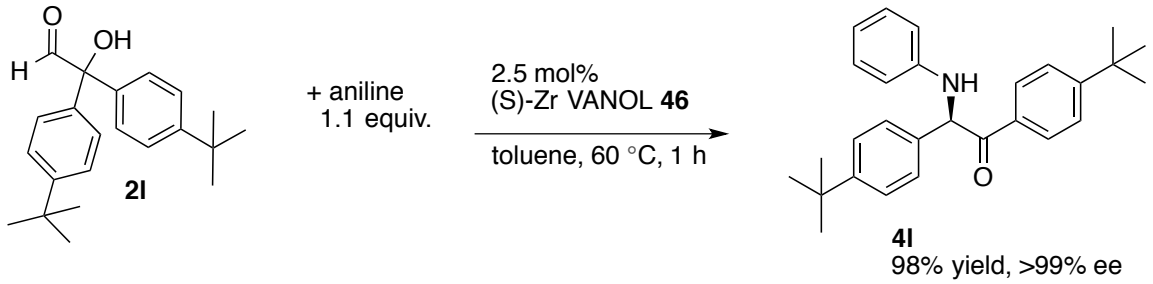
4v
60 °C, 1 h
91% yield, 97% ee



4w
120 °C, 2 h, N_2
95% yield, 10% ee

The condensation between the aldehydes **2** and aniline was spontaneous without any catalyst; therefore it was considered possible that the synthesis of amino ketone **4** could be achieved by reacting the aldehyde **2** with aniline in the presence of catalyst **46**. The tandem imine formation and α-iminol rearrangement of **2l** was performed by treating a mixture of aldehyde **2l** and aniline with 2.5 mol% VANOL Zr catalyst **46** which gave the α-amino ketone **4l** in 98% yield and >99% ee. This is essentially the same as the result of 100% yield and >99% ee when starting with the preformed imine **3l** (see Table 3.13 entry 12).

Scheme 3.11 Tandem imine formation and α-iminol rearrangement of **2l**



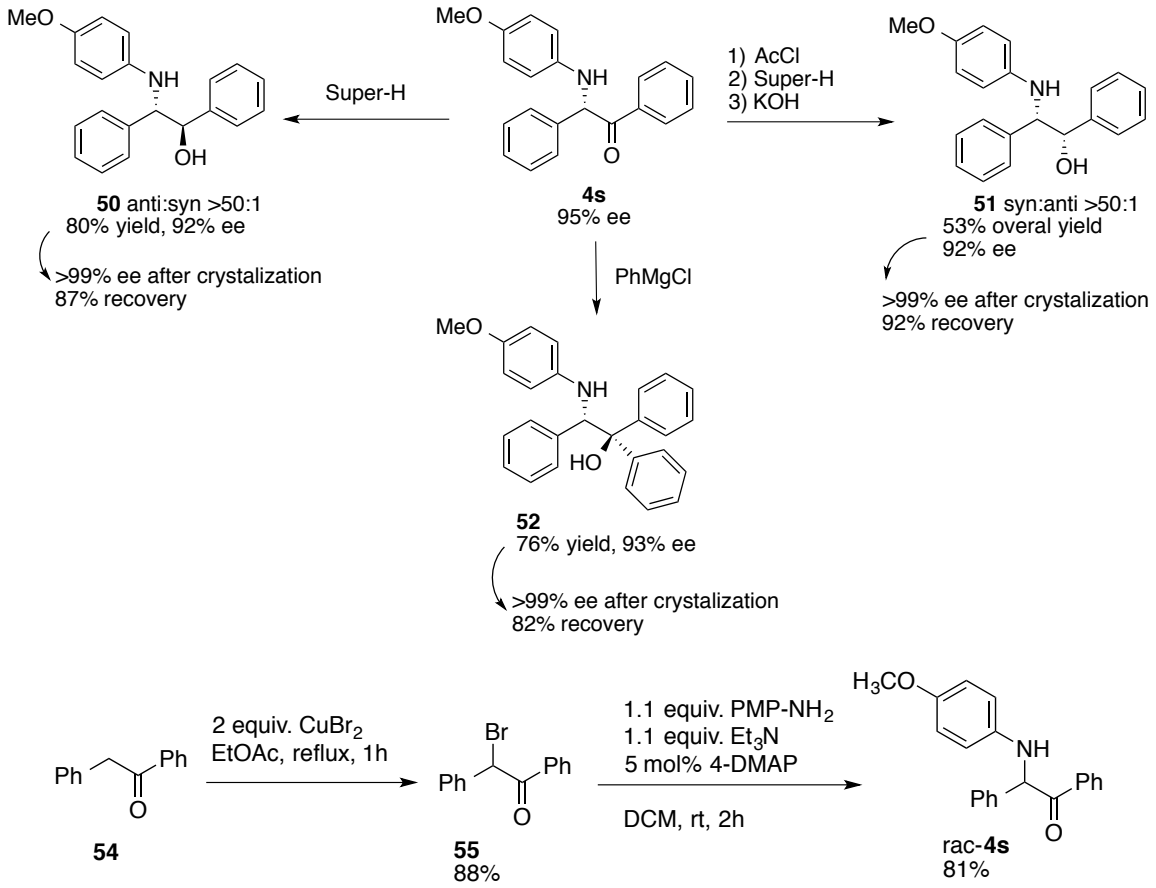
3.4.5 Preparation of amino alcohols from α-amino ketone 4s

The synthetic utility of α-iminol rearrangement methodology could be illustrated in the synthesis of amino alcohols **50** to **52** all of which are important as chiral ligands in asymmetric synthesis and catalysis (Scheme 3.12).[53-55] The amino ketone **4s** from the rearrangement reaction could be reduced to *anti*-amino alcohol **50** with Super Hydride in good yield and ee as a single diastereomer (*anti*:*syn* >50:1). If the nitrogen was protected with an acetyl group, and the resulting derivative was reduced with Super Hydride, it gave the *syn*-amino alcohol **51** as a single diastereomer (*syn*:*anti* >50:1). Lastly, another one equivalent of phenyl Grignard reagent could be added to the ketone **4s** to produce the third amino alcohol **52**. The enantiopurity of **50**, **51** and **52** could be enhanced to >99% ee after one crystallization from a mixture of hexanes and ethyl acetate with greater than 80% recovery as indicated in the Scheme 3.12.

The %ee of **50**, **51** and **52** were determined with the aid of an authentic racemic sample that was prepared from racemic **4s**. Racemic **4s** was prepared from **54**, by installation of a bromine atom at the alpha carbon with copper bromide, and

then substitution of the bromine with p-methoxyaniline to give rac-**4s**.

Scheme 3.12 Synthesis of amino alcohols from α-amino ketone **4s**



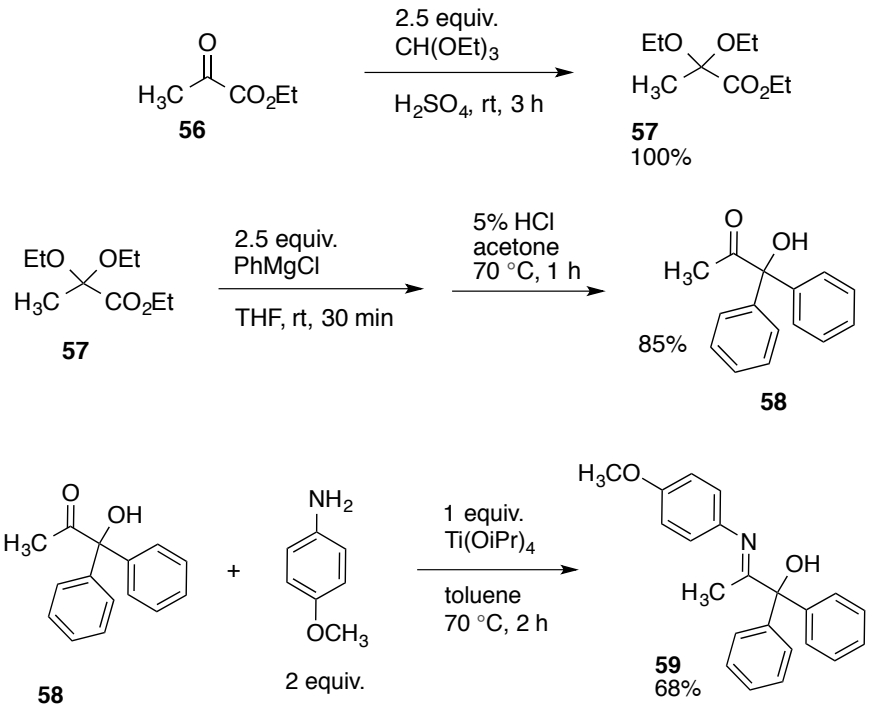
3.4.6 Iminol rearrangement with ketimines

All α-iminol substrates examined in this work were generated from aldehyde **2** and the resulting aldimines underwent facile and highly enantioselective α-iminol rearrangement with VANOL Zr catalyst **46**. To broaden the range of substrates, α-iminols derived from ketones were prepared and subjected to the same reaction conditions with catalyst **46**.

The synthesis of α-iminol **59** started from ethyl pyruvate **56**. The ketone for the rearrangement was protected in the form of a diethyl acetal in quantitative yield,

and the ester group reacted with two equivalents of Grignard reagent, followed by acidic hydrolysis to give the methyl ketone **58** in 85% yield over two steps from **57**. After extensive studies to effect the condensation of ketone **58** with p-methoxyaniline, the optimal catalyst was found to be Ti(O*i*Pr)$_4$, giving the desired α-iminol **59** in 68% yield.

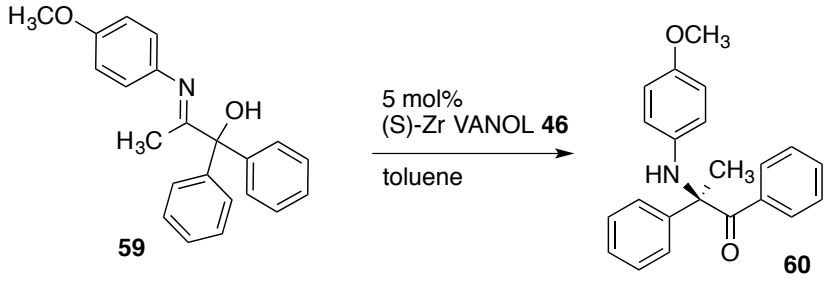
Scheme 3.13 Synthesis of α-iminol **59**



Unfortunately, it was found that α-iminol **59** did not undergo rearrangement with catalyst **46** at temperatures in the range 80 °C to 150 °C. Only the starting material **59** was observed in the ^{1}H NMR spectrum of the crude reaction mixture. The reason for this is probably that the presence of the methyl group changed the electronic nature of the imine and the increased electron rich character of the imine resulted in increased stability of the imine that the zirconium catalyst **46** was

not able to initiate the rearrangement. To test this theory, an electron withdrawing CF_3 group could be attached to the imine, but as of yet, this has not been done.

Table 3.14 Attempted rearrangement of α-iminol **59**



59 **60**

Entry	temp, time	result
1	80 °C, 1 h	No Reaction
2	100 °C, 1 h	No Reaction
3	120 °C, 1 h	No Reaction
4*	150 °C, 1 h	imine started to hydrolyze

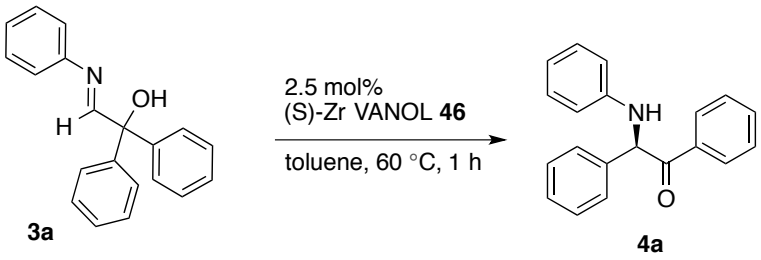
All reactions were run with 0.1 mmol **59**, 5 mol% catalyst **46** in 0.3 mL toluene at indicated temperature for 1 h in a Schlenk flask under air. *Entry 4 was done in mesitylene.

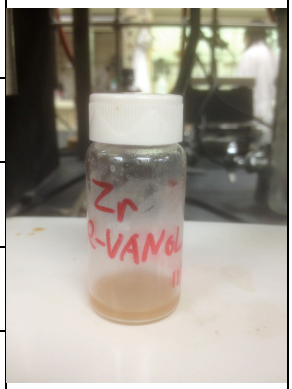
3.4.7 Stability of zirconium VANOL catalyst 46

For the preparation of zirconium VANOL catalyst **46**, a 2:1:1 mixture of VANOL:Zr(O*i*Pr)$_4$(HO*i*Pr):N-methylimidazole was added and stirred in toluene at room temperature for 30 minutes. The solution was clear initially, but after two minutes, a white solid precipitate began to appear in the solution, and this white slurry was used for the reaction. This solid catalyst was in fact stable for storage under air at room temperature. The catalyst was also remarkably stable as a

toluene suspension, which could be allowed to stand for 5 months and 10 days in a screw capped vial under air at room temperature as shown in Table 3.15 and still gave the same yield and asymmetric induction for **4a**.

Table 3.15 Stability of the catalyst **46**



Entry	Age of catalyst*	Yield of **4a**	Ee of **4a**	Photo of catalyst
1	Fresh	94%	97%	
2	1 day	97%	97%	
3	6 days	95%	97%	
4	14 days	98%	95%	
5	5 months 10 days	98%	97%	

*Time stored as a toluene suspension under air at room temperature.

3.4.8 Crystal structure of the zirconium VANOL catalyst

The structure of the VANOL Zr catalyst for the α-iminol rearrangement was assumed to be the structure **46** (see Scheme 3.8). Crystals of a VANOL Zr complex **61** were grown from the catalyst solution in toluene containing a 2:1:1 ratio of VANOL : Zr(O*i*Pr)$_4$(HO*i*Pr) : N-methylimidazole. The toluene was removed under high vacuum and the residue was dissolved in bromobenzene at 100 °C

and very slowly cooled to room temperature. These crystals were subjected to X-ray crystallographic analysis by Dr. Staples and Dr. Rheingold, and the result was not 2:1:1 VANOL : Zr : N-methylimidazole complex as expected, instead, it was the 3:1:2 complex **61** (see Figure 3.2 and 3.3).

Figure 3.2 Crystal structure of **61**

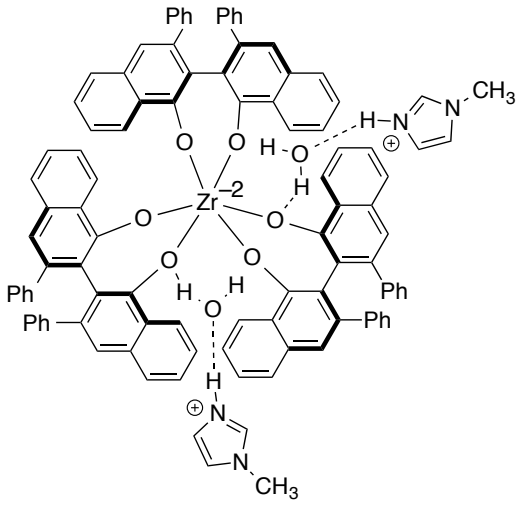
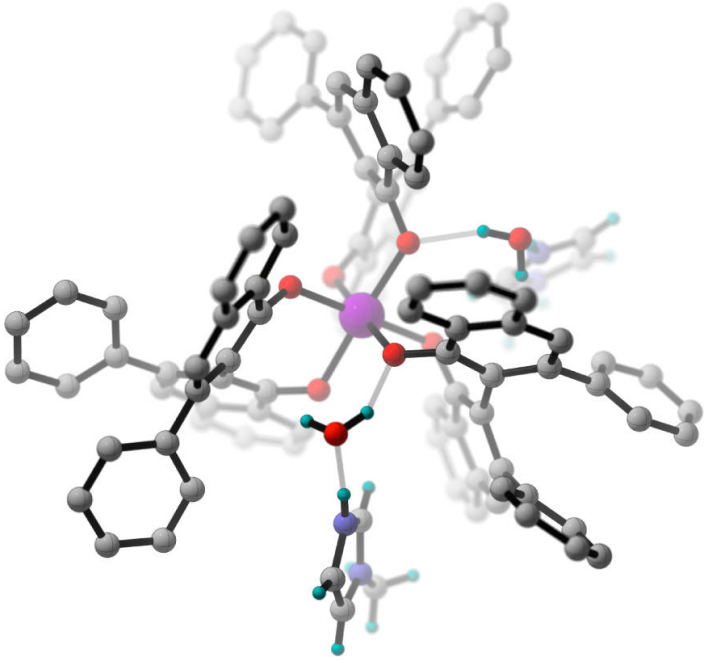


Figure 3.3 Crystal structure of **61** (visualization by Dr. Mathew Vetticatt)



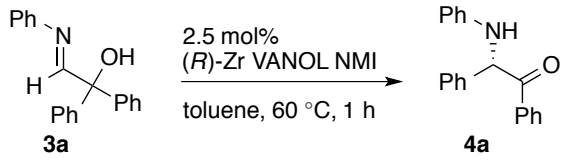
The zirconium metal is bonded to six oxygens from three VANOL ligands and it is charge balanced with two protonated N-methylimidazoles. These imidazoles are not coordinated to the zirconium but rather are protonated. The protonated imidazoles are not H-bonded to the polyoxygenated dianionic core but rather to two water molecules which are in turn H-bonded to the oxygens of the catalyst core. The protons on the imidazole were located, but the protons on water were not. Thus the hydrogen bonding was inferred from the N-O distance (2.701 Å) between imidazole and water, and the O-O distance (2.689 Å) between water and the VANOL ligand. A second sample that was prepared with a 3:1:2 mixture of VANOL : $Zr(O\textit{i}Pr)_4(HO\textit{i}Pr)$: N-methylimidazole exhibited the same unit cell as those grown from a 2:1:1 mixture above. See experimental section for the NMR study of the crystal **61** in d^6-DMSO solution. The formula of the crystal **61** for each unit cell is $Zr_2(C_{32}H_{20}O_2)_6(C_4H_7N_2)_4(H_2O)_4(C_6H_5Br)_6$, Figure 3.2 and 3.3 are two presentations of half of the unit cell omitting the bromobenzene.

3.4.9 Catalyst composition study

The chemical composition of compound **61** obtained by crystallization from the catalyst solution was 3:1:2, not 2:1:1. This suggested the possibility that compound **61** is the actual catalyst for α-iminol rearrangement. Given this discrepancy, catalysts generated with various ratios of VANOL : $Zr(O\textit{i}Pr)_4(HO\textit{i}Pr)$: N-methylimidazole were prepared and their effects on the rearrangement reaction of **3a** were examined and the results are presented in Table 3.16. In entries 1 and

6, no N-methylimidazole was added, and it turned out that this resulted in no formation of a detectible amount of product **4a**. This indicates that N-methylimidazole is a crucial component of the active catalyst. In entries 2 and 3, excess N-methylimidazole was added and this slowed down the reaction. In entry 4, only 1 equivalent VANOL was used, and the asymmetric induction remained unchanged although the reaction rate was lower. In entry 7, the exact ratio that was revealed in the crystals of **61** was employed and there was no significant change in yield and ee. In entry 8, crystals of **61** were used, and the yield and ee of **4a** was almost identical to that of the product with in-situ generated catalyst prepared from 2:1:1 ratio of the components. Apparently, both 2:1:1 and 3:1:2 stoichiometries gave the same catalyst and the real question is what is the actual structure of the catalyst in solution. Is it structure **61** or some other species? And also what is the mechanism of this reaction? This will have to await future studies.

Table 3.16 Catalyst composition study



[Zr] = $Zr(OiPr)_4(HOiPr)$
[L] = (R)-VANOL
[N] = N-Methylimidazole

entry	Ratio **[L]:[Zr]:[N]**	%yield **4a**	%ee **4a**
1	2:1:0	0	–
2	2:1:1	94	97
3	2:1:2	70	97
4	2:1:20	8	96
5	1:1:1	33	97
6	3:1:1	98	98
7	3:1:0	0	–
8	3:1:2	80	96
9	3:1:2[b]	96	98

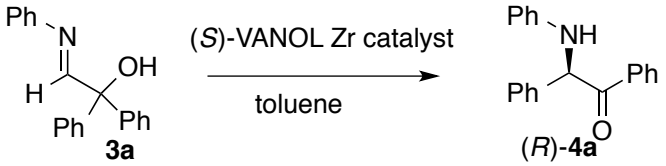
[a.] Unless otherwise specified, all reactions were run with 0.1 mmol **3a**, 2.5 mol% catalyst in 0.3 mL toluene in a screw capped vial under air at 60 °C and stopped after 1 h. [b.] Crystals of **61** were used.

3.4.10 Catalyst 46 recycle study

The catalyst **46** exhibited remarkable stability for storage in toluene under air (see Table 3.15). Thus it was of interest to determine how the catalyst would perform for more than one cycle. For the first cycle, the catalyst was prepared fresh and used immediately. The result was normal as expected (see Table 3.17 entry 1). After the first cycle was complete, excess hexane (10 times volume to toluene) was added to the solution at room temperature to precipitate the catalyst. After filtration through filter paper, the white solid catalyst was recovered and all was used directly in the next cycle. For the second cycle, the reaction time was

slightly longer than the first cycle, but the yield and ee of product was unchanged. For the third cycle, the catalyst performed poorly. However, the toluene solvent in this study was suspected to be somewhat wet, so this study needed to be reexamined. The loss of catalyst after each cycle is substantial, and thus perhaps a better method for precipitation of the catalyst would extend the number of cycles through which it can be reused.

Table 3.17 Catalyst recycle study



cycles	temp/time	cat. used	yield[a], ee
cycle 1[b]	60 °C/1 h	5 mol% (0.0522 g)	100%, 98%
cycle 2[c]	60 °C/3 h	0.0400 g recycled from cycle 1	100%, 98%
cycle 3[d]	70 °C/7 h	0.0225 g recycled from cycle 2	25%[e], 64%

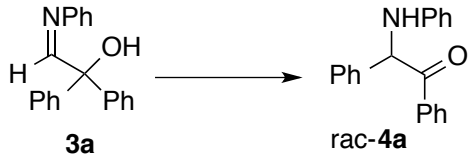
[a.] All reactions were run with 1.04 mmol **3a** in 2 mL toluene at the indicated temperature and time period. Yields were isolated yield, ee were determined by HPLC. [b.] The catalyst in cycle 1 was prepared from 0.05 mmol $Zr(O\textit{i}Pr)_4(HO\textit{i}Pr)$, 0.10 mmol (*S*)-VANOL and 0.05 mmol NMI. [c.] 0.0400 g catalyst was recycled from cycle 1 and all was used in cycle 2. [d.] 0.0225 g catalyst was recycled from cycle 2 and all was used in cycle 3. [e.] Yield determined by NMR, 70% unreacted starting material was also present.

3.4.11 Control experiment

To examine if there's a background reaction in the α-iminol rearrangement, control experiments were designed and the results are presented in Table 3.18.

The rearrangement without catalyst did not go at 80 °C but proceeded at 150 °C. However, the product was not stable at 150 °C in the presence of air (entry 3). In this reaction, the product **4a** is oxidized to give a 50% yield of a product tentatively assigned as **4x** (see Table 2.1). It was also found that Zr(O*i*Pr)$_4$(HO*i*Pr) did not catalyze the reaction, however, in entries 4 and 5 if Zr(O*i*Pr)$_4$(HO*i*Pr) and N-methylimidazole were both added, the reaction proceeds to a small extent, which means that N-methylimidazole was an important ingredient in the catalyst for the reactivity. This discovery is consistent with the results in Table 3.16 entries 1 and 6.

Table 3.18 Control experiments



3a rac-**4a**

entry	catalyst	Solvent	time	temp	yield rac-**4a**
1	None	toluene	42h	80 °C	0%
2	None	Mesitylene	2h	150 °C	28%[b]
3	None	Mesitylene	5h	150 °C	20%[c]
4	5 mol% Zr(O*i*Pr)$_4$(HO*i*Pr)	toluene	1h	80 °C	0%
5	5 mol% Zr(O*i*Pr)$_4$(HO*i*Pr) and NMI	toluene	1h	80 °C	12%[d]

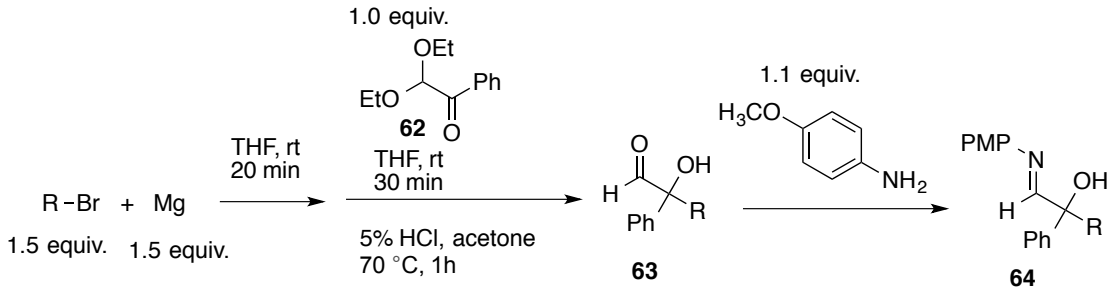
[a.] Unless otherwise specified, all reactions were run with 0.1 mmol **3a** under air and yields were determined by NMR. [b.] Reaction was run under N_2, 71% **3a** was unreacted. [c.] 30% **3a** was unreacted and 50% side-product **4x** (see Table 2.1). [d.]

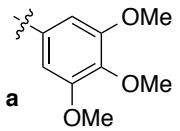
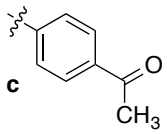
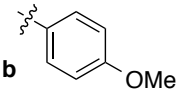
79% **3a** was unreacted.

3.5 Kinetic resolution of racemic α-iminol by VANOL zirconium complex

The α-iminol rearrangement of all substrates examined at this point containe two identical migrating groups in the molecule. If the two migrating groups are different, the starting iminol would be racemic, and thus there may be a possibility that the zirconium VANOL catalyst would preferably convert the matched enantiomer to the amino ketone product leaving the unmatched enantiomer unreacted. The first few substrates were prepared from commercial **62**. Addition of a Grignard reagent to the ketone in **62** followed by acidic hydrolysis gives aldehyde **63**, which was converted to the racemic α-iminol **64** with p-methoxylaniline.

Table 3.17 Synthesis of racemic iminols



R	yield Aldehyde **63**	yield Iminol **64**	R	yield Aldehyde **63**	yield Iminol **64**
a 	71%	100%	**c** 	52%	98%
b 	74%	95%	**d** 	40%	100%

For the kinetic resolution of **64a**, which contains 3,4,5-trimethoxylphenyl and phenyl as the migrating groups, it was found that the migration of phenyl group was more favorable than the trimethoxylphenyl group. The crude ^{1}H-NMR spectrum suggested that only phenyl group migrated, not the trimethoxylphenyl. It was also found that from the beginning up to 50% conversion (5.5 h), the reaction proceeded smoothly, but after 50% conversion, the reaction rate slowed down considerably. When the reaction was stopped at 50% conversion, the enantiopurity of **64a** was determined to be >99% ee. The absolute stereochemistry of **65a** was tentatively assigned as (*S*) according to previous results, and the remaining **64a** was assumed to be enriched in the (*R*) enantiomer if the chelation mechanism between substrate and catalyst **46** is operated. These results suggest that kinetic resolution of racemic α-iminols is feasible and that future investigation of this process is warranted.

Scheme 3.14 Initial study of kinetic resolution of **64a**

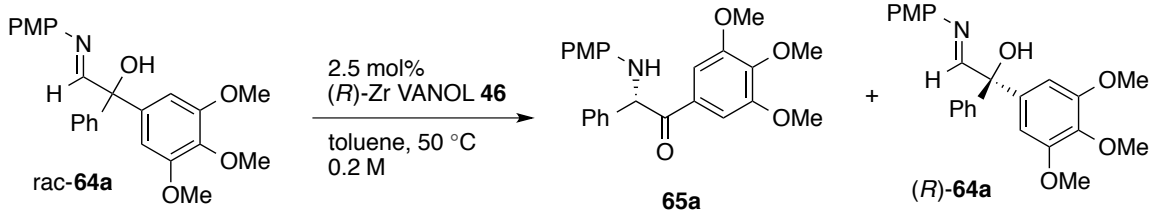
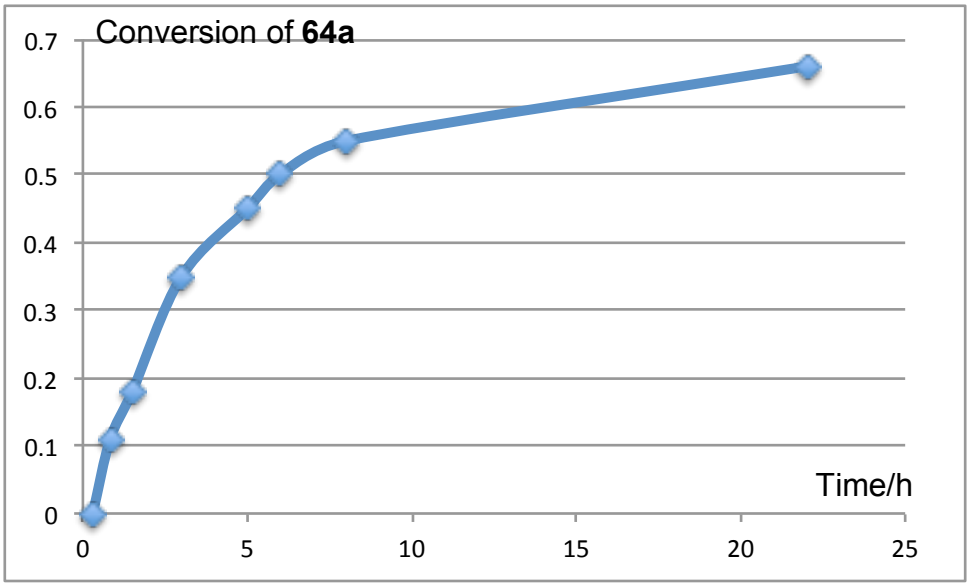


Figure 3.4 Reaction progress of **64a**



3.6 Conclusion

A successful catalytic asymmetric α-iminol rearrangement methodology was established with a zirconium VANOL complex. The yield and ee of the rearrangement product was up to 100% and >99%, respectively. The catalyst was incredibly stable such that after storage for 5 month in toluene under air, the product was formed without loss in yield or enantioselectivity. A crystal of the catalyst was obtained and analyzed. In the crystal, a 3:1:2 ratio of VANOL:Zr:NMI was found instead of the expected 2:1:1 ratio. The actual active catalyst and mechanism for this reaction remains unknown, and further investigation is needed.

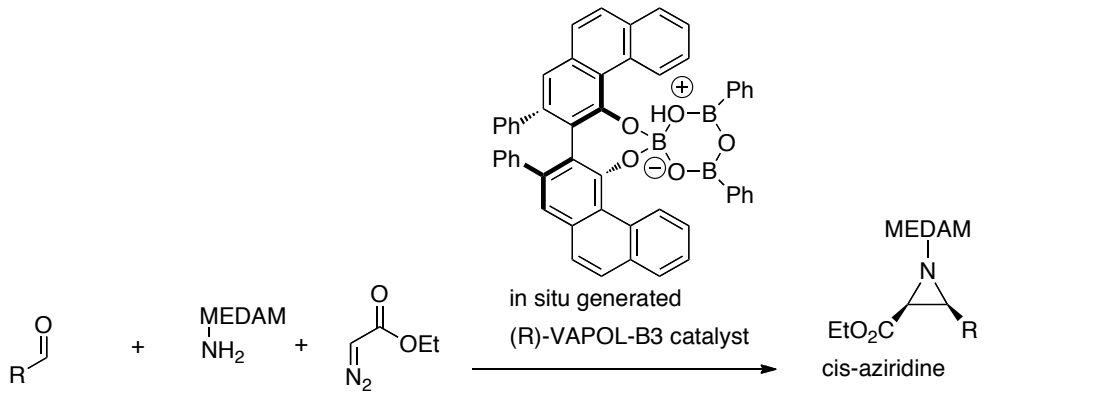
CHAPTER FOUR
MISCELLANEOUS PROJECTS

4.1 Total synthesis of Rhizochalin C

4.1.1 Introduction

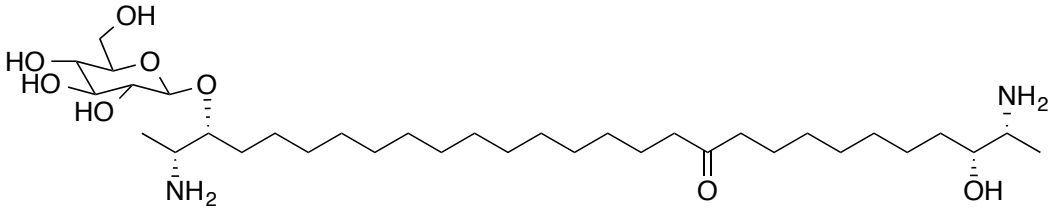
Asymmetric catalytic aziridination is one of the useful methodologies in organic synthesis that was developed in Dr. Wulff's group.[34] In this methodology, an imine and a diazoacetate or diazoacetamide, are the starting materials; their reaction can be catalyzed by a VAPOL/VANOL-B3 complex to afford the enantiopure aziridine as shown in Scheme 3.3. Recently, Dr. Anil Gupta developed the three-component cis-aziridination reaction as shown in Scheme 4.1.[35] The R group can be either electron-rich or electron-poor aromatic ring or 1°, 2°, and 3° aliphatic chain, or an alkyne.[56]

Scheme 4.1 Multi-component catalytic asymmetric synthesis of *cis*-aziridine

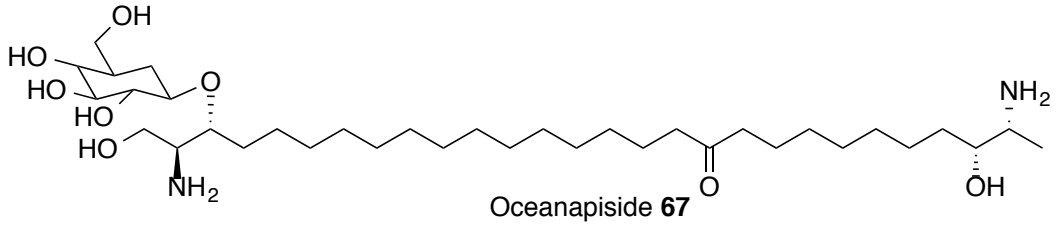


Two-headed sphingolipids (Figure 4.1) can be found in many marine sponges such as Rhizochalina incrustata,[57,58] Oceanapia phillipensis,[59] Oceanapia,[60] Calyx,[61] Leucetta leptorhapsis,[62] and one unidentified sponge.[63] It was found that the two-headed sphingolipids have different kinds of bioactivities: anti-bacterial activity,[57] cytotoxic activity,[57] antifungal activity, [59,60] selective DNA-damaging activity,[61] and inhibition of protein kinase C.[63] Rhizochalin is representative of the two-headed sphingolipid natural product with chiral amino alcohol functionalities on both ends. An asymmetric aziridination reaction followed by ring opening with an oxygen nucleophile could achieve both amino alcohol functionalities and the desired stereochemistry. Therefore, the two-headed sphinglipid compounds were chosen as an application of the asymmetric catalytic aziridination and subsequent ring opening methodology in natural product total synthesis.

Figure 4.1 Two-headed sphingolipids

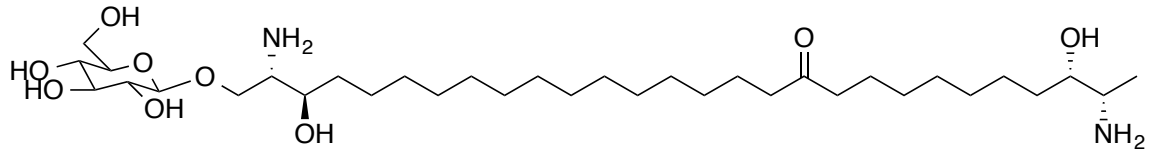


Rhizochalin **66**

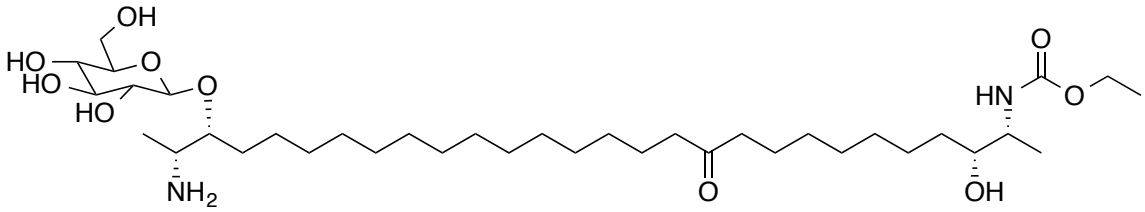


Oceanapiside **67**

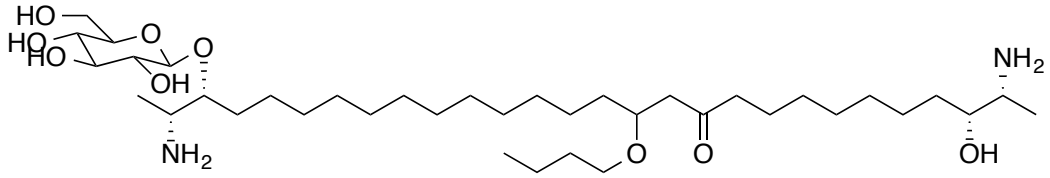
Figure 4.1 (cont'd)



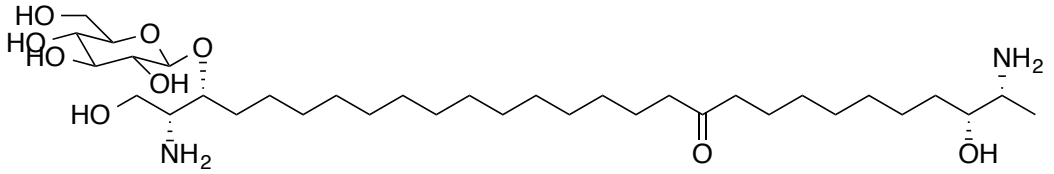
Calyxoside **68**



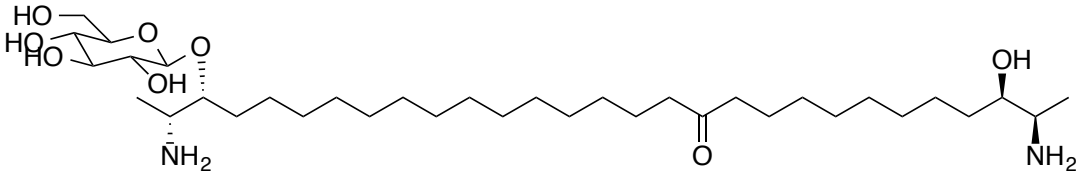
Rhizochalin A **69**



Rhizochalin B **70**



Rhizochalin C **71**



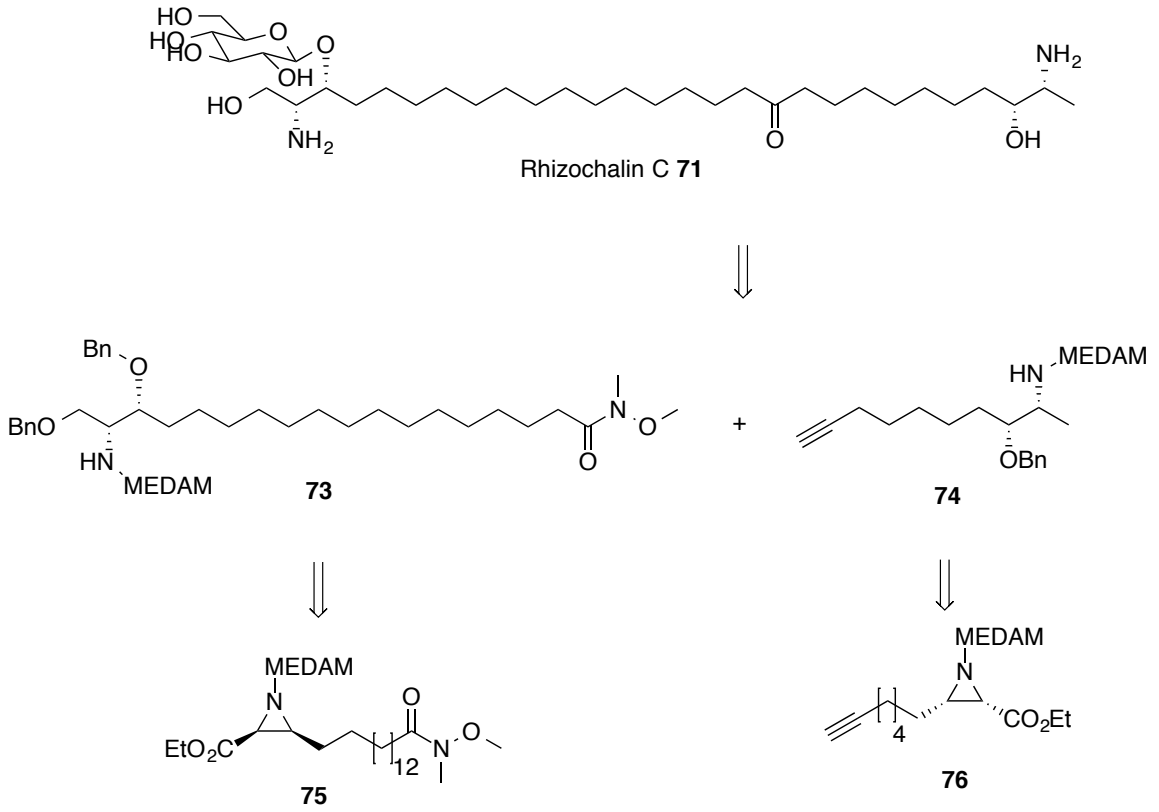
Rhizochalin D **72**

4.1.2 Retrosynthetic analysis of Rhizochalin C

Rhizochalin C was selected as the first target molecule because it is simpler than the rest and once Rhizochalin C was successfully synthesized, the rest could also be made via similar routes. The retrosynthetic strategy of Rhizochalin C is

displayed in Scheme 4.2. The key disconnection is at the ketone carbon; the long chain could be constructed by a coupling reaction between a Weinreb amide and an acetylide, not an alkyl Gringard reagent because of the acidic NH proton. The chiral centers are generated from catalytic asymmetric aziridination and subsequent ring opening reaction with an oxygen nucleophile.

Scheme 4.2 Retrosynthetic analysis of Rhizochalin C



4.1.3 Total synthesis of Rhizochalin C

The total synthesis of Rhizochalin C is envisioned by coupling between terminal alkyne fragment **83** and Weinreb amide fragment **88** (Schemes 4.3 and 4.4).

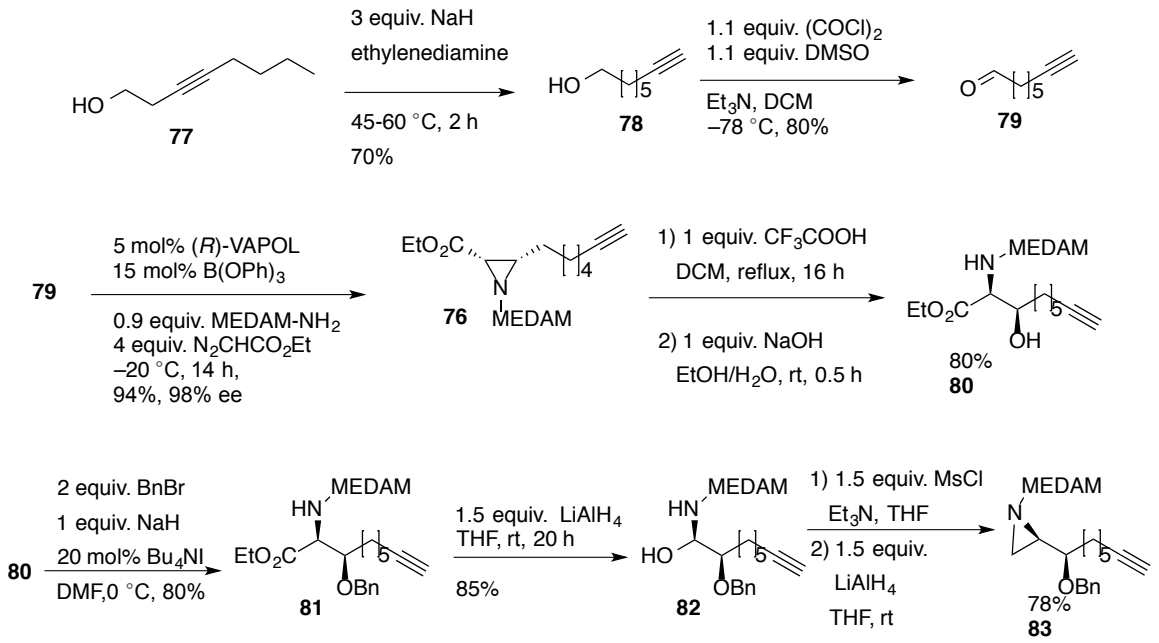
4.1.3.1 Synthesis of the alkyne fragment 83

Alkyne fragment **83** is to be synthesized from compound **78**, but in fact, the price of terminal alkyne **78** is too high for large scale synthesis. Therefore **78** was

actually made by the alkyne zipper reaction from the cheaper internal alkynol **77**. This reaction worked very well, yielding 70% of **78** on 120 mmol scale in Scheme 4.3. Next reaction was Swern oxidation of the terminal alcohol. This oxidation afforded an 80% yield of the corresponding aldehyde **79**. Asymmetric catalytic aziridination was carried out in a multi-component mode: the imine formation between aldehyde **79** and MEDAM-NH_2 was done in situ avoiding the isolation of the imine which provides for a broader substrate scope compared with the traditional aziridination reaction procedure beginning with a pre-formed imine. The multi-component aziridination was carried on a mixture of the aldehyde, amine and ethyl diazoacetate with 5 mol% of the (*R*)-VAPOL B3 catalyst, on a 40 mmol scale with 94% yield and 98% ee of the aziridine **76**. Aziridine **76** was treated with TFA to afford the ring-opened product **80** in 80% yield as a single regioisomer. The TFA presumably protonates the nitrogen, and then trifluoroacetate anion attacks the β-carbon because it's further from the electron withdrawing ester group. The positive charge would be expected to be better located on the β-carbon and thus giving the observed direction of ring opening. After the reaction, the trifluoroacetate was cleaved with NaOH in an ethanol water solution to afford the desired alcohol in 80% yield over two steps. The protection of the alcohol in **80** with BnBr was found be to solvent dependent: the reaction didn't proceed in THF but did in DMF. This is probably because the more polar solvent DMF favored the formation of the alkoxide and thus the S_N2 reaction. It was also found that a lower

temperature was necessary for this reaction because at room temperature a significant amount of an unidentified byproduct was formed. After the alcohol in **80** was protected with a benzyl group, reduction of the ester was carried out with $LiAlH_4$ and this worked very well, yielding the desired product **82** in 85% yield.

Scheme 4.3 Synthesis of alkyne fragment **83**

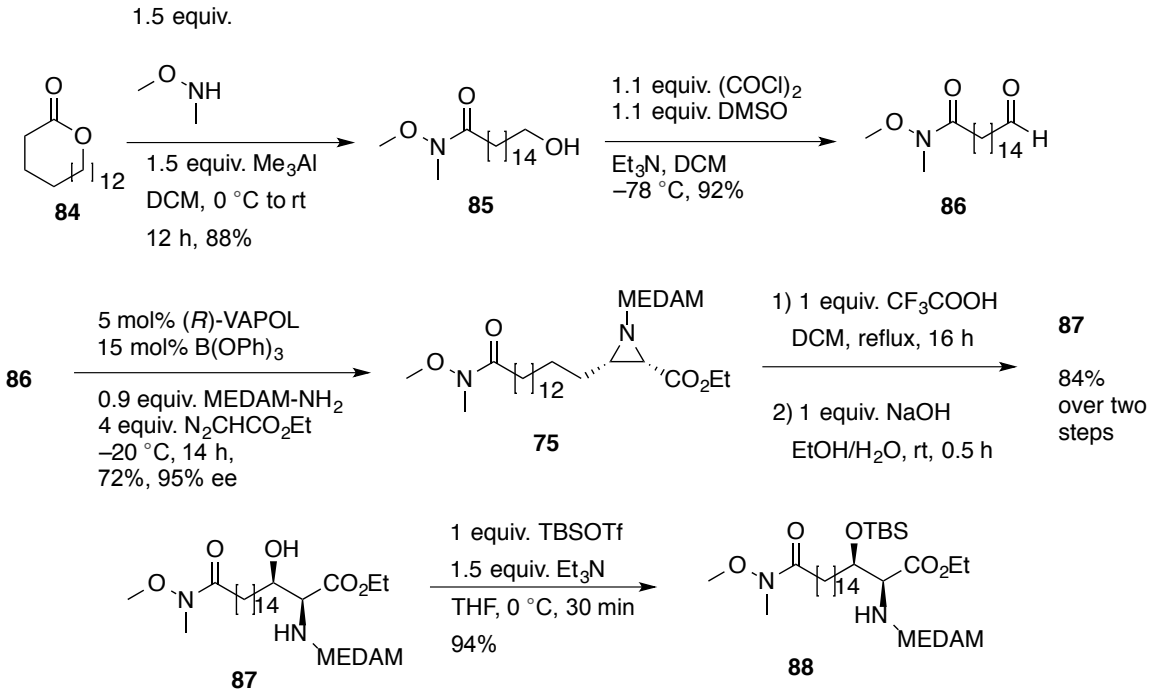


The next step was to convert the terminal alcohol in **82** to a leaving group and reduce it to a methyl group, however, when the MsCl and $LiAlH_4$ sequence was employed, the result was that the aziridine **83** was obtained in 78% yield over the two steps instead of the planned methyl compound **74** (Scheme 4.2). Although the aziridine **83** was an unexpected product, it was later found that the 3-membered ring could be opened with H_2 to give a methyl group. Therefore, the retrosynthesis in Scheme 4.2 was amended to include **83** in place of **74**.

4.1.3.2 Synthesis of the Weinreb amide fragment 88

The synthesis of the Weinreb amide fragment **88** was initiated with lactone **84**. Opening the lactone with N,O-dimethylhydroxylamine gave the alcohol **85** in 88% yield. Swern oxidation of the alcohol afforded the aldehyde **86** in 92%. The multi-component aziridination reaction of aldehyde **86** was carried out as normal on a small scale but became sluggish on a larger scale. Thus at the larger scale, reactions were carried out at room temperature in order to drive the reaction forward. Ring opening of the aziridine **75** with TFA as described in the synthesis of the alkyne fragment **83** in Scheme 4.3 gave the amino alcohol **87** in 84% yield over two steps.

Scheme 4.4 Synthesis of Weinreb amide fragment **88**



Finally protection of the alcohol with a TBS group afforded **88** in 94% yield.

Compounds **88** and **83** were ready to be coupled to form the long chain intermediate. This and additional steps are carried out by Wenjun Zhao. Please see Wenjun's thesis for more details.

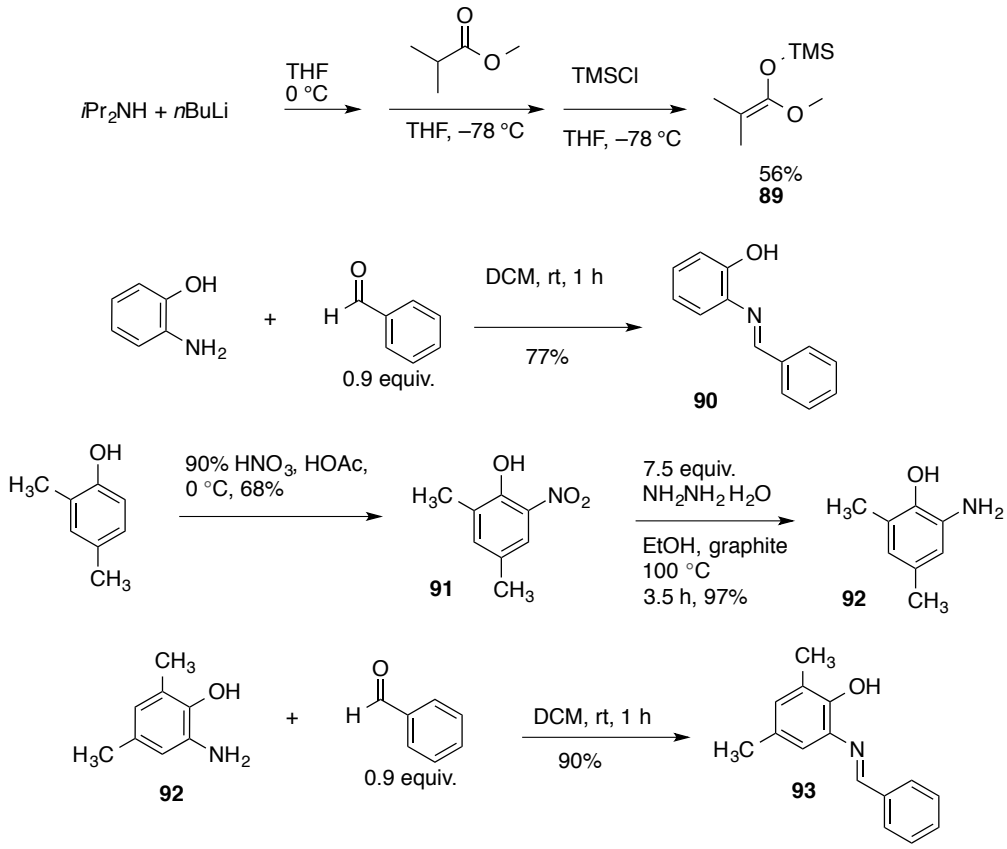
4.2 Mannich type reaction

4.2.1 Synthesis of Imine and ketene acetal

A successful catalyst system for the Mannich reaction has been reported by the Wulff group.[52] This catalyst was prepared from a 2:1:1 ratio of VAPOL:Zr(O*i*Pr)$_4$(HO*i*Pr):NMI and for this reason the catalyst was proposed to have the structure **45** (Schemes 3.8 and 3.9). The solid state structure of compound **61** (Figures 3.2 and 3.3) suggests that the VANOL Zr catalyst in the α-iminol rearrangement may contain three molecules of VANOL per zirconium. The question then arises, does the catalyst for the Mannich reaction have three molecules of VAPOL per zirconium? To investigate the possible answers to this question, imines **90**, **93** and ketene acetal **89** were synthesized to be examined in a new study on the Mannich reaction, which examines the effect of changing the ratio of ligand to the zirconium on the reaction outcome (Scheme 4.5). The ketene acetal was made from deprotonation of methyl 2-methylpropionate and quenched with TMSCl. Imine **90** was made via the condensation between 2-aminophenol and benzaldehyde, and imine **93** was made via the same condensation reaction but the starting 2-amino-4,6-dimethylphenol **92** needed two extra step to prepare. Nitration of 2,4-dimethylphenol gave **91** in 68% yield. The use of dilute HNO_3 resulted in lower yield, thus 90% HNO_3 was used. Fuming HNO_3 may give a

higher yield of **91**, but this reaction has not been tried. Reduction of the nitro group with hydrazine gave the aminophenol **92** in 97% yield.

Scheme 4.5 Synthesis of imines and ketene acetal

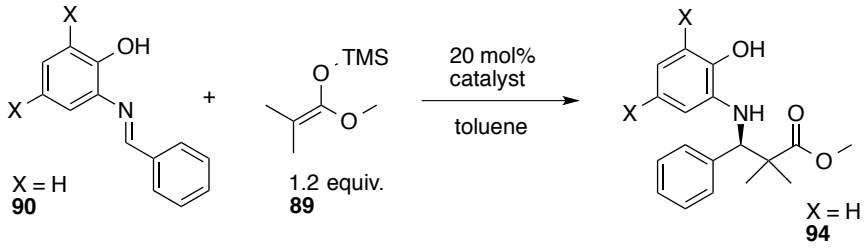


4.2.2 Mannich type reaction with zirconium VAPOL/VANOL catalyst

The Mannich type reaction was reported in 2001 with a zirconium VAPOL catalyst that was thought to be **45**, which was prepared from a 2:1:1 mixture of VAPOL:Zr:NMI.[52,64] This reaction was repeated with catalysts generated from VANOL and VAPOL as the ligand, and the results are summarized in Table 4.1 for imine **90** and 4.2 for imine **93**. In Table 4.1, for entries 1-4 the ratio of VANOL:Zr:NMI was 2:1:1 for the catalyst assembly. The result indicated that the asymmetric induction was temperature dependent: ee reached a peak at 60 °C

and was lower at 25 °C and 100 °C. One possible theory to explain this observation is that the catalyst exists in an equilibrium of a 2:1:1 and a 3:1:2 (or other unknown ratios) complex of VANOL:Zr:NMI, and that the equilibrium constant between the two species is temperature dependent. Note that the absolute stereochemistry switches upon going from –45 °C to 25 °C.

Table 4.1 Mannich type reaction with imine **90**



Entry	X	Catalyst	temp/time	yield, ee
1	H	1.0 : 1.2 : 2.2	–45 °C/24 h	53%, –18%[b]
2	H	1.0 : 1.2 : 2.2 Zr : NMI : S-VANOL	25 °C/24 h	73%, 60% (78%, 60%)[c]
3	H	1.0 : 1.2 : 2.2 Zr : NMI : S-VANOL	60 °C/2 h	76%, 77%
4	H	1.0 : 1.2 : 2.2 Zr : NMI : S-VANOL	100 °C/0.5 h	88%, 66%
5	H	1 : 2 : 3 Zr : NMI : S-VANOL	25 °C/24 h	89%, 77% (68%, 62%)[c]
6	H	1 : 2 : 3 Zr : NMI : S-VAPOL	25 °C/24 h	75%, 93%

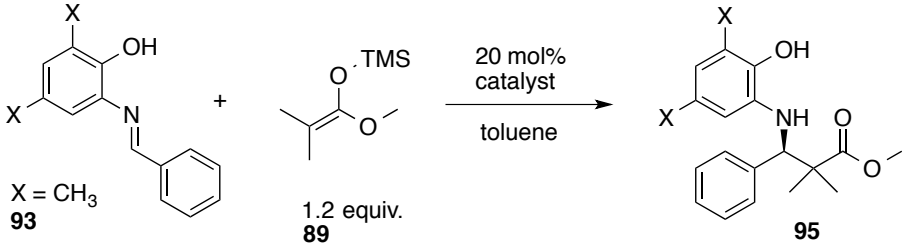
[a.] Unless otherwise specified, all reactions were run with 0.125 mmol imine, 0.15 mmol ketene acetal and 20 mol% catalyst in 1 mL toluene at indicated temperature and time. All yields are isolated yield, ee determined by HPLC. [b.] Anil Gupta's result. [c.] Data in parentheses was from a second run.

In entry 5 the catalyst was prepared with 3:1:2 ratio this is to be compared with the data in entry 2. Initially higher asymmetric induction was seen with 3:1:2, but a second run gave similar result to the 2:1:1 ratio. In entry 6 the catalyst was

prepared with 3:1:2 VAPOL:Zr:NMI, and the result was similar to the result with 2:1:1 that was previously reported,[52] which was 89% ee.

In Table 4.2, imine **93** was used for the reaction. The data in entries 1 and 2 allow for a comparison of 3:1:2 and 2:1:1 ratios with VANOL as ligand, it turns out that both are equally efficient for the reaction. Entry 3 presents the results of the reaction for 3:1:2 ratio with VAPOL as ligand, and this result was also similar to the result with a 2:1:1 ratio that was previously reported.[52]

Table 4.2 Mannich type reaction with imine **93**



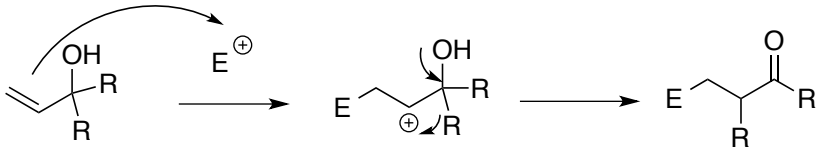
Entry	X	Catalyst	temp/time	yield, ee
1	CH_3	1.0 : 1.2 : 2.2 Zr : NMI : S-VANOL	25 °C/24 h	70%, 98%
2	CH_3	1 : 2 : 3 Zr : NMI : S-VANOL	25 °C/24 h	70%, 98%
3	CH_3	1 : 2 : 3 Zr : NMI : S-VAPOL	25 °C/24 h	83%, >99%

All reactions were run with 0.125 mmol imine, 0.15 mmol ketene acetal and 20 mol% catalyst in 1 mL toluene at indicated temperature and time. All yields were isolated yields, the %ee was determined by HPLC.

4.3 Cation induced rearrangement of allylic alcohols

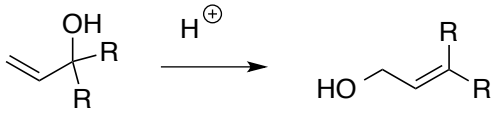
For a tertiary allylic alcohol, it is possible to undergo a rearrangement reaction if the alkene was activated with an electrophile (Scheme 4.6).

Scheme 4.6 Cation induced rearrangement of allylic alcohol



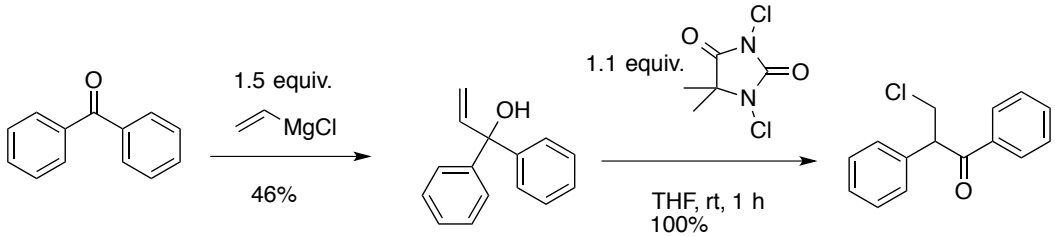
The electrophile can not be a proton because in this case the hydroxyl group would accept the proton and undergo a 1,3 hydroxyl shift reaction forming a more stable C=C double bond (Scheme 4.7).[65]

Scheme 4.7 1,3 hydroxyl shift of allylic alcohol



A halonium is a good candidate for this reaction because it doesn't react with tertiary alcohols. The reaction of an allylic alcohol **96** with a chloronium source gave a quantitative yield of the rearranged beta-chloroketone (Scheme 4.8). However, there are a number of research articles related to this reaction reported in the literature;[66,67] therefore it is not necessary to continue on this project to repeat other chemists' results.

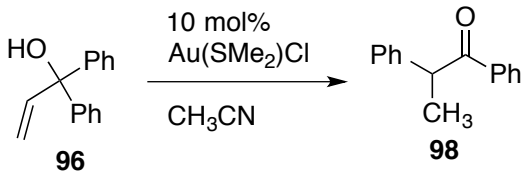
Scheme 4.8 Chloronium induced rearrangement of allylic alcohol



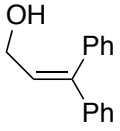
Another possible electrophile candidate is metal cation, for example, gold. Gold is known to have a strong affinity for olefin, so it is expected to coordinate to the double bond and hopefully will induce the rearrangement. Gold(I) chloride

dimethylsulfide complex was tested as the gold (I) source for this reaction (Table 4.3). Reactions were run with 0.1 mmol of **96** under the indicated conditions. The reaction in entry 1 was run at room temperature but there was no reaction. In entry 2, the reaction temperature was increased to 50 °C but the gold metal precipitated after 1 h, and no rearrangement was observed. The reaction in entry 3 was run under a N_2 atmosphere so that the gold would not precipitate, but it was found that only 3% of the 1,3 hydroxyl shift product was formed. Further investigation is needed for this reaction.

Table 4.3 Attempt in the gold induced rearrangement



96 **98**

entry	temp/time	atmosphere	result
1	25 °C, 1h	air	no reaction
2	50 °C, 30 min	air	gold precipitated
3	50 °C, 2h	N_2	3% 

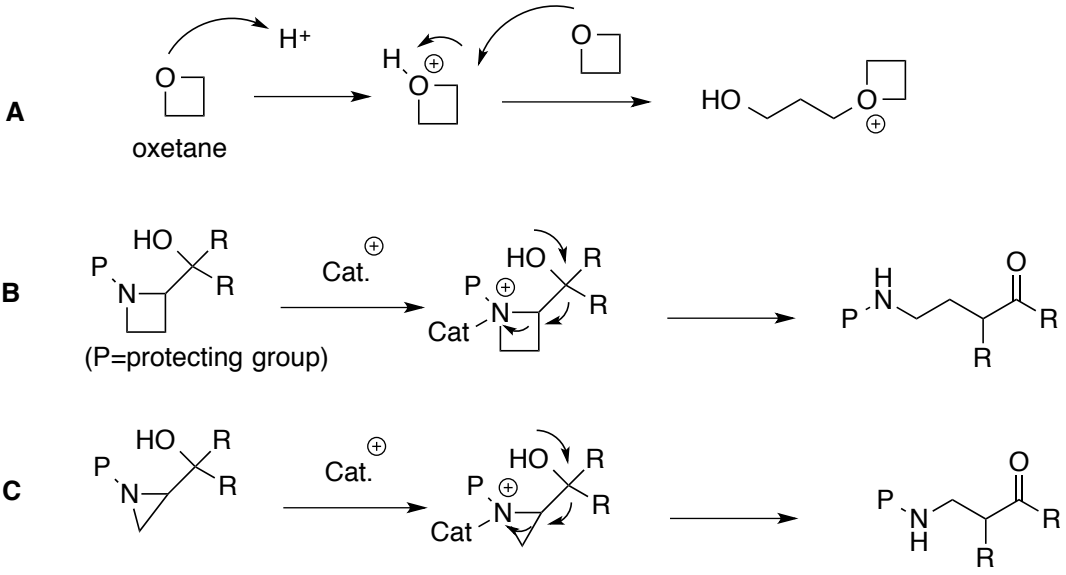
4.4 Aziridinol rearrangement

4.4.1 Introduction

The mechanism of polymerization of oxetane under acidic conditions begins with protonation of oxygen, followed by ring opening with another oxetane

molecule (Scheme 4.9 A). This process inspired the consideration of a pinacol type rearrangement of a tertiary alcohol attached to an azetidine or aziridine that could be activated by a Brønsted acid or Lewis acid catalyst. Subsequent rearrangement may occur to form a γ or β amino ketone as the product (Scheme 4.9 B and C).

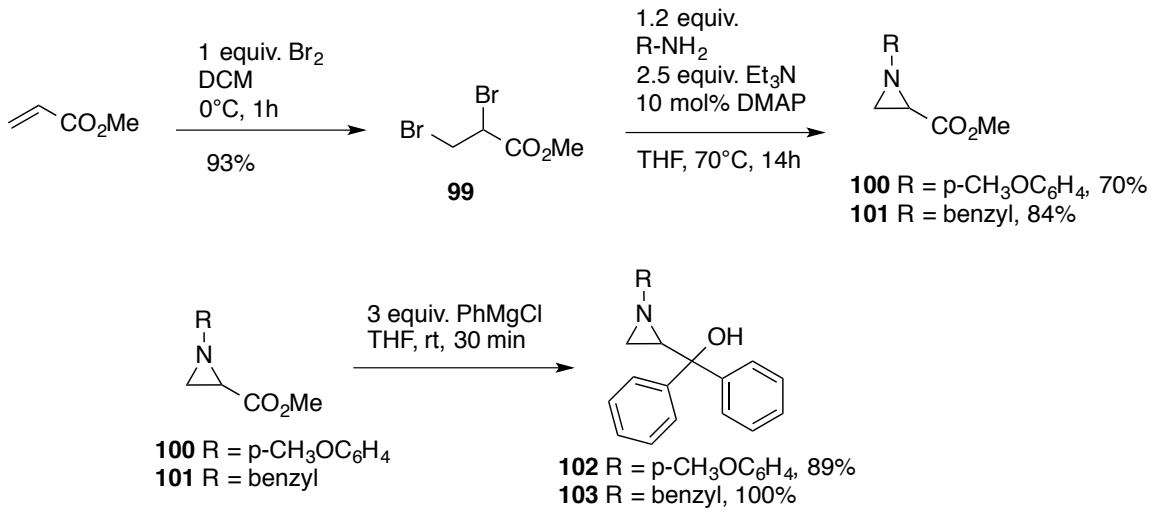
Scheme 4.9 Aziridinol rearrangement



4.4.2 Initial attempt and a catalyst screen

To test this idea, the simple aziridines **102** and **103** were synthesized for the initial attempt. The synthesis begins with bromination of methyl acrylate, and then substitution of the two bromine atoms with p-anisidine or benzyl amine, followed by Grignard addition to the ester (Scheme 4.10).

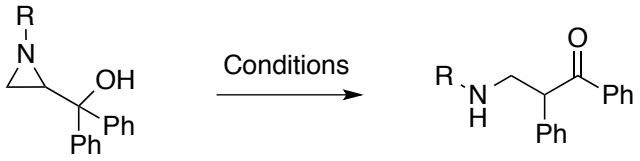
Scheme 4.10 Synthesis of aziridinol



The data in table 4.4 summarizes the results from the catalyst screen of the rearrangement reaction with **102** and **103**. Silica gel was found to be a good catalyst for the α-iminol rearrangement (chapter 2), but it was not able to give any product in this reaction. For $TiCl_4$ and H_2SO_4 catalyzed reactions, the ring was opened by Cl and H_2O respectively. It was found that $BF_3{\cdot}OEt_2$ was able to promote the reaction at room temperature in entries 4 and 5. After two hours the reaction was not complete, and if the reaction time was too long, some unidentified byproducts were formed as indicated by TLC and the yield of the desired product was moderate (entry 5). $Ti(O\textit{i}Pr)_4$ was not able to catalyze the reaction, while TfOH did. When the protecting group on the nitrogen was changed from anisyl to benzyl, the reaction with TfOH required substantially higher temperature, i. e. 100 °C, and a low yield of **105** was observed due to formation of unidentified byproducts. Thus, to obtain high yield of the rearranged product, an

anisyl protecting group appeared to be necessary.

Table 4.4 Catalyst screen of the aziridinol rearrangement



102 R = p-$CH_3OC_6H_4$
103 R = benzyl

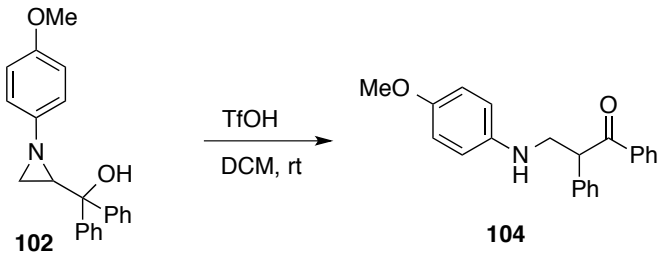
104 R = p-$CH_3OC_6H_4$
105 R = benzyl

Entry	S. M.	Catalyst	solvent	temp,time	result
1	**102**	100wt% silica gel	toluene	70°C, 1h	No RXN
2	**102**	$TiCl_4$ 1 equiv.	THF	rt, 1h	Cl opened the ring
3	**102**	H_2SO_4 1 equiv.	DMF	rt, 1h	H_2O opened the ring
4	**102**	BF_3Et_2O 1 equiv.	3:1 MeCN:DCM	rt, 2 h	**102:104** = 4:5
5	**102**	BF_3Et_2O 1 equiv.	3:1 MeCN:DCM	rt, 19 h	64% of **104**
6	**102**	$Ti(OiPr)_4$ 1 equiv.	DCM	rt, 2 h	No RXN
7	**102**	TfOH 1 equiv.	DCM	rt, 3h	87% of **104**
8	**103**	TfOH 1 equiv.	DCE	70°C, 3h	No RXN
9	**103**	TfOH 1 equiv.	PhCl	100°C, 3h	46% of **105**
10	**103**	BF_3Et_2O 1 equiv.	DCE	70°C, 1h	No RXN

Reactions were run with 0.1 mmol substrate in 0.3 mL solvent under the indicated conditions. Yields in entries 5, 7, 9 are isolated yields.

A TfOH loading study was carried out in order to determine the minimal amount of the acid required for the reaction (Table 4.5). Unfortunately, when 50 mol% was used, only a 6% yield was observed after 21 h, and with 10 mol%, no detectible amount of product was observed after 21 h. Thus 1 equivalent of acid was necessary for a satisfactory yield.

Table 4.5 TfOH loading screen



102 **104**

Entry	TfOH	time	result
1	100 mol%	3 h	87% **104**
2	50 mol%	21 h	6% **104**
3	10 mol%	21 h	0% **104**

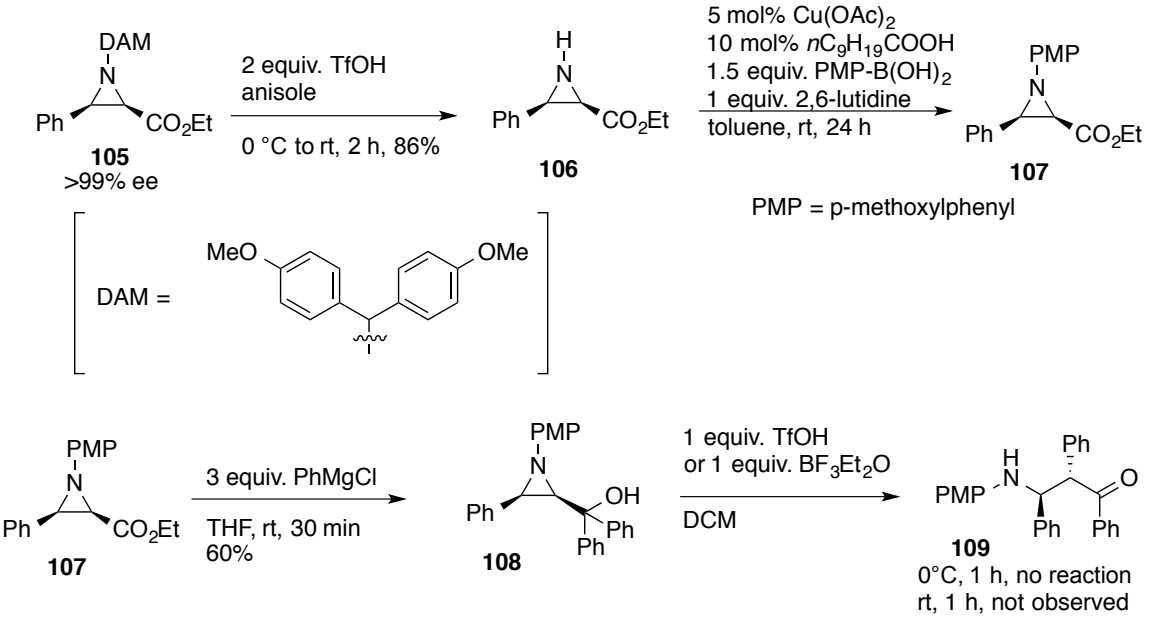
Reactions were run with 0.1 mmol **102** in 0.3 mL DCM with indicated conditions. Entry 1 was isolated yield, entries 2 and 3 were NMR yield.

4.4.3 Synthesis of 3-substituted aziridinol substrates and their rearrangement

The synthesis of enantiopure 2,3-di-substituted aziridine substrates started with the cis aziridine **105** (>99% ee). The DAM group on the aziridine was removed under acidic conditions in the presence of anisole to give the N-H aziridine **106**. The cleavage of DAM is necessary because 1) the DAM group is not stable under the acidic conditions of the rearrangement, 2) according to the results in Table 4.4, an aliphatic protecting group on the N would require very harsh condition in the rearrangement step, which may epimerize the alpha carbon. Thus, a PMP protecting group (PMP = p-methoxylphenyl) is desirable. The PMP group was installed via a copper mediated coupling reaction with aryl boronic acid.[68] The ester group in **107** could be converted to a tertiary alcohol with Grignard reagent

which gave **108** ready for the rearrangement. Unfortunately, it was found that neither TfOH or $BF_3{\cdot}OEt_2$ could induce a rearrangement of **108** at room temperature to give **109**. The 100% conversion of **108** was observed but it was not clear what happened in the reaction. At lower temperature, i. e. 0 °C, the reaction did not go after 1 h with either TfOH or $BF_3{\cdot}OEt_2$, only starting material was observed. A white precipitate was observed, and presumably it's the triflate salt or the BF_3–aziridine adduct pair precipitated out from the solution, thus a more polar solvent that dissolves the salt or adduct may promote the reaction, but it has never been tried.

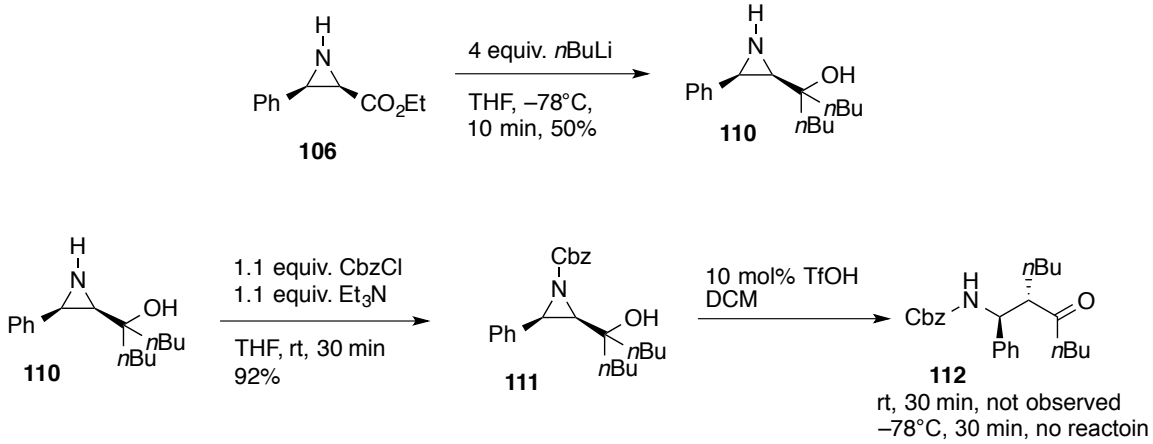
Scheme 4.11 Synthesis of PMP protected aziridinol and its rearrangement



Since the PMP protected aziridinol **108** did not gave the desired product, it was decided to replace the PMP group with electron withdrawing Cbz group to facilitate ring opening and hopefully the migration of a carbon group. The

synthesis started from the N-H aziridine **106**. The ester group was converted to the tertiary alcohol with *n*-butyllithium since phenyl Grignard failed to give the desired alcohol. The aziridine was protected with Cbz group in 92% yield.

Scheme 4.12 Synthesis of Cbz protected aziridinol and its rearrangement

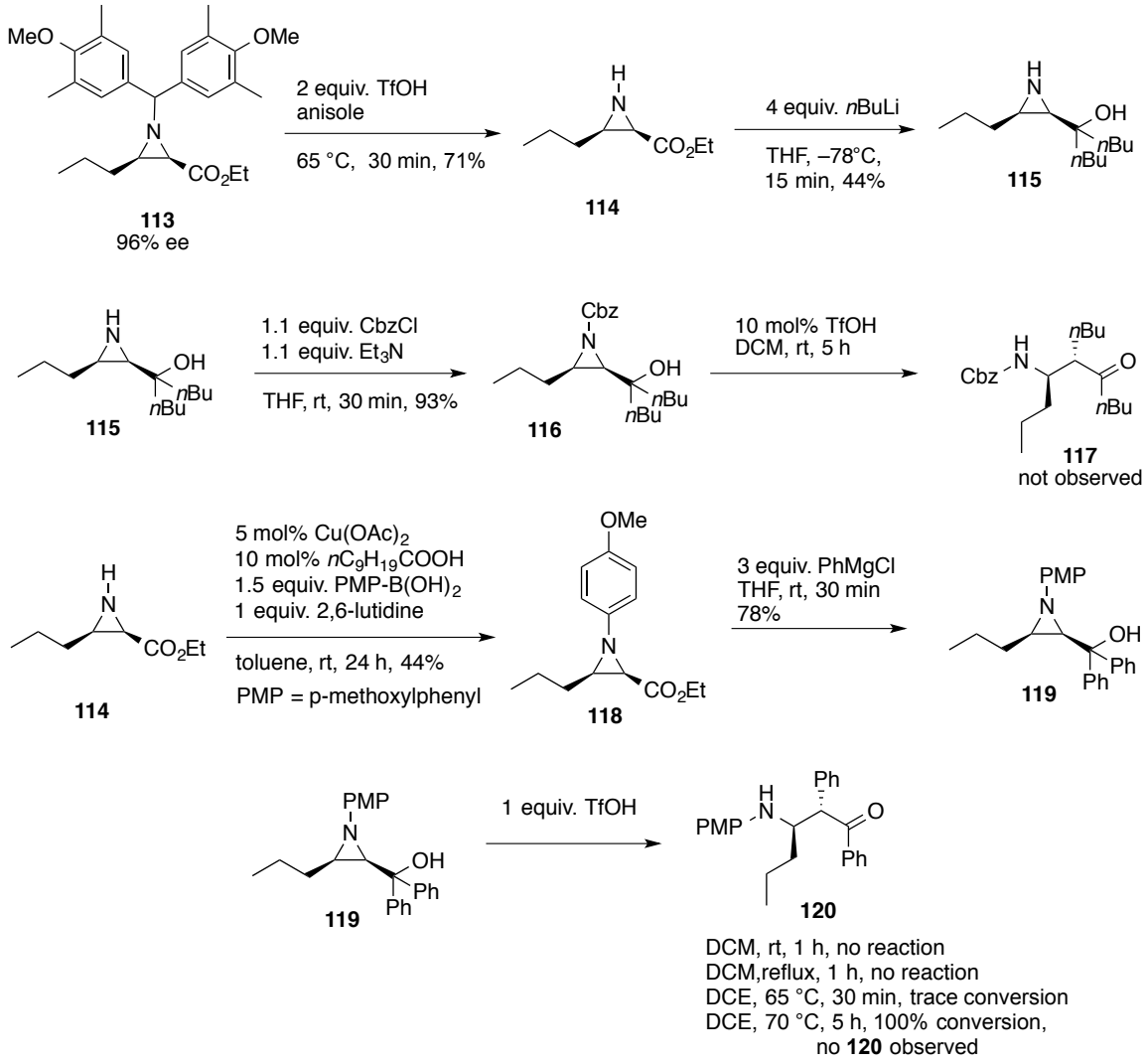


It is known that the lone pair on the aziridine N does not conjugate to an adjacent carbonyl group (in this case the Cbz group), thus the nitrogen should be able to accept a proton and undergo the rearrangement. Unfortunately the reaction went to 100% conversion with 10 mol% TfOH at room temperature in 30 min, no desired product **109** was observed. Another run at a lower temperature, –20 °C, There was no reaction with 10 mol% TfOH after 30 min at –78 °C or at –20 °C, only starting material was recovered. A white solid precipitate was observed at both –78 °C and –20 °C, which probably was the protonated **111** that did not dissolve in DCM at –20 °C. thus a more polar solvent that dissolves the salt or adduct may promote the reaction, but it has never been tried.

Since aziridines **108** and **111** with a phenyl group on C-3 did not give the

desired product, an aziridine with a propyl group on C-3 was synthesized since it is possible that ring opening at C-3 could be occurring via stabilization of positive charge on C-3 by the phenyl group. The synthesis of aziridinol with a propyl group at C-3 started with aziridine **113**. The cleavage of the MEDAM group with TfOH gave good yield of the N-H aziridine **114**. In the case of the Cbz protection, the butyl groups were added prior to the protection because a complex mixture was observed if both ester and Cbz groups are present in the molecule in the *n*-butyllithium addition step. Unfortunately, it was found that the treatment of aziridinol **116** with TfOH did not provide a clean rearrangement to the desired product. Instead, a complex mixture was observed according to TLC and the ^{1}H NMR spectrum of the crude reaction mixture. For the PMP protection, a copper catalyzed coupling reaction was carried out to install the PMP group on the nitrogen atom, and then phenyl Gringard addition to the ester gave the aziridinol **119**. Upon treatment with TfOH, it was found that there was no reaction at room temperature after 1 h, and reflux in DCM still gave no reaction. When the temperature was raised to 65 °C, reaction started to proceed very slowly, and at 70 °C for 5 h, the reaction was complete, but no desired product was observed. One new spot from the reaction mixture was isolated and judged from the NMR spectra it was tentatively identified as deoxybenzoin, which was formed possibly from a retro-Mannich reaction from **120**.

Scheme 4.13 Synthesis of propyl aziridinol at C-3 and its rearrangement

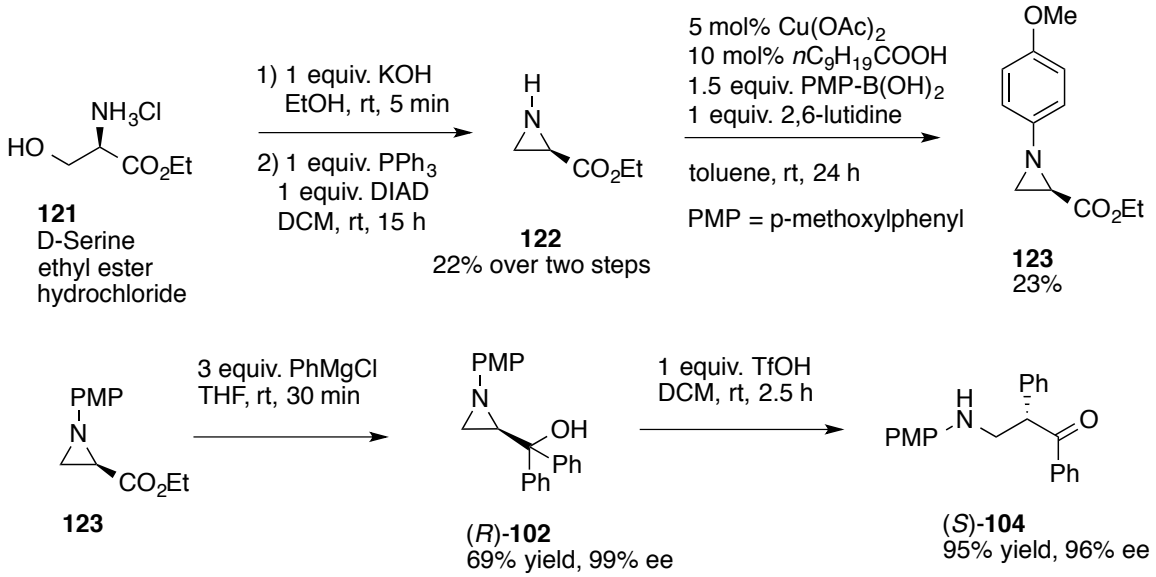


4.4.4 Aziridinol rearrangement from (*R*)-102

The rearrangement of 2,3-disubstituted aziridines **108**, **111**, **116** and **118** failed to produce a rearrangement product. The only aziridine that was found to undergo rearrangement was the racemic aziridine **102**, which has no substitution in the 3 position (Table 4.4). Thus it is of interest to examine the rearrangement of optically pure **102**. The synthesis started with commercial D-Serine ethyl ester hydrochloride **121** (Scheme 4.14). The yield of the aziridine **122** was low due to its

high volatility. It should be possible to achieve high yield because a similar synthesis that started from the butyl ester of D-Serine gave a much better yield.[69] The coupling reaction on the N-H aziridine has two known methods that have been reported for related aziridines involving either Cu[70,68] or Pd[70]. The copper protocol was attempted with **122** and **123** was observed in 23% yield. Further optimization is needed to improve the yield for this step.

Scheme 4.14 Synthesis of (*R*)-**102** and its rearrangement

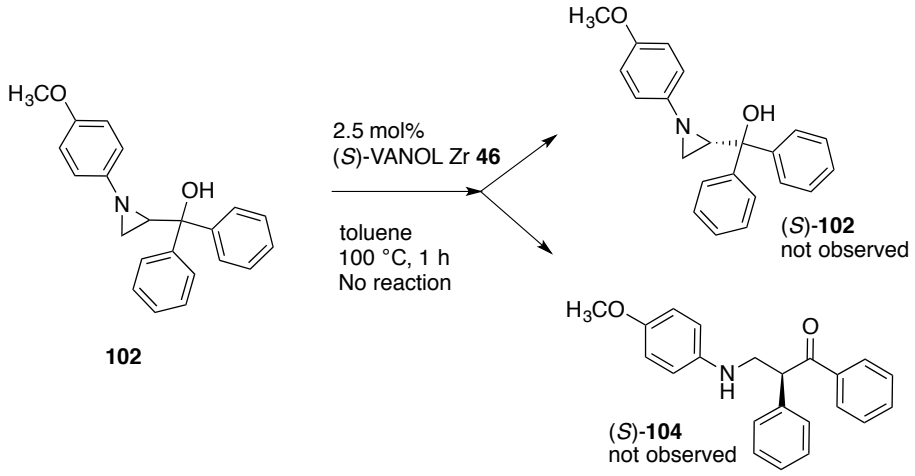


The final step is to convert the ester **123** to the tertiary alcohol (*R*)-**102** with phenyl Grignard reaction, which was achieved in 69% yield. The optical purity of (*R*)-**102** was determined to be 99% ee by HPLC analysis. The rearrangement of (*R*)-**102** with TfOH gave the final product **104** in 95% yield and 96% ee. The absolute configuration of product **104** has not been rigorously determined but is assumed to be *S*, because the migrating group is likely to open the ring from the opposite side of the nitrogen atom.

4.4.5 One attempt at the kinetic resolution of a racemic aziridinol

The aziridinol **102** contains one chiral center in the molecule and was prepared in racemic form as shown in Scheme 4.10. One attempt was carried out with 2.5 mol% (*S*)-VANOL Zr catalyst **46** in toluene at 100 °C for 1 h but no reaction was observed. Future work should thus focus on screening more active catalysts for this kinetic resolution.

Scheme 4.15 attempt in the kinetic resolution of racemic aziridinol



CHAPTER FIVE
EXPERIMENTAL SECTION

5.1 General information

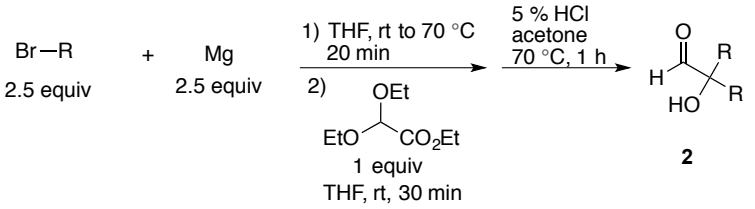
Solvents for reactions were dried appropriately before use: toluene was dried by refluxing with sodium, THF was dried by refluxing with sodium and benzophenone as indicator, dichloromethane was dried by refluxing with CaH_2. VANOL and VAPOL ligands, including their derivatives, were prepared according to procedures reported in literature.[51] All other reagents were directly used as purchased from either Aldrich or Alfa Aesar.

Melting points were measured on a Thomas Hoover capillary melting point apparatus. IR spectra were taken on a Galaxy series FTIR-3000 spectrometer. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded on VXR-500 MHz instrument in $CDCl_3$. $CDCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.26) and ^{13}C NMR (δ = 77.0). Thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol. The silica gel for column chromatography was purchased from Sorbent Technologies with the following specifications: standard grade, 60 Å porosity, 230 X 400 mesh particle size, 500-600 m^2/g surface area and 0.4 g/mL bulk density. Chiral HPLC analysis was done using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical

rotation was obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (Sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL.

5.2 Experimental procedures for chapter two

5.2.1 General procedure for the preparation of aldehyde 2

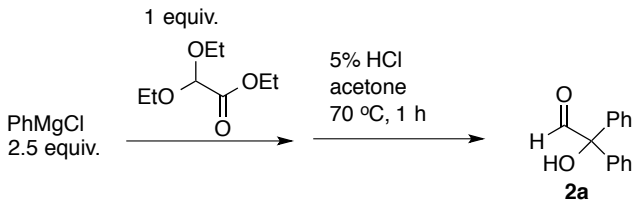


To a 50 mL clean and dry Schlenk flask was added Mg metal (40 mesh, 0.08g, 3.5 mmol, 2.5 equiv.), a small crystal of I_2 and 2 mL THF. While stirring, the appropriate aryl or alkyl bromide (3.5 mmol, 2.5 equiv.) was added via a syringe (for solid bromide compound, it was dissolve in minimal amount of THF before addition). The flask was tightly sealed and the solution was stirred at room temperature for 10 min, then heated in a 70 °C oil bath until the Mg metal completely dissolved (usually it took less than 20 min). After being cooled down to room temperature, the flask was placed in a water bath and ethyl diethoxyacetate (0.25 mL in 2 mL THF, 1.4 mmol, 1 equiv.) was added dropwise and slowly via a syringe. The resulting mixture was stirred for another 30 min at room temperature then quenched by 5 mL saturated NH_4Cl solution. The two layers were separated and the aqueous layer was extracted by ether (5 mL x 3). The combined organic

layer was concentrated under rotary vaporization and the crude residue was subjected to hydrolysis without purification.

The crude acetal intermediate was transferred to a 20 mL Schlenk flask with 0.5 mL 5% HCl and enough acetone (usually it took 5 mL) to obtain a single layer homogenous solution. Thereafter, the flask was sealed and heated in a 70 °C oil bath for 1 h. After being cooled to room temperature, the solution was diluted by 10 mL CH_2Cl_2. The aqueous layer was separated and discarded; the organic layer was successively washed by $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated under rotary vaporization. The crude residue was purified by silica gel column chromatography, 20:1 hexanes:EtOAc as eluent.

2-hydroxy-2,2-diphenylacetaldehyde (2a)



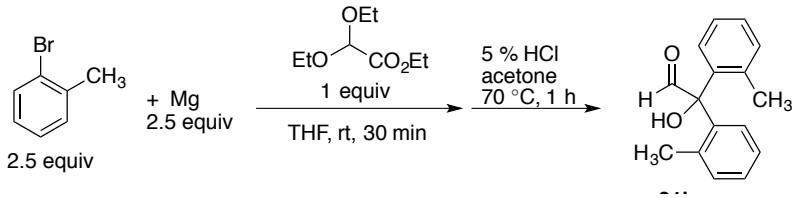
2a

Following the general procedure with a commercial 2M solution of phenylmagnesium chloride in THF (3.5 mL, 7.0 mmol, 2.5 equiv; 13.8 mL, 27.5 mmol and 50.0 mL, 100 mmol scale), the reaction afforded the product **2a** as a white solid in 70-90% yield over several trials. mp = 55-57 °C (Lit[71] 52-55 °C).

Spectral data for **2a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.41 (s, 1H), 7.38-7.42 (m, 10H), 10.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 83.45, 127.44, 128.51, 128.84,

139.29, 198.05; these NMR data are in agreement with the literature data.[71]

2-hydroxy-2,2-di-o-tolylacetaldehyde (2b)

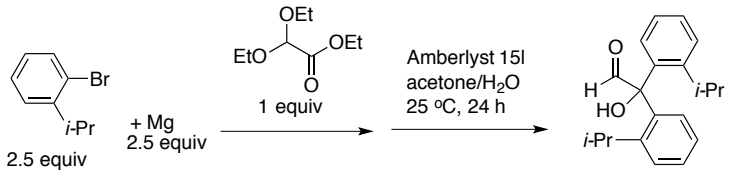


2b

Following the general procedure with 2-bromotoluene (0.42 mL, 3.5 mmol, 2.5 equiv), the reaction afforded the product **2b** as a white wax-like solid (83%, 0.279 g, 1.16 mmol). mp = 46-49 °C.

Spectral data for **2b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 6H), 4.36 (s, 1H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.21 (td, *J* = 7.5, 1.5 Hz, 2H), 7.26 (td, *J* = 7.5, 1.5 Hz, 2H), 7.30 (dd, *J* = 7.5, 1.5 Hz, 2H), 10.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.30, 84.82, 126.33, 127.36, 128.53, 132.55, 137.13, 137.73, 197.99; IR (thin film) 3472s, 3063m, 3018m, 2930m, 2870m, 1716s, 1458s, 1336m, 1163m, 754s cm^{-1}; HRMS (ESI-TOF) *m/z* found 223.1127 [$(M-H_2O+H)^+$; calcd. 223.1123 for $C_{16}H_{15}O$.

2-hydroxy-2,2-bis(2-isopropylphenyl)acetaldehyde (2c).

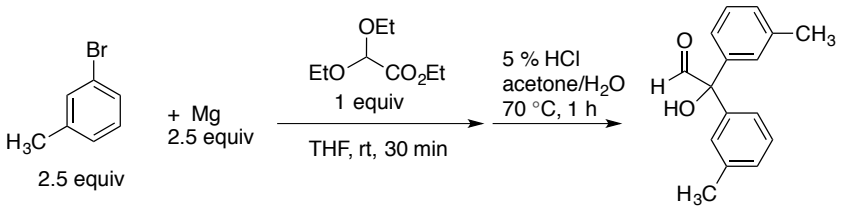


2c

The general procedure was followed with 1-bromo-2-isopropylbenzene (0.54 mL, 3.5 mmol, 2.5 equiv) and the Grignard reaction between the ester and 2-isopropylphenylmagnesium bromide was worked up and concentrated, the crude acetal was hydrolyzed with 0.5 g Amberlyst 15 ion-exchange resin (strongly acidic) in 10 mL 1:1 H_2O:acetone solution at room temperature for 24 h. The resulting mixture was neutralized with 10 mL saturated $NaHCO_3$ and diluted with 20 mL CH_2Cl_2. The aqueous layer was extracted with ether (10 mL x 3), the combined organic layer was washed with brine, dried over $MgSO_4$, filtered through filter paper in Büchner funnel and concentrated under rotary evaporation. The crude product was purified by column chromatography with 20:1 hexanes:EtOAc as eluent. The product that was collected from the column was not pure by NMR, therefore it was washed with a small amount of hexanes. This afforded product **2c** as a white solid (56%, 0.232 g, 0.784 mmol); mp = 119-121 °C.

Spectral data for **2c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (d, *J* = 7.0 Hz, 6H), 1.03 (d, *J* = 7.0 Hz, 6H), 3.15 (septet, *J* = 7.0 Hz, 2H), 4.46 (s, 1H), 7.19-7.23 (m, 3H), 7.34-7.40 (m, 5H), 10.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.08, 24.18, 29.84, 84.59, 125.96, 127.17, 127.92, 128.88, 137.51, 148.13, 198.98; IR (thin film) 3474br s, 3020m, 2966s, 2930s, 2868s, 1726s, 1483m, 1444m, 1153m, 1057m, 760s cm^{-1}; HRMS (ESI-TOF) *m/z* found 279.1749 [$(M-H_2O+H)^+$; calcd. 279.1749 for $C_{20}H_{23}O$].

2-hydroxy-2,2-di-m-tolylacetaldehyde (2d).

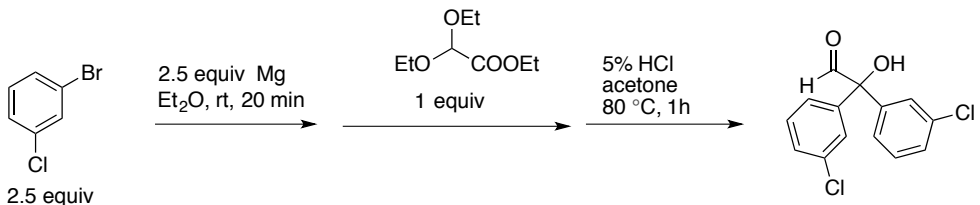


2d

Following the general procedure with 3-bromotoluene (0.42 mL, 3.5 mmol, 2.5 equiv), the reaction afforded the product **2d** as a white wax-like solid (77%, 0.261 g, 1.09 mmol). mp = 33-35 °C.

Spectral data for **2d:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 6H), 4.33 (s, 1H), 7.14-7.19 (m, 6H), 7.28 (t, *J* = 7.5 Hz, 2H), 9.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.51, 83.38, 124.51, 127.97, 128.62, 129.18, 138.62, 139.34, 198.18; IR (thin film) 3481br s, 3028m, 2922m, 2860m, 1722s, 1604m, 1487m, 1332m, 1155s, 702s cm^{-1}; HRMS (ESI-TOF) *m/z* found 223.1122 [$(M-H_2O+H)^+$; calcd. 223.1123 for $C_{16}H_{15}O$].

2,2-bis(3-chlorophenyl)-2-hydroxyacetaldehyde (2e).



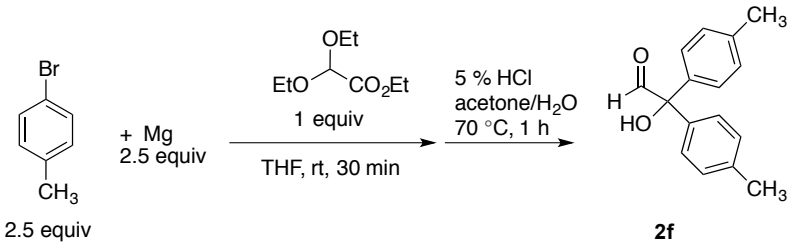
2e

The general procedure was followed with 1-bromo-3-chlorobenzene (0.50 mL, 4.1 mmol) with three exceptions: 1. The formation of the Grignard reaction

was carried out in diethyl ether in a round bottom flask with a condenser, 2. The hydrolysis of the acetal intermediate was carried out at 80 °C, and 3. The eluent was 8:1 hexane:EtOAc for the purification of the final product. This reaction afforded the product **2e** (0.31g, 1.1 mmol, 67%) as a wax-like white solid; mp = 42-43 °C.

Spectral data for **2e**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.44 (s, 1H), 7.23-7.27 (m, 2H), 7.34-7.39 (m, 6H), 9.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.55, 125.39, 127.46, 129.01, 130.20, 135.15, 140.80, 196.75; IR (thin film) 3456s, 1726s, 1653s, 1576m, 1473m, 1419m, 1180m, 1082m cm^{-1}; HRMS (ESI-TOF) m/z found 263.0024 [$(M-H_2O+H)^+$; calcd. 263.0030 for $C_{14}H_9OCl_2$].

2-hydroxy-2,2-di-p-tolylacetaldehyde (2f).



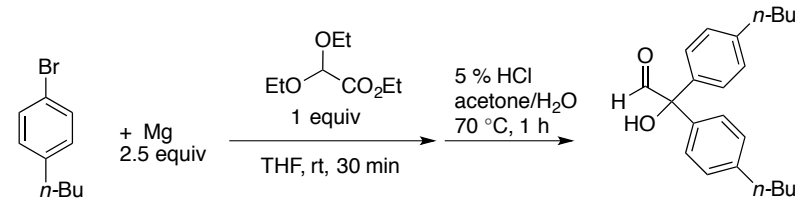
2f

Following the general procedure with 4-bromotoluene (0.86 mL, 7.0 mmol, 2.5 equiv, the scale was doubled), this reaction afforded the product **2f** as a colorless liquid (78%, 0.526 g, 2.18 mmol).

Spectral data for **2f**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.38 (s, 6H), 4.32 (s, 1H) 7.22 (d, *J* = 5.0 Hz, 4H), 7.25 (d, *J* = 5.0 Hz, 4H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.14, 83.21, 127.35, 129.48, 136.41, 138.32, 198.11; IR (neat)

3481br s, 3028m, 2922m, 1718s, 1510m, 1170m, 815m cm^{-1}; HRMS (ESI-TOF) *m/z* found 223.1121 $[(M-H_2O+H)^+$; calcd. 223.1123 for $C_{16}H_{15}O]$.

2,2-bis(4-*n*-butylphenyl)-2-hydroxyacetaldehyde (2g).

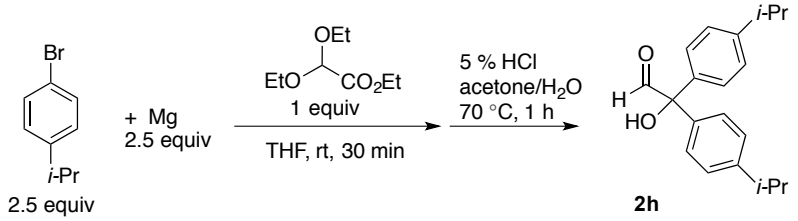


2.5 equiv **2g**

Following the general procedure with 1-bromo-4-*n*-butylbenzene (0.62 mL, 3.5 mmol, 2.5 equiv), the reaction afforded the product **2g** as a colorless liquid (73%, 0.332 g, 1.02 mmol).

Spectral data for **2g**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, *J* = 7.5 Hz, 6H), 1.35 (sextet, *J* = 7.5 Hz, 4H), 1.59 (qt, *J* = 7.5, 2.0 Hz, 4H) 2.61 (t, *J* = 7.5 Hz, 4H), 4.29 (s, 1H), 7.20 (d, *J* = 7.5 Hz, 4H), 7.26 (d, *J* = 7.5 Hz, 4H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.89, 22.32, 33.44, 35.26, 83.20, 127.31, 128.79, 136.57, 143.26, 198.10; IR (neat) 3487s, 3057s, 2930s, 2858s, 1718s, 1510s, 1414m, 1338m, 1170m, 831m cm^{-1}; HRMS (ESI-TOF) *m/z* found 307.2064 $[(M-H_2O+H)^+$; calcd. 307.2062 for $C_{22}H_{27}O]$.

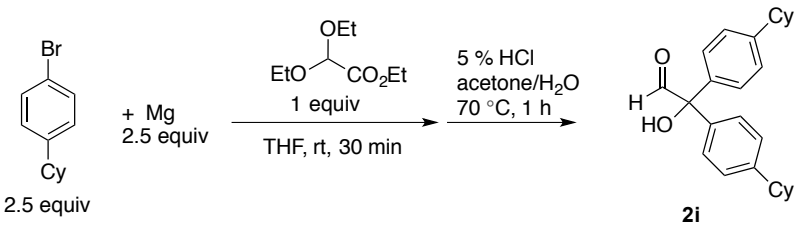
2,2-bis(4-isopropylphenyl)-2-hydroxyacetaldehyde (2h).



Following the general procedure with 1-bromo-4-isopropylbenzene (0.53 mL, 3.5 mmol, 2.5 equiv), this reaction afforded the product **2h** as a white solid (49%, 0.203 g, 0.686 mmol); mp = 80-81.5 °C.

Spectral data for **2h**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (d, *J* = 7.5 Hz, 12H) 2.92 (septet, *J* = 7.5 Hz, 2H), 4.30 (s, 1H), 7.25 (d, *J* = 7.5 Hz, 4H), 7.29 (d, *J* = 7.5 Hz, 4H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.86, 33.79, 83.19, 126.83, 127.39, 136.70, 149.14, 198.11; IR (thin film) 3406s, 3028m, 2961s, 2870s, 1718s, 1506m, 1458m, 1342m, 1178m, 825m cm^{-1}; HRMS (ESI-TOF) *m/z* found 279.1752 [$(M-H_2O+H)^+$; calcd. 279.1749 for $C_{20}H_{23}O$].

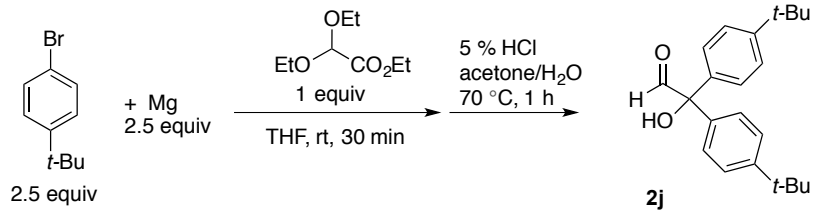
2,2-bis(4-cyclohexylphenyl)-2-hydroxyacetaldehyde (2i).



Following the general procedure with 1-bromo-4-cyclohexylbenzene (0.65 mL, 3.5 mmol, 2.5 equiv), thi reaction afforded the product **2i** as a white solid (69%, 0.362 g, 0.966 mmol); mp = 155-156 °C.

Spectral data for **2i**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22-1.28 (m, 2H), 1.34-1.44 (m, 8H), 1.73-1.76 (m, 2H), 1.82-1.87 (m, 8H), 2.48-2.53 (m, 2H), 4.29 (s, 1H), 7.22 (d, *J* = 7.0 Hz, 4H), 7.28 (d, *J* = 7.0 Hz, 4H), 9.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.08, 26.81, 34.32, 44.22, 83.20, 127.20, 127.35, 136.65, 148.34, 198.11; IR (thin film) 3397s, 2920s, 2851s, 1720s, 1506m, 1448m, 1329m, 1170m cm^{-1}; HRMS (ESI-TOF) *m/z* found 359.2375 [$(M-H_2O+H)^+$; calcd. 359.2375 for $C_{26}H_{31}O$].

2,2-bis(4-*t*-butylphenyl)-2-hydroxyacetaldehyde (2j).

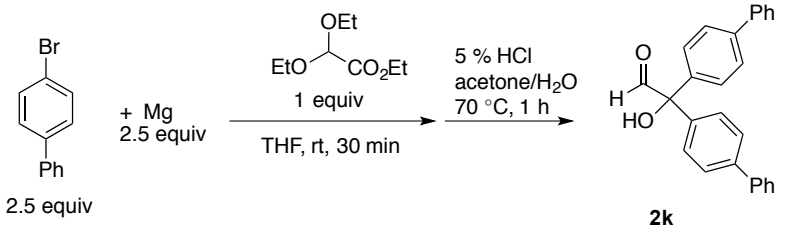


Following the general procedure with 1-bromo-4-tert-butylbenzene (1.21 mL, 7.00 mmol, 2.5 equiv, the scale was doubled), the product was purified by recrystallization from hexanes to afford the product **2j** as a white solid (61%, 0.555 g, 1.71 mmol); mp = 140-142 °C.

Spectral data for **2j**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.32 (s, 18H), 4.30 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 4H), 7.41 (d, *J* = 8.5 Hz, 4H), 9.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.24, 34.57, 83.08, 125.69, 127.10, 136.28, 151.40, 198.11; IR (thin film) 3427br s, 2963s, 2868m, 1720s, 1506m, 1404m, 1109m, 823m cm^{-1};

HRMS (ESI-TOF) *m/z* found 307.2064 [(M-H_2O+H)$^+$; calcd. 307.2062 for $C_{22}H_{27}O$].

2,2-di([1,1'-biphenyl]-4-yl)-2-hydroxyacetaldehyde (2k).

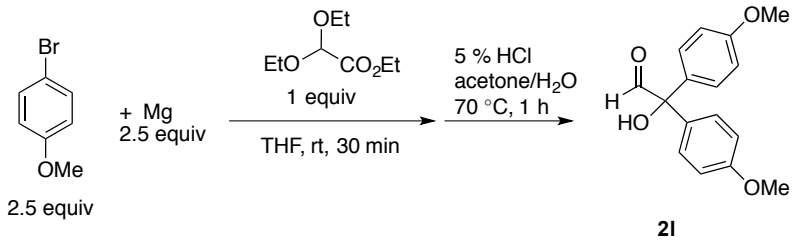


2k

Following the general procedure with 4-bromobiphenyl (0.81g, 3.5 mmol, 2.5 equiv), the reaction afforded the product **2k** as a white solid (77%, 0.393 g, 1.08 mmol); mp = 142-143 °C.

Spectral data for **2k**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.44 (s, 1H), 7.37 (tt, *J* = 7.0, 1.5 Hz, 2H), 7.45 (tt, *J* = 8.0, 1.5 Hz, 4H), 7.49 (dt, *J* = 8.5, 2.0 Hz, 4H), 7.60 (dt, *J* = 8.5, 2.0 Hz, 4H), 7.65 (dt, *J* = 8.5, 2.0 Hz, 4H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 83.22, 127.12, 127.58, 127.62, 127.85, 128.83, 138.18, 140.29, 141.48, 197.74; IR (thin film) 3596br s, 3081m, 3053m, 3025m, 1718s, 1485s, 1174m, 1006m, 827m cm^{-1}; HRMS (ESI-TOF) *m/z* found 347.1435 [(M-H_2O+H)$^+$; calcd. 347.1436 for $C_{26}H_{19}O$].

2,2-bis(4-methoxylphenyl)-2-hydroxyacetaldehyde (2l).

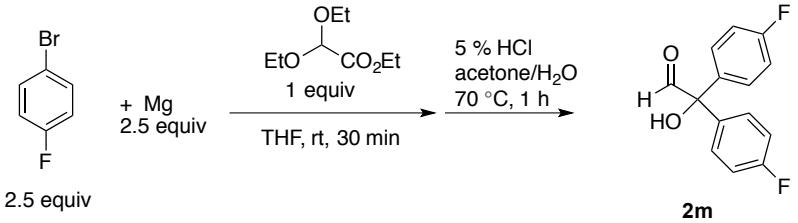


2l

The general procedure was followed with 4-bromoanisole (0.44 mL, 3.5 mmol, 2.5 equiv) except the eluent for column chromatography was 3:1 to 2:1 hexanes:EtOAc. The reaction afforded the product **2l** as a white solid (63%, 0.241 g, 0.882 mmol); mp = 90-91 °C.

Spectral data for **2l**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 6H), 4.26 (s, 1H), 6.91 (d, *J* = 8.5 Hz, 4H), 7.27 (d, *J* = 8.5 Hz, 4H), 9.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.30, 82.79, 114.17, 128.74, 131.40, 159.62, 197.78. The ^{1}H NMR data are in agreement with the literature data.[72]

2,2-bis(4-fluorophenyl)-2-hydroxyacetaldehyde (2m).

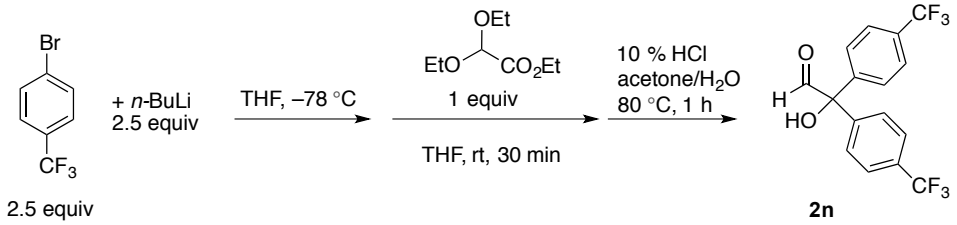


2m

Following the general procedure with 1-bromo-4-fluorobenzene (0.39 mL, 3.5 mmol, 2.5 equiv), the reaction afforded the product **2m** as a white wax-like solid (99%, 0.359g, 1.39 mmol); mp = 24-25 °C.

Spectral data for **2m:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.40 (s, 1H), 7.11 (tt, *J* = 9.0, 2.5 Hz, 4H), 7.34 (tt, *J* = 9.0, 2.5 Hz, 4H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.57, 115.94 (d, *J* = 21.8 Hz), 129.24 (d, *J* = 8.5 Hz), 134.89, 162.73 (d, *J* = 247.5 Hz), 197.23; ^{19}F NMR ($CDCl_3$, 470 MHz) δ –112.79; IR (thin film) 3474br s, 2853w, 1724s, 1603s, 1508s, 1230s, 1159m, 835s cm^{-1}; HRMS (ESI-TOF) *m/z* found 231.0620 [$(M-H_2O+H)^+$; calcd. 231.0621 for $C_{14}H_9OF_2$].

2,2-bis(4-trifluoromethylphenyl)-2-hydroxyacetaldehyde (2n).



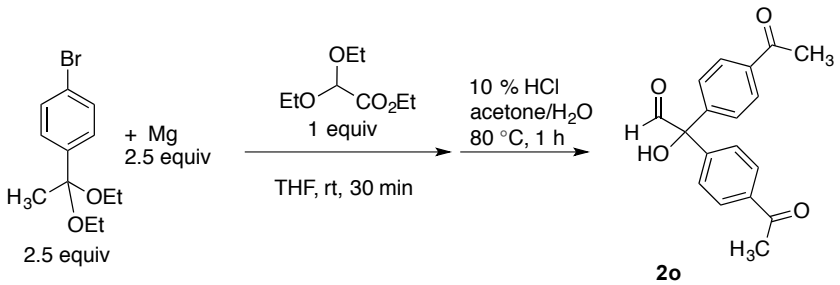
2n

The acetal intermediate of this substrate was synthesized via a different method. To a 100 mL clean and dry round bottom flask were added 10 mL THF and 1-bromo-4-(trifluoromethyl)benzene (0.49 mL, 3.5 mmol, 2.5 equiv). The flask was sealed by a septum with a N_2 balloon attached via a needle, and cooled to –78 °C in an acetone dry ice bath for 5 min. Then a solution of *n*-butyllithum (2.2 M in pentane, 1.60 mL, 3.5 mmol, 2.5 equiv) was added dropwise via a syringe. The resulting solution was stirred at –78 °C for another 10 min before addition of ethyl diethoxyacetate (0.30 mL in 2 mL THF, 1.68 mmol, 1.25 equiv). Thereafter, the solution was gradually warmed up to room temperature and allowed to stir for 30 min. It was then quenched with saturated NH_4Cl solution 10 mL. The two layers

were separated and the aqueous layer was extracted with ether (5 mL x 3). The combined organic layer was concentrated under rotary evaporation and the crude residue was subjected to hydrolysis without purification. The hydrolysis followed the general procedure except that a 10% solution of HCl was used and the temperature was 80 °C. A mixture of 20:1 to 5:1 hexanes:EtOAc was employed as the eluent during column chromatography. The reaction afforded the product **2n** as a white solid (53%, 0.31 g, 0.89 mmol); mp = 72-74 °C.

Spectral data for **2n**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.53 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 4H), 7.70 (d, *J* = 8.0 Hz, 4H), 10.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.85, 123.71 (q, *J* = 270.8 Hz), 126.01 (q, *J* = 3.7 Hz), 127.68, 131.09 (q, *J* = 32.5 Hz), 142.62, 196.66; ^{19}F NMR ($CDCl_3$, 470 MHz) δ –62.82; IR (thin film) 3395s, 1732s, 1329s, 1126s, 1070s, 833m cm^{-1}; HRMS (ESI-TOF) *m/z* found 331.0558 [$(M-H_2O+H)^+$; calcd. 331.0558 for $C_{16}H_9OF_6$].

2,2-bis(4-acetylphenyl)-2-hydroxyacetaldehyde (2o).



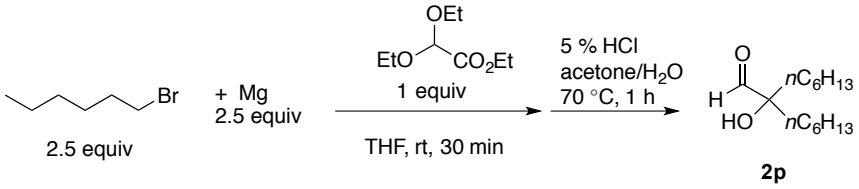
2o

Following the general procedure with 4-bromoacetophenone diethyl ketal (0.76 mL, 3.5 mmol, 2.5 equiv), the hydrolysis of all three acetals was carried out

with 10% HCl at 80 °C for 1 h. A mixture of 4:1 to 2:1 hexanes:EtOAc was used as eluent for column chromatography. The reaction afforded the product **2o** as a light yellow solid (55%, 0.228 g, 0.771 mmol); mp = 106-107 °C. R_f = 0.25 in 2:1 hexanes:EtOAc.

Spectral data for **2o**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.59 (s, 6H), 4.59 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 4H), 7.97 (d, *J* = 8.5 Hz, 4H), 10.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.70, 83.13, 127.47, 128.86, 137.12, 143.80, 196.92, 197.43; IR (thin film) 3443 br s, 3063w, 3005w, 2924w, 1732s, 1684s, 1603s, 1408s, 1359s, 1289s, 1190m, 1012m cm^{-1}; HRMS (ESI-TOF) *m/z* found 297.1134 [(M+H)$^+$; calcd. 297.1127 for $C_{18}H_{17}O_4$].

2-hexyl-2-hydroxyoctanal (2p).



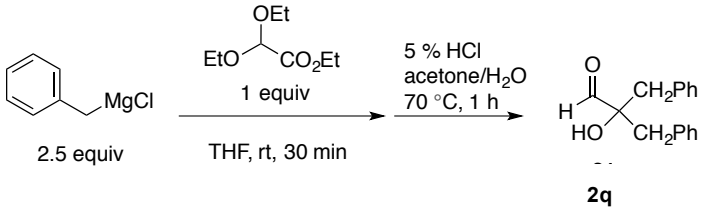
2p

Following the general procedure with 1-bromohexane (0.49 mL, 3.5 mmol, 2.5 equiv), the reaction afforded the product **2p** as a colorless liquid (71%, 0.227 g, 0.994 mmol).

Spectral data for **2p:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 7.0 Hz, 6H), 1.03-1.09 (m, 2H), 1.22-1.29 (m, 12H), 1.35-1.41 (m, 2H), 1.62-1.67 (m, 4H), 3.16 (s, 1H), 9.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.02. 22.50, 22.95, 29.55,

31.59, 36.25, 80.58, 204.69. IR (neat) 3516 br s, 2957s, 2930s, 2858s, 1728s, 1468m, 1379w, 1087m cm^{-1}. HRMS (ESI-TOF) *m/z* found 211.2051 [$(M-H_2O+H)^+$; calcd. 211.2056 for $C_{14}H_{27}O$].

2-benzyl-2-hydroxy-3-phenylpropanal (2q).

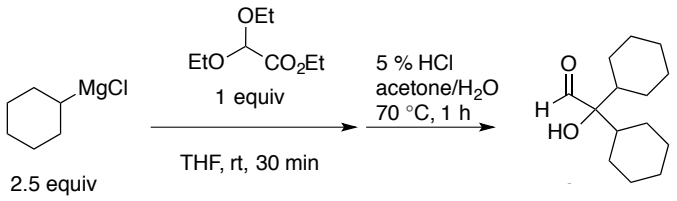


2q

Following the general procedure with commercial benzylmagnesium chloride (1M in ether, 7.0 mL, 7.0 mmol, 2.5 equiv, the scale was doubled), this reaction afforded the product **2q** as a white solid (46%, 0.313 g, 1.29 mmol); mp = 66-70 °C.

Spectral data for **2q:** ^1H NMR ($CDCl_3$, 500 MHz) δ 3.00 (d, *J* = 14.0 Hz, 2H), 3.08 (s, 1H), 3.17 (d, *J* = 14.0 Hz, 2H), 7.19-7.21 (m, 4H), 7.26-7.32 (m, 6H), 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.85, 80.86, 127.09, 128.40, 130.30, 134.75, 203.58; IR (thin film) 3493br s, 3086m, 3030s, 2928m, 1720s, 1641m, 1454s, 1109m, 814s, 752s, 700s cm^{-1}; HRMS (ESI-TOF) *m/z* found 223.1119 [$(M-H_2O+H)^+$; calcd. 223.1123 for $C_{16}H_{15}O$].

2,2-dicyclohexyl-2-hydroxyacetaldehyde (2r)

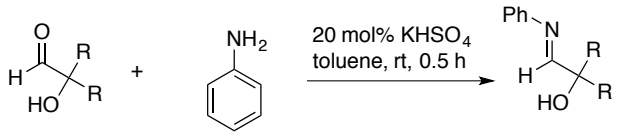


2r

Following the general procedure with commercial cyclohexylmagnesium chloride (2M in ether, 3.5 mL, 7.0 mmol, 2.5 equiv, the scale was doubled), this reaction afforded the product **2r** as a white solid (57%, 0.359 g, 1.60 mmol); mp = 65-67 °C.

Spectral data for **2r:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (qd, *J* = 8.0, 2.5 Hz, 2H), 1.06-1.15 (m, 2H), 1.17-1.25 (m, 6H), 1.52 (dd, *J* = 6.0, 2.5 Hz, 2H), 1.66 (d, *J* = 12.5 Hz, 2H), 1.75-1.86 (m, 8H), 3.21 (s, 1H), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.01, 26.27, 26.43, 26.59, 27.33, 40.36, 83.92, 206.61; IR (thin film) 3468 br s, 2930s, 2853s, 1720s, 1448s, 1329m, 1101m cm^{-1}; HRMS (ESI-TOF) *m/z* found 225.1852 [(M+H)$^{+}$; calcd. 225.1855 for $C_{14}H_{25}O_2$].

5.2.2 General procedure for the preparation of iminol 3

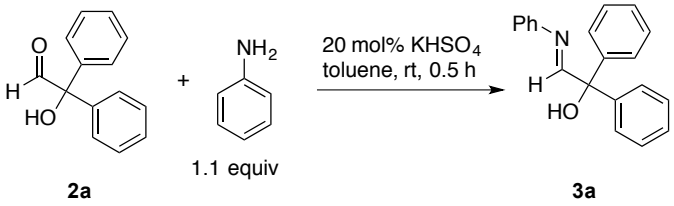


2 **3**

To a 20 mL vial was added the appropriate α-hydroxyl aldehyde (0.3-0.5 mmol, 1 equiv), solid $KHSO_4$ (20 mol%), aniline (1.1 equiv) and toluene (1 mL). The vial was capped and the mixture was stirred at room temperature for 0.5 h.

Upon completion, the reaction mixture was neutralized with 0.1 mL Et_3N and dried over $MgSO_4$, then it was filtered through a filter paper in Buchner funnel and concentrated under rotary evaporation. The crude solid iminols were purified by recrystallization from hexanes; crude oil iminols were purified by a short flash column chromatography, 10:1 hexanes:EtOAc as eluent.

1,1-diphenyl-2-(phenylimino)ethan-1-ol (3a).

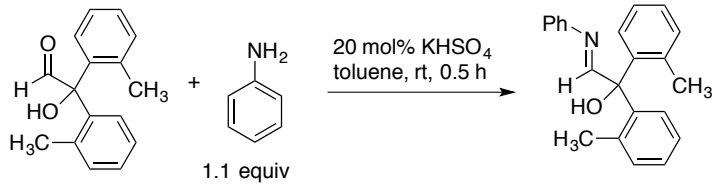


2a **3a**

Following the general procedure with **2a** (0.5 mmol, 10 mmol and 40 mmol scale), the reaction afforded 78-100% yield of the product **3a** as a white solid over several trials; mp = 86-88 °C.

Spectral data for **3a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.74 (br s, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.0 Hz, 2H), 7.32 (tt, *J* = 7.5, 1.0 Hz, 2H), 7.35-7.39 (m, 5H), 7.44 (d, *J* = 7.0 Hz, 4H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.76, 121.17, 126.81, 127.19, 127.78, 128.52, 129.21, 143.23, 148.58, 164.92; IR (thin film) 3399s, 3059s, 3028s, 1647s, 1595s, 1487s, 1448s, 1385m, 1325m, 1170m cm^{-1}; HRMS (ESI-TOF) *m/z* found 270.1270 [$(M-H_2O+H)^+$; calcd. 270.1277 for $C_{20}H_{16}N$].

2-(phenylimino)-1,1-di-o-tolylethan-1-ol (3b).

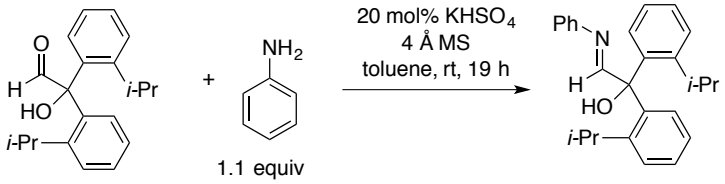


2b **3b**

Following the general procedure with **2b** (0.117 g, 0.487 mmol), the reaction afforded the product **3b** as a colorless liquid (88%, 0.135 g, 0.428 mmol).

Spectral data for **3b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.12 (s, 6H), 5.78 (br s, 1H), 7.15-7.27 (m, 9H), 7.36-7.42 (m, 4H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.47, 80.33, 115.15, 121.12, 126.01, 126.72, 127.12, 127.86, 129.23, 132.43, 136.90, 141.24, 164.43; IR (neat) 3395br s, 3061s, 3018s, 2964s, 2928s, 1693s, 1645s, 1601s, 1502s, 1487s, 1460s, 1381s, 1325s, 1161m, 989m, 970m, 868m cm^{-1}; HRMS (ESI-TOF) *m/z* found 298.1596 [$(M-H_2O+H)^+$; calcd. 298.1596 for $C_{22}H_{20}N$].

1,1-bis(2-isopropylphenyl)-2-(phenylimino)ethan-1-ol (3c).

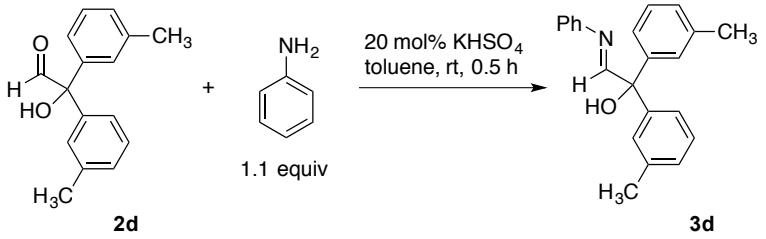


2c **3c**

Following the general procedure with **2c** (0.101g, 0.343 mmol), the formation of imine **3c** was not complete after 19 h even in the presence of 0.30 g 4Å molecular sieves. The crude residue was a 1:3.2 mixture of aldehyde:imine as

judged from the ^{1}H NMR spectrum (δ 10.19 for the aldehyde and δ 8.59 for the imine). This crude imine was taken directly on to the next step.

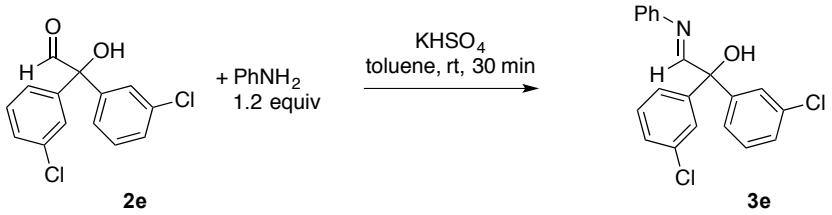
2-(phenylimino)-1,1-di-m-tolylethan-1-ol (3d).



Following the general procedure with **2d** (0.129 g, 0.533 mmol), the reaction afforded the product **3d** as a colorless liquid (84%, 0.142 g, 0.448 mmol).

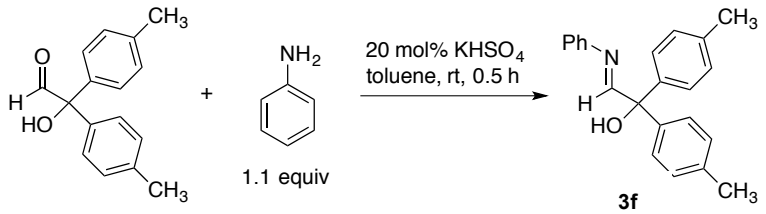
Spectral data for **3d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 6H), 5.71 (br s, 1H), 7.13-7.22 (m, 6H), 7.25-7.28 (m, 5H), 7.38 (t, *J* = 8.0 Hz, 2H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.61, 78.69, 115.13, 121.20, 124.24, 126.74, 127.75, 128.31, 128.49, 129.19, 138.24, 143.27, 165.11; IR (neat) 3381br s, 3032s, 2920s, 1647s, 1603s, 1498s, 1487s, 1153m, 1026w, 873m cm^{-1}; HRMS (ESI-TOF) *m/z* found 298.1583 [(M+H)$^+$; calcd. 298.1596 for $C_{22}H_{22}NO$].

1,1-bis(3-chlorophenyl)-2-(phenylimino)ethan-1-ol (3e).



Following the general procedure with **2e** (0.10 g, 0.35 mmol), this reaction afforded the product **3e** (0.12g, 0.35 mmol, 100%) as a colorless oil. Spectral data for **3e:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (s, 1H), 7.17 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.27-7.36 (m, 7H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.44-7.45 (m, 2H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.04, 121.19, 125.21, 127.23, 127.26, 128.25, 129.31, 129.89, 134.72, 144.76, 147.88, 163.09; IR (thin film) 3409s, 1660s, 1448s, 1330m, 1190m, 1050m cm^{-1}; HRMS (ESI-TOF) m/z found 356.0611 [$(M+H)^+$; calcd. 356.0609 for $C_{20}H_{16}ONCl_2$].

2-(phenylimino)-1,1-di-p-tolylethan-1-ol (3f).

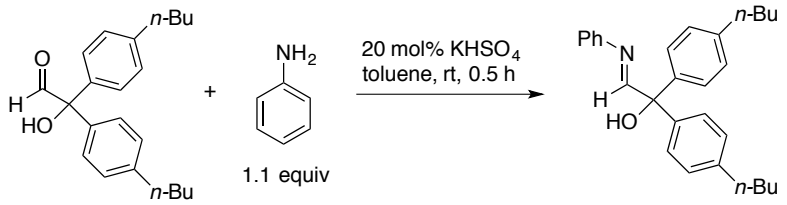


Following the general procedure with **2f** (0.087 g, 0.36 mmol), the reaction afforded the product **3f** as a white solid (93%, 0.106 g, 0.334 mmol); mp = 116-119 °C.

Spectral data for **3f**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 6H), 5.66 (br s, 1H), 7.15-7.19 (m, 5H), 7.25-7.26 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 2H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.10, 78.49, 121.14, 126.65, 127.09, 129.16, 137.43, 140.42, 148.76, 165.20 (1 aromatic carbon was not located); IR (thin film) 3402br s, 3026s, 2922s, 1647s, 1595s, 1510s, 1487s,

1452m, 1410m, 1379m, 1327m, 1167s, 985s cm^{-1}; HRMS (ESI-TOF) *m/z* found 298.1592 [$(M-H_2O+H)^+$; calcd. 298.1596 for $C_{22}H_{20}N$].

1,1-bis(4-butylphenyl)-2-(phenylimino)ethan-1-ol (3g).

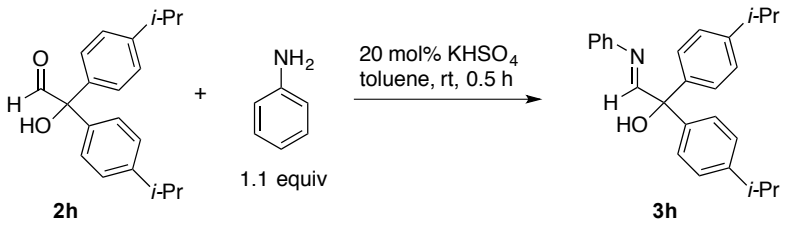


2g **3g**

Following the general procedure with **2g** (0.114 g, 0.350 mmol), this reaction afforded the product **3g** as a white solid (93%, 0.130 g, 0.325 mmol); mp = 75-77 °C.

Spectral data for **3g**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.37 (sextet, *J* = 7.5 Hz, 4H), 1.61 (qt, *J* = 7.5, 2.5 Hz, 4H), 2.62 (d, *J* = 7.5 Hz, 4H), 5.68 (br s, 1H), 7.17-7.27 (m, 7H), 7.34-7.39 (m, 6H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.97, 22.39, 33.56, 35.29, 78.49, 121.18, 126.65, 127.06, 128.50, 129.16, 140.53, 142.42, 148.76, 165.27; IR (thin film) 3402s, 3024m, 2957s, 2930s, 2858s, 1647s, 1595m, 1508s, 1415m, 1167s, 981m cm^{-1}; HRMS (ESI-TOF) *m/z* found 400.2638 [$(M+H)^+$; calcd. 400.2640 for $C_{28}H_{34}NO$].

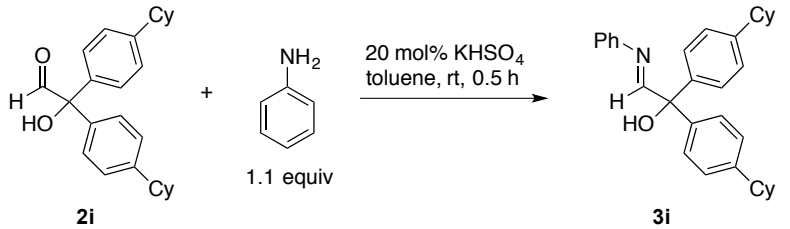
1,1-bis(4-isopropylphenyl)-2-(phenylimino)ethan-1-ol (3h).



Following the general procedure with **2h** (0.106 g, 0.355 mmol), this reaction afforded the product **3h** as a white solid (95%, 0.125 g, 0.337 mmol); mp = 138-139 °C.

Spectral data for **3h**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.26 (d, *J* = 7.0 Hz, 12H), 2.92 (septet, *J* = 7.0 Hz, 2H), 5.68 (br s, 1H), 7.16-7.18 (m 2H), 7.23-7.25 (m, 4H), 7.26-7.27 (m, 2H), 7.36-7.39 (m, 5H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.95, 33.78, 78.44, 121.18, 126.52, 126.64, 127.11, 129.16, 140.66, 148.28, 148.77, 165.29; IR (thin film) 3412 br s, 2961s, 2870w, 1647s, 1484m, 1172m, 1055m cm^{-1}; HRMS (ESI-TOF) *m/z* found 354.2220 [$(M-H_2O+H)^+$; calcd. 354.2222 for $C_{26}H_{28}N$].

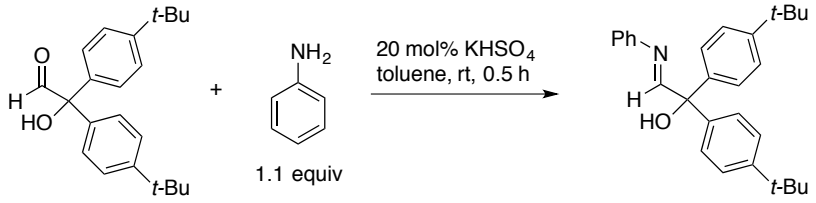
1,1-bis(4-cyclohexylphenyl)-2-(phenylimino)ethan-1-ol (3i).



Following the general procedure with **2i** (0.105 g, 0.278 mmol), the reaction afforded the product **3i** as a white solid (93%, 0.117 g, 0.259 mmol); mp = 153-155 °C.

Spectral data for **3i**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22-1.30 (m, 2H), 1.35-1.46 (m, 8H), 1.75 (dt, *J* = 12.5, 1.0 Hz, 2H), 1.84-1.89 (m, 8H), 2.48-2.53 (m, 2H), 5.68 (s, 1H), 7.16-7.18 (m, 2H), 7.21 (d, J = 8.0 Hz, 4H), 7.25 (tt, *J* = 7.5, 1.0 Hz, 2H), 7.35-7.39 (m, 5H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.14, 26.88, 34.39, 44.21, 78.46, 121.20, 126.63, 126.90, 127.08, 129.15, 140.63, 147.51, 148.77, 165.30; IR (thin film) 3375br s, 3032w, 2924s, 2851s, 1603s, 1498s, 1448m, 1278m, 1172m cm^{-1}; HRMS (ESI-TOF) *m/z* found 452.2957 [$(M+H)^+$; calcd. 452.2953 for $C_{32}H_{38}NO$].

1,1-bis(4-*t*-butylphenyl)-2-(phenylimino)ethan-1-ol (3j).

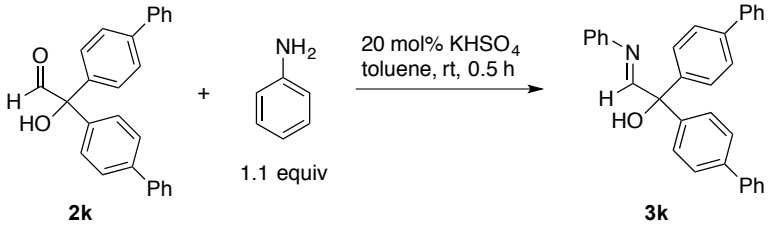


2j **3j**

Following the general procedure with **2j** (0.137 g, 0.422 mmol), this reaction afforded the product **3j** as a white solid (98%, 0.165 g, 0.414 mmol); mp = 137-140 °C. Spectral data for **3j:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (s, 18H), 5.69 (br s, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.24-7.27 (m, 2H), 7.36-7.41 (m, 9H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.32, 34.53, 78.32, 121.19, 125.38,

126.63, 126.83, 129.16, 140.22, 148.78, 150.52, 165.29; IR (thin film) 3402br s, 3032m, 2963s, 2905m, 1647s, 1597s, 1506s, 1404m, 1363s, 1269m, 1109s, 831m cm^{-1}; HRMS (ESI-TOF) *m/z* found 382.2534 $[(M-H_2O+H)^+$; calcd. 382.2535 for $C_{28}H_{32}N]$.

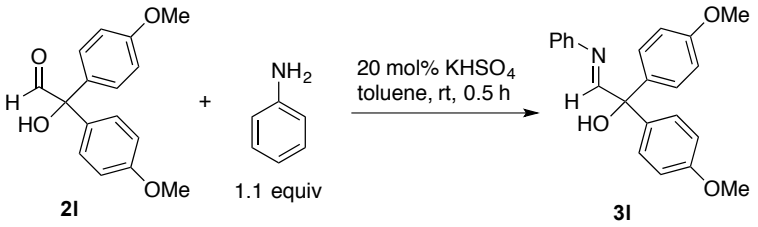
1,1-di([1,1'-biphenyl]-4-yl)-2-(phenylimino)ethan-1-ol (3k).



Following the general procedure with **2k** (0.131 g, 0.360 mmol), the reaction afforded the product **3k** as a white solid (95%, 0.150 g, 0.342 mmol); mp = 183-185 °C.

Spectral data for **3k**: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.82 (s, 1H), 7.22 (dt, *J* = 7.5, 1.0 Hz, 2H), 7.28 (tt, *J* = 7.5, 1.0 Hz, 2H), 7.35-7.42 (m, 4H), 7.46 (t, *J* = 7.5 Hz, 4H), 7.57 (dt, *J* = 7.5, 1.0 Hz, 4H), 7.61-7.65 (m, 7H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.56, 121.21, 126.89, 127.14, 127.32, 127.44, 127.62, 128.80, 129.25, 140.60, 140.74, 142.17, 148.55, 164.61; IR (thin film) 3402br s, 1645s, 1485s, 1174m cm^{-1}; HRMS (ESI-TOF) *m/z* found 440.2026 $[(M+H)^+$; calcd. 440.2014 for $C_{32}H_{26}NO]$.

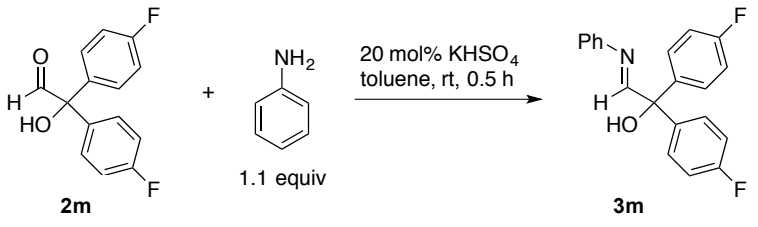
1,1-bis(4-methoxylphenyl)-2-(phenylimino)ethan-1-ol (3l)



Following the general procedure with **2l** (0.086 g, 0.308 mmol), the reaction afforded the product **3l** as a white solid (97%, 0.104 g, 0.300 mmol); mp = 90-94 °C.

Spectral data for **3l**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.82 (s, 6H), 5.67 (br s, 1H), 6.92 (dt, *J* = 9.0, 3.0 Hz, 4H), 7.16-7.18 (m, 3H), 7.25-7.27 (m, 1H), 7.35-7.39 (m, 5H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.32, 78.15, 113.83, 115.12, 121.14, 126.67, 128.46, 129.20, 135.46, 159.07, 165.12; IR (thin film) 3385br s, 3034m, 3003m, 2934m, 1647s, 1606s, 1508s, 1302m, 1251s, 1172s, 1033s, 831s cm^{-1}; HRMS (ESI-TOF) *m/z* found 330.1492 [$(M-H_2O+H)^+$; calcd. 330.1494 for $C_{22}H_{20}NO_2$].

1,1-bis(4-fluorophenyl)-2-(phenylimino)ethan-1-ol (3m)

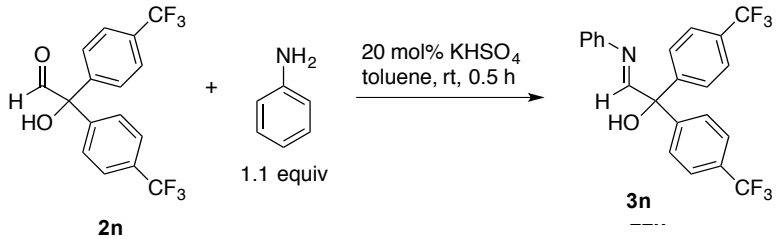


Following the general procedure with **2m** (0.084 g, 0.36 mmol), this reaction afforded the product **3m** as a colorless liquid (95%, 0.106 g, 0.346 mmol),

which was purified by flash column chromatography on silica gel with a 10:1 mixture of hexanes:EtOAc.

Spectral data for **3m**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.78 (br s, 1H), 7.08 (tt, *J* = 9.0, 2.5 Hz, 4H), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 1H), 7.38-7.42 (m, 5H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.00, 115.14, 115.48 (d, *J* = 20.9 Hz), 118.62, 121.13, 128.93 (d, *J* = 8.0 Hz), 129.29, 138.85 (d, *J* = 2.9 Hz), 162.32 (d, *J* = 245.6 Hz), 164.06; ^{19}F NMR ($CDCl_3$, 470 MHz) δ –114.25; IR (neat) 3381br s, 3078s, 3029s, 1649s, 1603s, 1506s, 1224s, 1159s, 1091m, 1014m cm^{-1}; HRMS (ESI-TOF) *m/z* found 306.1090 [$(M-H_2O+H)^+$; calcd. 306.1094 for $C_{20}H_{14}NF_2$].

1,1-bis(4-trifluoromethylphenyl)-2-(phenylimino)ethan-1-ol (3n).

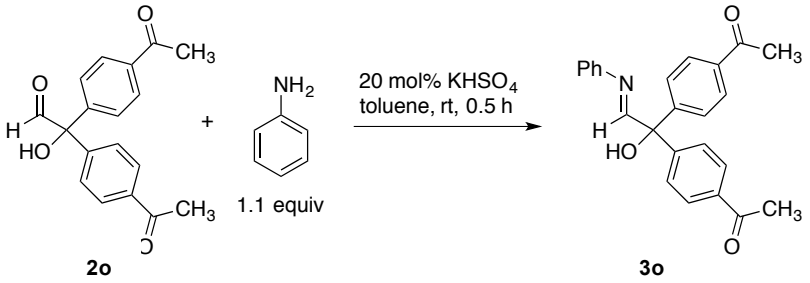


Following the general procedure with **2n** (0.121 g, 0.349 mmol), the reaction afforded the product **3n** as a white solid (90%, 0.133 g, 0.314 mmol); mp = 95-100 °C.

Spectral data for **3n**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.89 (br s, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.29 (t, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 4H), 7.66 (d, *J* = 8.5 Hz, 4H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.30, 121.13, 123.89 (q, *J* = 270.0 Hz), 125.69 (q, *J* = 3.7 Hz), 126.66, 127.43,

129.38, 130.34 (q, *J* = 32.7 Hz), 146.53, 147.76, 162.81; ^{19}F NMR ($CDCl_3$, 470 MHz) δ –62.65; IR (thin film) 3391br s, 1653s, 1616s, 1489m, 1414s, 1325s, 1167s, 1126s, 1068s, 1018m, 841m cm^{-1}; HRMS (ESI-TOF) *m/z* found 406.1040 [$(M-H_2O+H)^+$; calcd. 406.1030 for $C_{22}H_{14}NF_6$].

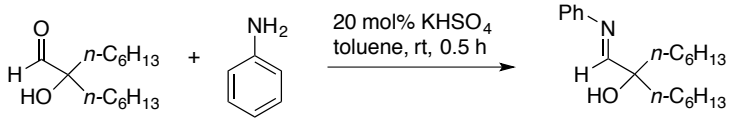
1,1'-((1-hydroxy-2-(phenylimino)ethane-1,1-diyl)bis(4,1-phenylene))bis(etha n-1-one) (3o).



Following the general procedure with **2o** (0.0455 g, 0.154 mmol), the crude product was purified by flash column chromatography on silica gel with 10:1 CH_2Cl_2:EtOAc as eluent. This reaction afforded the product **3o** as a light yellow solid (88%, 0.0502 g, 0.136 mmol); mp = 168-169 °C.

Spectral data for **3o**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.62 (s, 6H), 5.88 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 4H), 7.99 (d, *J* = 8.5 Hz, 4H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.72, 78.57, 121.15, 127.25, 127.33, 128.69, 129.35, 136.65, 147.75, 147.92, 163.00, 197.56; IR (thin film) 3387 br s, 1684s, 1603s, 1408m, 1358m, 1267s cm^{-1}; HRMS (ESI-TOF) *m/z* found 372.1595 [$(M+H)^+$; calcd. 372.1600 for $C_{24}H_{22}NO_3$].

7-((phenylimino)methyl)tridecan-7-ol (3p).

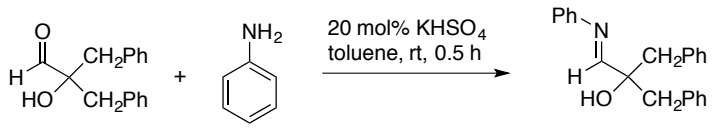


2p **3p**

Following the general procedure with **2p** (0.104 g, 0.458 mmol), this reaction afforded the product **3p** as a colorless liquid (88%, 0.122 g, 0.402 mmol), which was purified by flash column chromatography on silica gel with a 10:1 mixture of hexanes:EtOAc.

Spectral data for **3p**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, *J* = 7.5 Hz, 6H), 1.14-1.31 (m, 14H), 1.43-1.51 (m, 2H), 1.63 (td, *J* = 7.5, 5.0 Hz, 2H), 1.71 (td, *J* = 7.5, 5.0 Hz, 2H), 4.23 (br s, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.08, 22.60, 23.30, 29.76, 31.78, 39.07, 75.60, 120.77, 126.14, 129.12, 149.81, 168.47; IR (thin film) 3458br s, 3030w, 2930s, 2858s, 1653s, 1595s, 1489m, 1466m, 1396m, 1136m, 1072m, 868m cm^{-1}; HRMS (ESI-TOF) *m/z* found 286.2542 [$(M-H_2O+H)^+$; calcd. 286.2535 for $C_{20}H_{32}N$].

2-benzyl-1-phenyl-3-(phenylimino)propan-2-ol (3q).

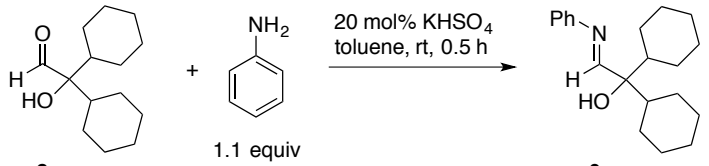


2q **3q**

Following the general procedure with **2q** (0.147 g, 0.606 mmol), the reaction afforded the product **3q** as a light yellow oil (100%, 0.191 g, 0.606 mmol), which was purified by flash column chromatography on silica gel with a 10:1 mixture of hexanes:EtOAc.

Spectral data for **3q:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.13 (s, 4H), 4.15 (br s, 1H), 7.16-7.34 (m, 15H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 45.61, 76.03, 120.26, 125.78, 126.65, 128.04, 128.94, 130.58, 136.13, 150.15, 167.19; IR (neat) 3412 br s, 2063m, 3028s, 2920m, 1657m, 1599s, 1495s, 1254s, 1321m, 1086m, 1032m cm^{-1}; HRMS (ESI-TOF) *m/z* found 316.1703 [(M+H)$^{+}$; calcd. 316.1701 for $C_{22}H_{22}NO$].

1,1-dicyclohexyl-2-(phenylimino)ethan-1-ol (3r).

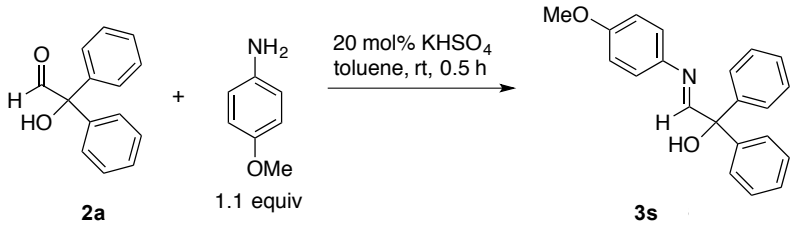


Following the general procedure with **2r** (0.198 g, 0.882 mmol), the reaction afforded the product **3r** as a white solid (88%, 0.246 g, 0.776 mmol); mp = 84-86 °C.

Spectral data for **3r**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97-1.27 (m, 11H), 1.58-1.93 (m, 11H), 4.22 (br s, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.21-7.25 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.38, 26.51,

26.61, 26.76, 27.52, 41.94, 78.92, 120.73, 126.04, 129.12, 150.07, 168.69; IR (thin film) 3447br s, 2928s, 2853s, 1651s, 1597m, 1487m, 1448m, 1425m, 1099m, 1074m cm^{-1}; HRMS (ESI-TOF) *m/z* found 300.2338 $[(M-H_2O+H)^+$; calcd. 300.2327 for $C_{20}H_{30}NO]$.

2-((4-methoxyphenyl)imino)-1,1-diphenylethan-1-ol (3s).



Following the general procedure with **2a** (0.961 g, 4.52 mmol) and 4-anisidine (0.607 g, 4.93 mmol, 1.1 equiv.), this reaction afforded the product **3s** as a white solid (99%, 1.42 g, 4.48 mmol); mp = 77-79 °C.

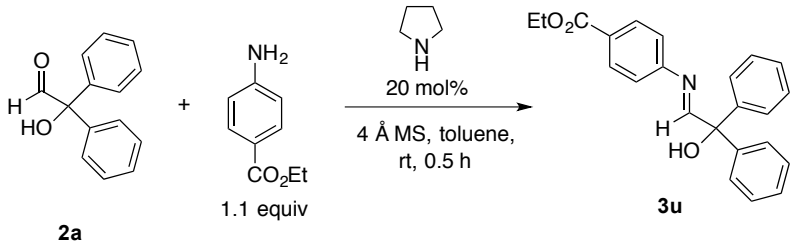
Spectral data for **3s**: ^1H NMR ($CDCl_3$, 500 MHz) δ 3.82 (s, 3H), 5.85 (br s, 1H), 6.91 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.20 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.32 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.38 (tt, *J* = 7.5, 1.5 Hz, 4H), 7.44 (dt, *J* = 7.0, 1.5 Hz, 4H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.52, 78.62, 114.35, 122.63, 127.18, 127.68, 128.64, 141.13, 143.49, 158.81, 162.42; IR (thin film) 3385br s, 3059s, 3026s, 2932s, 1643s, 1603s, 1506s, 1448s, 1248s, 1032s cm^{-1}; HRMS (ESI-TOF) *m/z* found 318.1500 $[(M+H)^+$; calcd. 318.1494 for $C_{21}H_{20}NO_2]$.

1,1-dicyclohexyl-2-((4-methoxyphenyl)imino)ethan-1-ol (3t).

The general procedure was followed with **2r** (0.104 g, 0.465 mmol) and 4-anisidine (0.063 g, 0.51 mmol, 1.1 equiv) except that the reaction temperature was 50 °C for 2h. The reaction afforded the product **3t** as a light yellow solid (81%, 0.124 g, 0.377 mmol); mp = 94-97 °C.

Spectral data for **3t:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (qd, *J* = 12.5, 3.5 Hz, 2H), 1.13 (td, *J* = 12.5, 3.5 Hz, 2H), 1.17-1.28 (m, 6H), 1.28 (d, *J* = 10.0 Hz, 2H), 1.67 (d, *J* = 12.5 Hz, 2H), 1.75-1.83 (m, 6H), 1.92 (d, *J* = 12.5 Hz, 2H), 3.82 (s, 3H), 4.33 (br s, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.40, 26.52, 26.62, 26.78, 27.55, 42.01, 55.54, 78.87, 114.31, 122.03, 142.68, 158.27, 166.65; IR (thin film) 3437 br s, 2928s, 2853s, 1647s, 1506s, 1448m, 1246s, 1035m cm^{-1}; HRMS (ESI-TOF) *m/z* found 330.2434 [$(M+H)^{+}$; calcd. 330.2433 for $C_{21}H_{32}NO_2$].

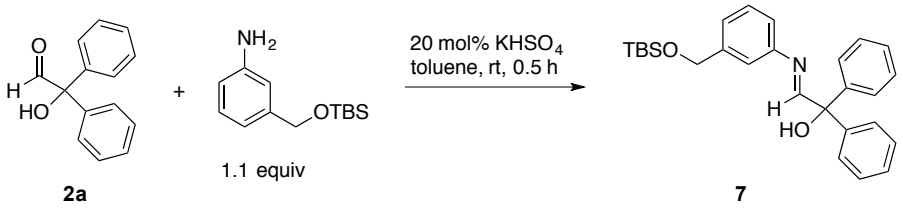
ethyl 4-((2-hydroxy-2,2-diphenylethylidene)amino)benzoate (3u).



Following the general procedure with **2a** (0.041 g, 0.19 mmol), ethyl 4-aminobenzoate (0.034 g, 0.21 mmol), in the presence of 20 mol% pyrrolidine and 0.050 g 4Å molecular sieves (no $KHSO_4$ was added), the reaction afforded the product **3u** as a colorless liquid (89%, 0.061 g, 0.17 mmol).

Spectral data for **3u**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (t, *J* = 7.0 Hz, 3H), 4.38 (q, *J* = 7.0 Hz, 2H), 5.51 (s, 1H), 7.15 (dt, *J* = 8.0, 2.0 Hz, 2H), 7.33 (tt, *J* = 7.5, 2.0 Hz, 2H), 7.37-7.40 (m, 4H), 7.44 (dt, *J* = 7.0, 2.0 Hz, 4H), 8.05 (d, *J* = 9.0 Hz, 2H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.31, 61.02, 78.94, 120.86, 126.09, 127.15, 127.91, 128.58, 130.81, 142.87, 152.80, 160.04, 166.73; IR (neat) 3449br s. 3059m, 2980m, 1714s, 1653m, 1603s, 1493m, 1448s, 1277s, 1170s, 1101s cm^{-1}; HRMS (ESI-TOF) *m/z* found 360.1602 $[(M+H)^+$; calcd. 360.1600 for $C_{23}H_{22}NO_3$].

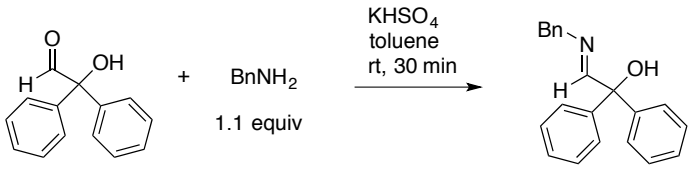
2-((3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)imino)-1,1-diphenylethan-1-ol (7).



Following the general procedure with **2a** (0.15 g, 0.70 mmol, 1 equiv) and 3-(((*tert*-butyldimethylsilyl)oxy)methyl)aniline (0.18 g, 0.77 mmol, 1.1 equiv), the reaction afforded the product **7** as a colorless liquid (100%, 0.31 g, 0.77 mmol).

Spectral data for **7**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.10 (s, 6H), 0.94 (s, 9H), 4.75 (s, 2H), 5.74 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.30-7.33 (m, 3H), 7.38 (t, *J* = 8.0 Hz, 4H), 7.44 (d, *J* = 8.0 Hz, 4H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.26, 18.41, 25.93, 64.46, 78.72, 118.41, 119.76, 124.20, 127.16, 127.73, 128.49, 129.02, 142.87, 143.26, 148.68, 164.89; IR (neat) 3393s, 2955s, 2932s, 2889s, 2856s, 1647s, 1601s, 1491s, 1375s, 1253s, 1172s, 1105s cm^{-1}; HRMS (ESI-TOF) *m/z* found 432.2365 $[(M+H)^{+}$; calcd. 432.2359 for $C_{27}H_{34}NO_2Si$].

2-(benzylimino)-1,1-diphenylethan-1-ol (3w)

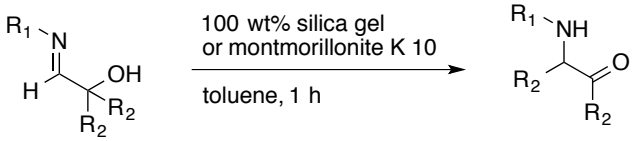


2a **3w**

Following the general procedure with **2a** (0.12 g, 0.55 mmol, 1 equiv) and benzyl amine (66 µL, 0.60 mmol, 1.1 equiv), this reaction afforded the product **3w** (0.13 g, 0.44 mmol, 80%) as a white solid; mp = 78-80 °C.

Spectral data for **3w:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.80 (s, 2H), 5.78 (br s, 1H), 7.27-7.33 (m, 5H), 7.35-7.40 (m, 10H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 61.92, 78.28, 127.10, 127.27, 127.59, 127.81, 128.39, 128.60, 138.21, 143.62, 166.11; IR (thin film) 3408s, 1662s, 1448m, 1363m, 1172m, 1028w cm^{-1}; HRMS (ESI-TOF) m/z found 302.1532 [$(M+H)^+$; calcd. 302.1545 for $C_{21}H_{20}ON$].

5.2.3 Synthesis of amino ketone with silica gel and Montmorillonite K 10



3 **4**

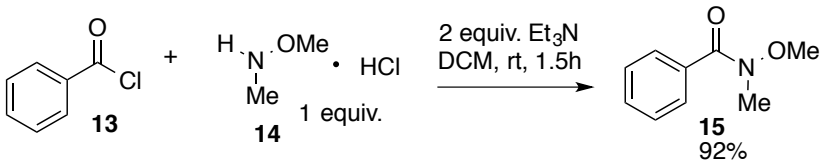
General procedure: To a 20 mL screw cap vial was added iminol **3** (0.1 mmol), silica gel or montmorillonite K 10 (100 wt%) and 0.3 mL toluene. The cap was screwed tight and heated to 80 °C for silica gel and 60 °C for montmorillonite

under air for 1 h. After cooling to room temperature, the solution was directly subjected to silica gel column to afford the pure product **4**.

The complete analytical data for 4a-4w were all presented in section 5.3.4.

5.2.4 Synthesis of Ketamine analog 20

***N*-methoxy-*N*-methylbenzamide (15)**

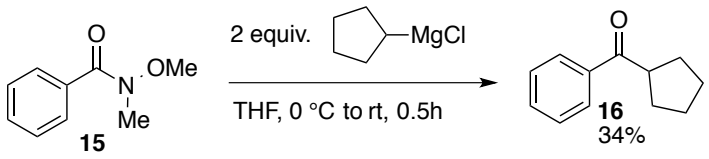


N,O-dimethylhydroxyamine **14** (2.03 g, 19.2 mmol, 2.2 equiv.) was suspended and vigorously stirred in 10 mL CH_2Cl_2, followed by addition of Et_3N (5.0 mL, 34 mmol, 4 equiv.). The resulting solution was vigorously stirred. After 30 min, benzoyl chloride **13** (2.0 mL, 16 mmol, 1 equiv) was added dropwise and allowed to stir at room temperature for 1 h. The mixture was washed with brine, dried over $MgSO_4$, filtered on filter paper and concentrated on rotary vaporization. The crude product was purified by silica gel column chromatography, a 1:1 mixture of hexane:EtOAc as the eluent, to afford **15** (2.61 g, 15.8 mmol, 92%) as a colorless oil.

Spectral data for **15:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.34 (s, 3H), 3.54 (s. 3H), 7.38 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.44 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 33.76, 61.01, 127.98, 128.10, 130.52, 134.09, 169.91. These NMR data are in agreement with literature data.[73]

Cyclopentyl phenyl ketone (16)

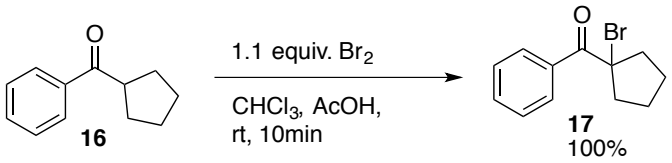


To a 100 mL clean and dry Schlenk flask purged with N_2 was added Mg (0.74 g, 31 mmol, 2 equiv.), a small crystal of I_2, chlorocyclopentane (3.2 mL, 31 mmol, 2 equiv.) and 20 mL THF. The flask was sealed and the resulting mixture was heated in 70 °C oil bath for 1 h or until all Mg dissolved. The solution was allowed to cool to room temperature and 0 °C in ice bath. This cooled solution was transferred to a solution of **15** (2.61 g, 15.8 mmol, 1 equiv.) in 10 mL THF in a 250 mL round bottom flask with a pipette dropwise. After completion of the transfer, it was allowed to stir at room temperature for 30 min under N_2 atmosphere. The reaction was quenched with 20 mL saturated NH_4Cl solution and extracted with Et_2O (10 mL x 2). The combined organic phase was washed with brine 10 mL, dried over $MgSO_4$, filtered through filter paper and concentrated on rotary vaporization. The crude product was purified by silica gel column chromatography, a 20:1 mixture of hexane:EtOAc as the eluent, to afford **16** (0.93 g, 5.3 mmol, 34%) as a colorless oil.

Spectral data for **16:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.50-1.77 (m, 5H), 1.89-1.94 (m, 3H), 3.71 (quint. *J* = 8.0 Hz, 1H), 7.45 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.54 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.98 (dt, *J* = 7.5, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.31, 29.96, 46.33, 128.44, 128.47, 132.68, 136.89, 202.77. These NMR data are in agreement with literature data.[74]

Note: benzaldehyde (0.63 g, 38%) was also isolated as a byproduct. Synthesis of **16** via the reaction between **15** and Wittig reagent may give a better yield.[73] Or via the reaction between benzonitrile and Grignard reagent.

(1-bromocyclopentyl)(phenyl)methanone (17)

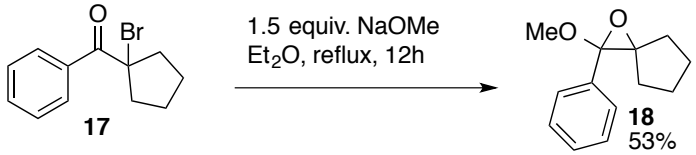


To a clean and dry 20 mL round bottom flask was added the ketone **16** (0.63 g, 3.6 mmol, 1 equiv.), acetic acid (1 mL) and chloroform (4 mL), while stirring, Br_2 (0.2 mL, 4 mmol, 1.1 equiv.) was added dropwise via a syringe. During the addition of each drop of Br_2, the dark color faded away instantaneously. The resulting solution was allowed to stir at room temperature for 10 min. Then the solution was successively washed with 10 mL saturated $Na_2S_2O_4$ solution, 10 mL saturated Na_2CO_3 solution and 10 mL brine. The organic phase was dried over $MgSO_4$, filtered through filter paper and concentrated on rotary vaporization. The crude product was purified by silica gel column chromatography, a 20:1

mixture of hexane:EtOAc as the eluent, to afford **17** (0.91 g, 3.6 mmol, 100%) as a white semi-solid.

Spectral data for **17:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.76-1.84 (m, 2H), 2.02-2.11 (m, 2H), 2.40-2.46 (m, 2H), 2.49-2.54 (m, 2H), 7.44 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.54 (tt, *J* = 7.5, 1.5 Hz, 1H), 8.15 (dt, *J* = 7.5, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.49, 40.99, 71.12, 128.14, 130.21, 132.77, 134.72, 195.26. The ^{1}H NMR data are in agreement with literature data.[75]

2-methoxy-2-phenyl-1-oxaspiro[2.4]heptane (18)



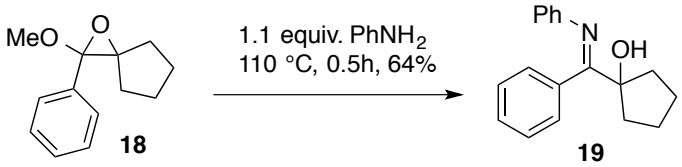
Compound **18** is synthesized according to a literature procedure.[4]

To a clean and dry 50 mL round bottom flask was added 5 mL methanol and sodium metal (cut into small chunks, 0.0644 g, 2.80 mmol. 1 equiv.), after addition of Na metal, the flask was seal with a septum and a N_2 balloon was attached via a needle. After disappearance of the sodium metal, the solvent was removed under high vacuum and flushed with N_2. To the flask was added 10 mL Et_2O and bromoketone **17** (0.71 g in 10 mL Et_2O, 2.8 mmol, 1 equiv.) and equipped with a water condenser, the top was seal with a septum and a N_2 balloon was attached via a needle. The resulting mixture was heated to reflux for 18 h. After cooling to room temperature, the suspension was filtered through filter paper and

concentrated on rotary vaporization. The crude product was purified by vacuum distillation (0.2 mmHg, 160 °C) to afford the product **18** (0.30 g, 1.5 mmol, 53%) as a colorless oil.

Spectral data for **18:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.31-1.37 (m, 1H), 1.40-1.52 (m, 2H), 1.61-1.68 (m, 1H), 1.70-1.76 (m, 1H), 1.77-1.85 (m, 2H), 2.13-2.20 (m, 1H), 3.08 (s, 3H), 7.33 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.38 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.43 (dt, *J* = 7.5, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.14, 25.23, 52.79, 78.35, 89.63, 127.47, 128.16, 128.29, 134.97.

1-(phenyl(phenylimino)methyl)cyclopentan-1-ol (19)

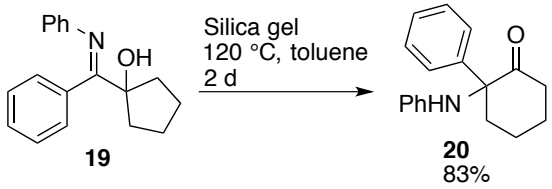


Compound **19** is synthesized according to a literature procedure.[4]

To a 10 mL round bottom flask was added the methoxy epoxide **18** (0.30 g, 1.5 mmol, 1 equiv.) and aniline (0.14 mL, 1.6 mmol, 1.1 equiv.). The resulting solution was heated to 110 °C under air for 30 min. After it was cooled to room temperature, allow it to crystalize in the freezer. Then recrystallize in hexane to afford the pure product **19** (0.25 g, 0.94 mmol, 64%) as a yellow solid. mp = 77-81 °C.

Spectral data for **19:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59-1.66 (m, 2H), 1.79-1.84 (m, 2H), 1.92-2.03 (m, 4H), 5.40 (s, 1H), 6.65 (d, *J* = 7.5 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 7.02-7.03 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 2H), 7.19-7.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.09, 38.61, 84.40, 120.86, 123.66, 127.79, 128.10, 128.16, 128.31, 134.72, 148.90, 176.57.

2-phenyl-2-(phenylamino)cyclohexan-1-one (20)



19 **20** 83%

Synthesis of compound **20** from compound **19** has been reported in the literature by refluxing in decalin without a catalyst.[4] Below is a new procedure that has not been reported before.

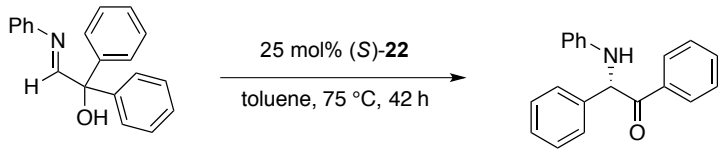
To a clean and dry 20 mL Schlenk flask was added **19** (0.0379 g, 0.143 mmol), silica gel (0.04 g, 100 wt%) and toluene 0.3 mL. The flask was purged with N2, sealed and heated to 120 °C for 48 h. Then cooled to room temperature. The solution was directly subjected to silica gel column chromatography, a 2:1 mixture of chloroform:hexane as the eluent, to afford **20** (0.0314 g, 0.118 mmol, 83%) as a white solid. mp = 157-158°C.

Spectral data for **20:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.82-1.89 (m, 1H), 1.94-2.06 (m, 4H), 2.30 (td, *J* = 13.0, 5.0 Hz, 1H), 2.45-2.48 (m, 1H), 3.15-3.21 (m,

1H), 5.46 (s, 1H), 6.46 (d, *J* = 8.0 Hz, 2H), 6.60 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.80, 28.38, 38.72, 39.32, 68.17, 115.02, 117.60, 127.49, 127.66, 128.64, 128.81, 139.09, 144.70, 209.10.

5.3 Experimental procedures for chapter three

5.3.1 Procedure 1: Reaction with (*S*)-VANOL BOROX catalyst 22



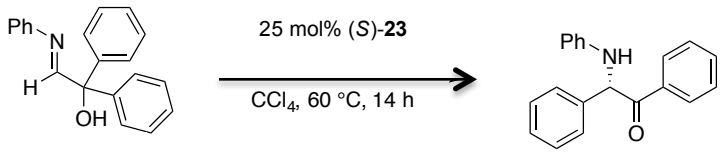
3a **4a**

The catalyst (S)-VANOL BOROX **22** was prepared as follows. To a 20 mL flame dried Schlenk flask was added (*S*)-VANOL (0.0438 g, 0.1 mmol, 1 equiv.), $B(OPh)_3$ (0.0870 g, 0.3 mmol, 3 equiv) and toluene (1 mL), the flask was sealed and heated in an 80 °C oil bath under N_2 for 30 min. Then the reaction mixture was cooled to room temperature. This catalyst stock solution was directly used in the rearrangement reaction without further treatment.

To a 20 mL flame dried Schlenk flask was added the catalyst solution (0.25 mL, 0.025 mmol, 25 mol%), iminol **3a** (0.0287 g, 0.100 mmol, 1 equiv) and 0.05 mL toluene. The flask was sealed and heated in a 75 °C oil bath under N_2 for 42 h. After being cooled to room temperature, the crude product was purified by silica gel column chromatography with 2:1 hexanes:$CHCl_3$ as eluent. The reaction

afforded the product **4a** as a yellow solid (60%, 0.0172 g, 0.0600 mmol); the optical purity was determined to be –17% ee as described in section 5.3.4. (the detailed analytical data for **4a** are listed after procedure 4).

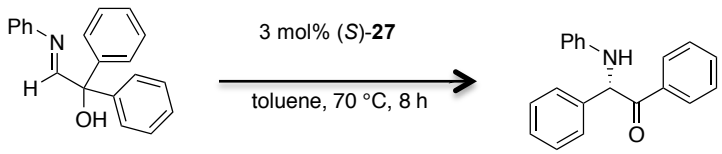
5.3.2. Procedure 2: Reaction with (*S*)-VAPOL hydrogen phosphate 23



3a **4a**

To a 20 mL flame dried Schlenk flask was added the catalyst (*S*)-VAPOL POH **7**[4b] (0.015 g, 0.025 mmol, 25 mol%), iminol **3a** (0.0287g, 0.100 mmol, 1 equiv.) and 0.3 mL CCl_4. The flask was sealed and heated in a 60 °C oil bath under N_2 for 14 h. After being cooled to room temperature, the crude product was purified by flash silica gel column chromatography with $CHCl_3$ as eluent. The reaction afforded the product **4a** as a yellow solid (100%, 0.0287 g, 0.100 mmol), the optical purity was determined to be –8% ee as described in section 5.3.4 (the detailed analytical data for **4a** are listed after procedure 4).

5.3.3. Procedure 3: Reaction with (*R*)-VANOL Al 27



3a **4a**

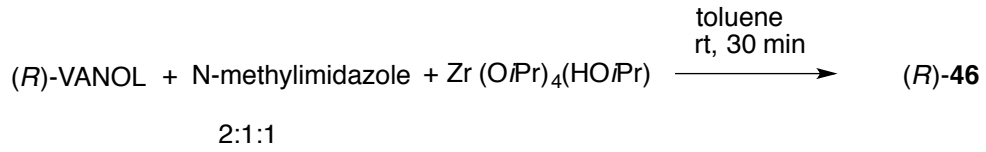
The catalyst (*R*)-VANOL Al **27** was prepared as follows. To a 10 mL flame dried round bottom flask was added (*R*)-VANOL (0.0219 g, 0.0500 mmol, 2 equiv)

and THF (2.5 mL) under a nitrogen atmosphere, and then the solution was stirred for 1 min to dissolve the ligand. Then $LiAlH_4$ (0.0010g, 0.025 mmol, 1 equiv) was added as a solid in one portion. The resulting solution was stirred at room temperature for 10 min before being used in the rearrangement reaction. Note: this aluminum catalyst solution was unstable for storage; it is necessary to prepare fresh catalyst for each reaction.

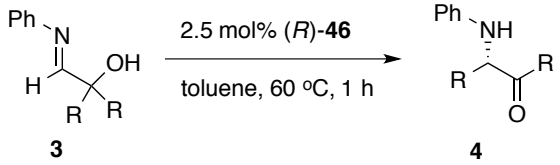
To a 20 mL flame dried Schlenk flask was added the catalyst solution 11 (0.3 mL, 0.003 mmol, 3 mol%), the solvent was carefully removed by high vacuum and then iminol **3a** (0.0287 g, 0.100 mmol, 1 equiv.) and 0.3 mL toluene were added. The flask was sealed and heated in a 70 °C oil bath under N_2 for 8 h. After being cooled to room temperature, the crude product was purified by silica gel column chromatography with 2:1 hexanes:$CHCl_3$ as eluent. The reaction afforded the product **4a** as a yellow solid (100%, 0.0287 g, 0.100 mmol), the optical purity was determined to be 68% ee as described in section 5.3.4 (the detailed analytical data for **4a** are listed after procedure 4)

*Ligand Screen on Derivatives of Catalyst **27**.* All reactions below were carried out according to procedure 3 at 85 °C under N_2 for 1h, with various VANOL ligands which have substituents at both the 7 and 7' positions. All ligands were synthesized according to a literature procedure.[51] The experimental results are listed in Scheme 3.5.

5.3.4. Procedure 4: General procedure for rearrangement with catalyst (*R*)-46



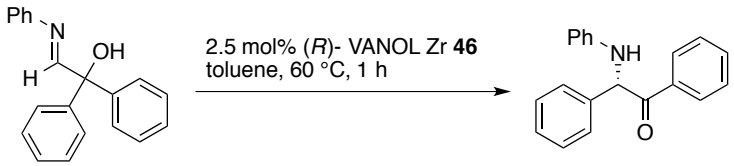
The (*R*)-VANOL Zr catalyst **46** was prepared as follows. (*R*)-VANOL (44 mg, 0.1 mmol, 2 equiv), $Zr(OiPr)_4(HOiPr)$ zirconium(IV) isopropoxide isopropanol complex (19 mg, 0.05 mmol, 1 equiv) and 1 mL toluene were mixed under air at room temperature in a 20 mL vial, then N-methylimidazole (4 μL, 0.05 mmol, 1 equiv.) was added via a syringe. Soon after addition of N-methylimidazole, a white solid precipitate started to form. The resulting slurry was stirred at room temperature under air for 30 min before being used in the following asymmetric catalytic rearrangement of α-iminols. This catalyst solution (*R*)-**46** could be stored in toluene for extended periods, with no compromise to the yield or ee of the rearranged product (see Table 3.15).



The rearrangement reaction was carried out with the following optimal conditions: To a 20 mL vial under air was added 0.25 mL toluene, appropriate α-iminol **3** (0.1 mmol, 1 equiv) and the Zr-VANOL complex catalyst solution (*R*)-**46** (0.05 M in toluene, 50 μL, 2.5 x 10^{-3} mmol, 2.5 mol%, this white slurry was

vigorously swirled and agitated while being drawn by a syringe). The vial was then capped, placed in a 60 °C oil bath and stirred under air for 1 h. Upon completion, the solution was cooled to room temperature and the crude product purified by flash column chromatography on silica gel with 3:1 to 1:1 hexanes:$CHCl_3$ as eluent. Unless otherwise specified, all the following substrates were synthesized via this procedure 4.

(*S*)-1,2-diphenyl-2-(phenylamino)ethan-1-one (4a).



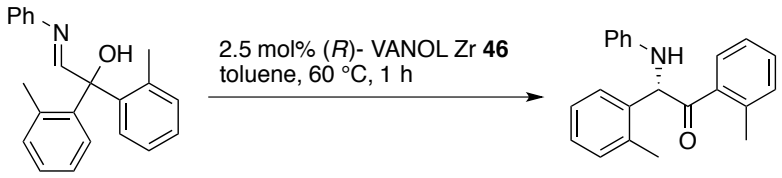
3a (*S*)-**4a**

This reaction was carried out with procedure 4 on **3a** (0.0286 g, 0.100 mmol) and afforded the product (*S*)-**4a** as a yellow solid (94%, 0.0269 g, 0.0943 mmol); mp = 89-92 °C; the optical purity was determined to be 97% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 11.4 min for the minor peak and 18.9 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.62 (br s, 1H), 6.04 (s, 1H), 6.70-6.72 (m, 3H), 7.14 (t, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.42-7.46 (m, 4H), 7.52 (t, *J* = 7.5 Hz, 1H), 8.00 (dd, *J* = 7.5, 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.88, 113.72, 118.04, 128.11, 128.15, 128.66, 128.85, 129.04, 129.22, 133.49, 135.05, 137.56, 145.90, 196.97; $[\alpha]^{20}_D$ =

+132.1° (c = 1.0, CH_2Cl_2) on 97% ee. These NMR data are in agreement with the literature data.[76]

(*S*)-2-(phenylamino)-1,2-di-o-tolylethan-1-one (4b).

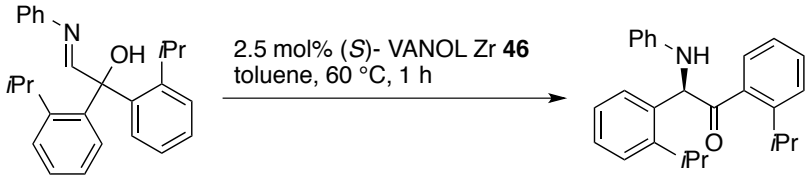


3b (*S*)-**4b**

Following procedure 4 with **3b** (0.0317 g, 0.101 mmol) afforded the product (*S*)-**4b** (88%, 0.0279 g, 0.0886 mmol) as a light yellow liquid. The optical purity was determined to be 84% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 5.8 min for the minor peak and 9.5 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.09 (s, 3H), 2.24 (s, 3H), 5.40 (br s, 1H), 5.94 (s, 1H), 6.59 (dd, *J* = 8.5, 0.5 Hz, 2H), 6.69 (dt, *J* = 8.5, 0.5 Hz, 1H), 7.06 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.11-7.15 (m, 5H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.31 (td, *J* = 7.5, 1.0 Hz, 1H) 7.34-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.42, 19.57, 62.65, 113.27, 117.80, 125.28, 126.67, 126.99, 127.76, 128.17, 129.28, 130.92, 131.09, 131.23, 134.42, 136.59, 137.27, 137.64, 146.08, 201.35; IR (thin film) 3399s, 3053m, 2926m, 1695s, 1603s, 1504s, 1300m, 1248m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 316.1702 [(M+H)$^+$; calcd. 316.1701 for $C_{22}H_{22}NO$]; $[\alpha]^{20}_D$ = +81.8° (c = 1.0, CH_2Cl_2) on 84% ee.

(*R*)-1,2-bis(2-isopropylphenyl)-2-(phenylamino)ethan-1-one (4c).



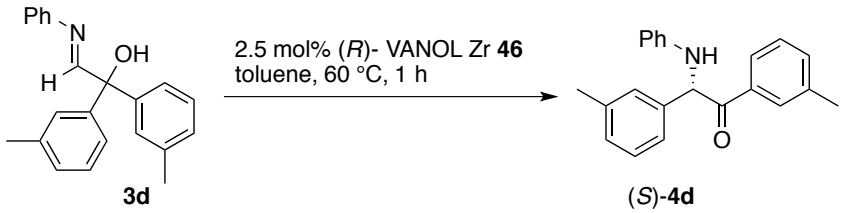
3c (*R*)-**4c**

The reaction was performed with procedure 4 with catalyst (*S*)-**46** on a sample of **3c** (0.0522 g that was a mixture of **2c**:**3c** (aldehyde:imine) = 1:3.2 (0.0422 g, 0.114 mmol of **3c**). The reaction afforded the product (*R*)-**4c** as a white semi-solid (95%, 0.0402 g, 0.108 mmol), the optical purity was determined to be 54% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 4.0 min for the major peak and 6.6 min for the minor peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*R*)-**4c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.50 (d, *J* = 7.0 Hz, 3H), 0.55 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 2.56 (septet, *J* = 7.0 Hz, 1H), 3.24 (septet, *J* = 7.0 Hz, 1H), 5.50 (d, *J* = 5.0 Hz, 1H), 6.11 (d, *J* = 5.0 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 2H), 6.67 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 3H), 7.15-7.19 (m, 3H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.25, 23.49, 24.46, 24.52, 28.54, 29.79, 62.03, 113.28, 117.65, 125.24, 125.90, 126.30, 126.38, 127.34, 128.52, 129.18, 130.78, 132.39, 137.71, 145.91, 147.39, 147.58, 202.07 (one aromatic carbon was not located); IR (thin film) 3402br s, 2964s, 2928s, 2868s, 1695s, 1606s, 1506s, 1487m, 1319m, 1032m, 760m cm^{-1}; HRMS (ESI-TOF) *m/z* found 372.2331

[(M+H)$^+$; calcd. 372.2327 for $C_{26}H_{30}NO$]; $[\alpha]^{20}_D$ = –39.3° (c = 0.66, CH_2Cl_2) on 54% ee.

(*S*)-2-(phenylamino)-1,2-di-m-tolylethan-1-one (4d).



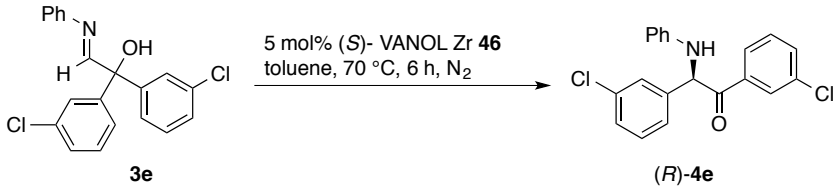
3d (*S*)-**4d**

Following procedure 4 with **3d** (0.0310 g, 0.0985 mmol), the reaction afforded the product (*S*)-**4d** as a light yellow liquid (96%, 0.0298 g, 0.0946 mmol). The optical purity was determined to be 97.5% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 7.8 min for the minor peak and 11.7 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 3H), 2.38 (s, 3H), 5.42 (br s, 1H), 5.99 (s, 1H), 6.68 (d, *J* = 7.5 Hz, 2H), 6.69 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.24-7.28 (m, 2H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.37, 21.45, 62.66, 113.48, 117.76, 125.45, 126.07, 128.46, 128.50, 128.82, 128.91, 129.22, 129.44, 134.32, 135.03, 137.65, 138.55, 138.80, 146.23, 197.31; IR (neat) 3399s, 3051m, 2922m, 1682s, 1603s, 1506s, 1267m, 1151m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 316.1700

[(M+H)$^+$; calcd. 316.1701 for $C_{22}H_{22}NO$]; $[\alpha]^{20}_D$ = +117.0° (c = 1.0, CH_2Cl_2) on 97.5% ee.

(*R*)-1,2-bis(3-chlorophenyl)-2-(phenylamino)ethan-1-one (4e).



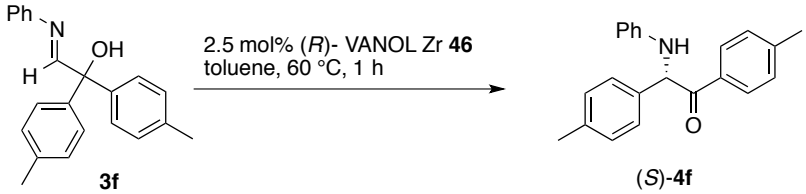
3e (*R*)-**4e**

General procedure 4 was followed with **3e** (0.0356 g, 0.1 mmol) with three exceptions: 1. 5 mol% (*S*)-**46** catalyst was used, 2. The reaction was at 70 °C for 6 h under N_2 atmosphere (reaction was done in a Schlenk flask under N_2 because the product was not stable under heat in presence of air). 3. The purification was as follows: hexanes (5 mL) was added to precipitate the catalyst after the reaction mixture was cooled to room temperature, and then the solid was removed by filtering through filter paper. The filtrate was concentrated on rotary vaporization and the residue was subjected to column chromatography with 1:1 hexane:$CHCl_3$. The reaction afforded the product (*R*)-**4e** (0.0327g, 0.092 mmol, 92%) as a yellow oil. The optical purity was determined to be 93% ee with Chiralcel OD-H column, 90:10 hexane:*i*PrOH, 1 mL/min, 245 nm, 8.2 min for the major peak and 21.0 min for the minor peak.

Spectral data for (*R*)-**4e**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.42 (br s, 1H), 5.95 (s, 1H), 6.67 (d, *J* = 7.5 Hz, 2H), 6.74 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz,

2H), 7.21-7.27 (m, 2H), 7.35 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.40-7.44 (m, 2H), 7.53-7.55 (m, 1H), 7.86 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.95 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.37, 113.53, 118.36, 126.34, 126.82, 128.03, 128.66, 128.93, 129.36, 130.10, 130.40, 133.75, 135.12, 135.26, 136.26, 139.40, 145.52, 195.35; IR (thin film) 3404 s, 1684s, 1603s, 1506s, 1419m, 1204m cm^{-1}; HRMS (ESI-TOF) m/z found 356.0595 [(M+H)$^+$; calcd. 356.0609 for $C_{20}H_{16}ONCl_2$].]; $[\alpha]^{20}_D$ = –105.5° (c = 1.0, CH_2Cl_2) on 93% ee.

(*S*)-2-(phenylamino)-1,2-di-p-tolylethan-1-one (4f)



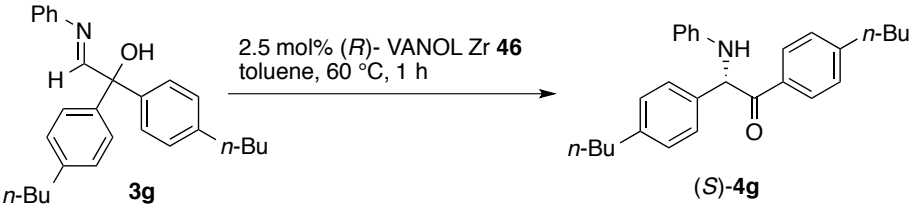
3f (*S*)-**4f**

Following procedure 4 with **3f** (0.0353 g, 0.112 mmol), the reaction afforded the product (*S*)-**4f** as a light yellow solid (92%, 0.0325 g, 0.103 mmol); mp = 96-98 °C. The optical purity was determined to be 98% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 8.4 min for the minor peak and 18.4 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4f**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 3H), 2.38 (s, 3H), 5.44 (s, 1H), 5.99 (s, 1H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.69 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.09,

21.69, 62.16, 113.47, 117.66, 127.98, 129.02, 129.19, 129.36, 129.73, 132.42, 134.87, 137.77, 144.44, 146.20, 196.58; IR (thin film) 3399s, 3049m, 2922m, 1678s, 1604s, 1506s, 1319m, 1261m, 1174m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 316.1700 $[(M+H)^+$; calcd. 316.1701 for $C_{22}H_{22}NO]$; $[\alpha]^{20}_D$ = +127.6° (c = 1.0, CH_2Cl_2) on 98% ee.

(*S*)-1,2-bis(4-n-butylphenyl)-2-(phenylamino)ethan-1-one (4g).

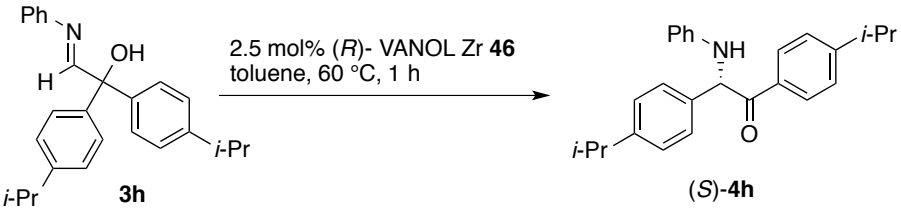


Following procedure 4 with **3g** (0.0434 g, 0.109 mmol), the reaction afforded the product (*S*)-**4g** as a light yellow solid (95%, 0.0413 g, 0.104 mmol); mp = 75-77 °C. The optical purity was determined to be 99% ee by Chiralcel OD-H column, 95:5 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 5.5 min for the minor peak and 11.6 min for the major peak; R_f=0.60 in $CHCl_3$;

Spectral data for (*S*)-**4g**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 1.27-1.39 (m, 4H), 1.53 (q, *J* = 8.0 Hz, 2H), 1.60 (q, *J* = 8.0 Hz, 2H), 2.52 (t, *J* = 8.0 Hz, 2H), 2.64 (t, *J* = 8.0 Hz, 2H), 5.38 (br s, 1H), 6.00 (s, 1H), 6.67-6.70 (m, 3H), 7.11 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.91, 13.93, 22.35, 22.40, 33.10, 33.37, 35.27, 35.71,

62.17, 113.44, 117.64, 127.96, 128.71, 128.89, 129.07, 129.20, 132.66, 135.03, 142.77, 146.32, 149.31, 196.67; IR (thin film) 3406s, 3051m, 2930s, 2858m, 1678s, 1604s, 1506s, 1317m, 1261m, 1174m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 400.2640 [$(M+H)^+$; calcd. 400.2640 for $C_{28}H_{34}NO$]; $[\alpha]^{20}_D$ = +126.0° (c = 1.3, CH_2Cl_2) on 99% ee.

(*S*)-1,2-bis(4-isopropylphenyl)-2-(phenylamino)ethan-1-one (4h).

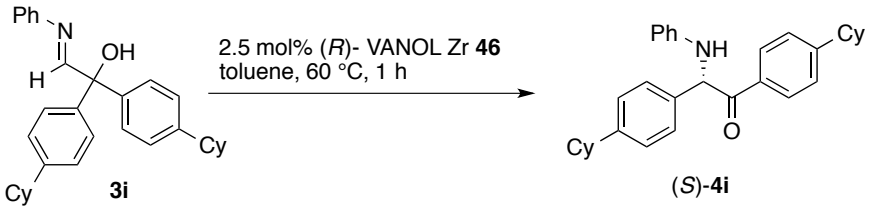


Following procedure 4 with **3h** (0.0409 g, 0.110 mmol), the reaction afforded the product (*S*)-**4h** as a light yellow solid (98%, 0.0401 g, 0.108 mmol); mp = 72-74 °C. The optical purity was determined to be 99% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 12.1 min for the minor peak and 20.5 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4h**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, *J* = 6.5 Hz, 6H), 1.25 (d, *J* = 6.5 Hz, 6H), 2.83 (septet, *J* = 7.0 Hz, 1H), 2.94 (septet, *J* = 7.0 Hz, 1H), 5.44 (br s, 1H), 6.00 (s, 1H), 6.67-6.70 (m, 3H), 7.12-7.16 (m, 4H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.57, 23.58, 23.82, 33.69, 34.24, 62.15, 113.49, 117.71, 126.80, 127.16, 128.02, 128.88, 129.20, 132.80, 135.05, 146.26, 148.62, 155.07, 196.57

(one aliphatic carbon was not located); IR (thin film) 3406s, 3051m, 2961s, 2870m, 1676s, 1604s, 1506s, 1315m, 1176m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 372.2327 $[(M+H)^+$; calcd. 372.2327 for $C_{26}H_{30}NO]$. $[\alpha]^{20}_D$ = +107.9° (c = 1.0, CH_2Cl_2) on 99% ee.

(*S*)-1,2-bis(4-cyclohexylphenyl)-2-(phenylamino)ethan-1-one (4i).

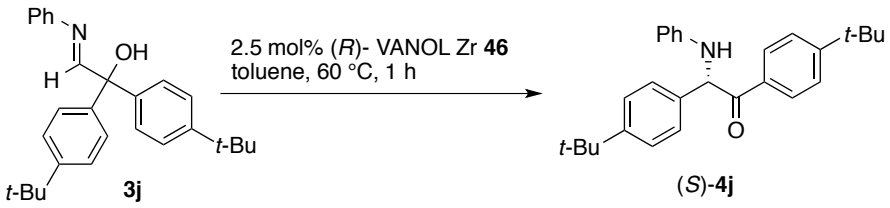


Following procedure 4 with **3i** (0.0446 g, 0.0990 mmol), the reaction afforded the product (*S*)-**4i** as a light yellow solid (97%, 0.0433 g, 0.0960 mmol); mp = 170-171 °C. The optical purity was determined to be 94% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 12.6 min for the minor peak and 26.0 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4i**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18-1.43 (m, 10H), 1.69-1.85 (m, 10H), 2.38-2.42 (m, 1H), 2.50-2.54 (m, 1H), 5.38 (br s, 1H), 5.97 (s, 1H), 6.65-6.68 (m, 3H), 7.10-7.13 (m, 4H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.98, 26.07, 26.66, 26.80, 33.96, 34.24, 44.10, 44.65, 62.12, 113.44, 117.66, 127.5, 127.50, 127.96, 129.16, 129.18, 132.76, 135.03, 146.29, 147.85, 154.23, 196.59; IR (thin film) 3400 br s, 2924s, 2851s, 1672s, 1604s, 1508s, 1172m, 997m cm^{-1}; HRMS

(ESI-TOF) *m/z* found 434.2863 [(M-H_2O+H)$^+$; calcd. 434.2848 for $C_{32}H_{36}N$]; $[\alpha]^{20}_D$ = +69.3° (c = 1.0, CH_2Cl_2) on 94% ee.

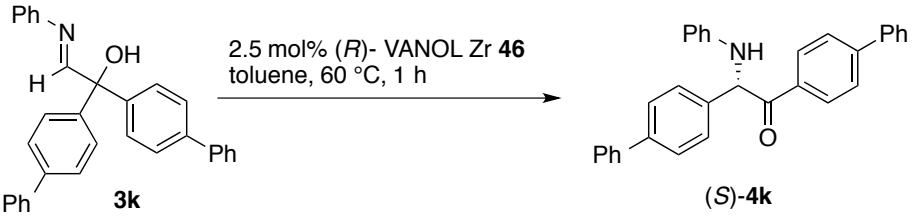
(*S*)-1,2-bis(4-t-butylphenyl)-2-(phenylamino)ethan-1-one (4j).



Following procedure 4 with **3j** (0.0426 g, 0.106 mmol), this reaction afforded the product (*S*)-**4j** as a light yellow solid (100%, 0.0425 g, 0.106 mmol); mp = 151-153 °C. The optical purity was determined to be >99% ee by Chiralcel OD-H column, 95:5 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 7.6 min for the minor peak and 11.8 min for the major peak; R_f=0.60 in $CHCl_3$.

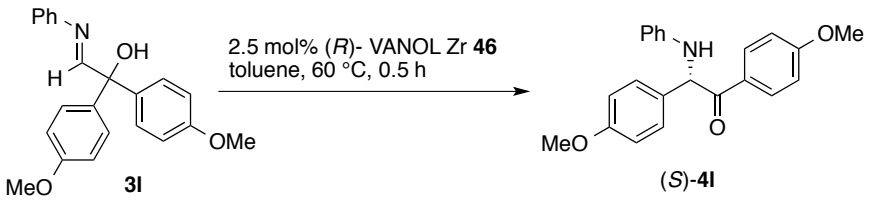
Spectral data for (*S*)-**4j**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.26 (s, 9H), 1.33 (s, 9H), 5.30 (br s, 1H), 6.01 (s, 1H), 6.65-6.70 (m, 3H), 7.14 (td, *J* = 8.0, 2.0 Hz, 2H), 7.32 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.40 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.46 (dd, *J* = 8.0, 2.0 Hz, 2H), 8.00 (dd, *J* = 8.0, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.02, 31.25, 34.50, 34.17, 61.98, 113.39, 117.63, 125.67, 126.03, 127.73, 128.95, 129.21, 132.41, 134.72, 146.39, 150.89, 157.31, 196.61; IR (thin film) 3408s, 2964s, 1678s, 1603s, 1506s, 1267m, 1109m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 400.2643 [(M+H)$^+$; calcd. 400.2640 for $C_{28}H_{34}NO$]; $[\alpha]^{20}_D$ = +92.9° (c = 1.0, CH_2Cl_2) on >99% ee.

(*S*)-1,2-di([1,1'-biphenyl]-4-yl)-2-(phenylamino)ethan-1-one (4k)



Following procedure 4 with **3k** (0.0343 g, 0.0779 mmol), this reaction afforded the product (*S*)-**4k** as a yellow solid (100%, 0.0342 g, 0.0779 mmol); mp = 196-199 °C. The optical purity was determined to be >99% ee by (R, R)-WHELK-O1 column, 99:1 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 63.0 min for the major peak and 69.2 min for the minor peak; R_f=0.60 in $CHCl_3$. Spectral data for (*S*)-**4k**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.48 (br s, 1H), 6.12 (s, 1H), 6.70-6.75 (m, 3H), 7.17 (td, *J* = 7.5, 1.0 Hz, 2H), 7.31 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.38-7.42 (m, 3H), 7.46 (tt, *J* = 7.5, 1.0 Hz, 2H), 7.50-7.54 (m, 4H), 7.57 (dd, *J* = 6.5, 2.0 Hz, 2H), 7.61 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.68 (dt, *J* = 8.5, 2.0 Hz, 2H), 8.14 (dt, *J* = 8.5, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.32, 113.51, 117.89, 127.01, 127.25, 127.36, 127.43, 127.84, 128.40, 128.53, 128.73, 128.97, 129.29, 129.56, 133.58, 136.73, 139.56, 140.32, 140.98, 146.10, 146.29, 196.38; IR (thin film) 3393s, 3031m, 2931m, 1666s, 1603s, 1506s, 1311m, 1170m, 743m cm^{-1}; HRMS (ESI-TOF) *m/z* found 440.2028 [(M+H)$^+$; calcd. 440.2014 for $C_{32}H_{26}NO$]; $[\alpha]^{20}_D$ = –13.0° (c = 1.0, CH_2Cl_2) on >99% ee.

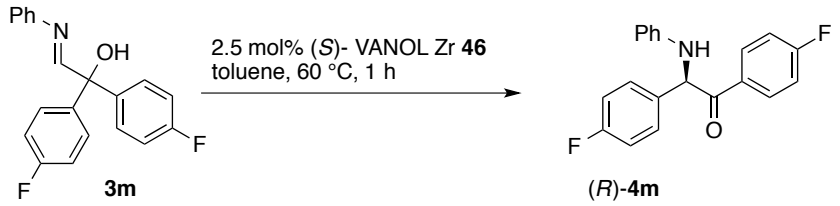
(*S*)-1,2-bis(4-methoxylphenyl)-2-(phenylamino)ethan-1-one (4l)



Procedure 4 was followed with **3l** (0.0332 g, 0.0961 mmol), except that the eluent for chromatography was $CHCl_3$ and the reaction was complete after 0.5 h. The reaction afforded the product (*S*)-**4l** as a light yellow solid (90%, 0.0300 g, 0.0865 mmol); mp = 96-97 °C. The optical purity was determined to be 98% ee by Chiralcel OD-H column, 95:5 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 16.9 min for the minor peak and 60.7 min for the major peak; R_f=0.10 in $CHCl_3$.

Spectral data for (*S*)-**4l**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72 (s, 3H), 3.84 (s, 3H), 5.19 (br s, 1H), 5.94 (s, 1H), 6.65-6.69 (m, 3H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 8.01 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.18, 55.47, 61.50, 113.46, 113.88, 114.42, 115.23, 117.61, 127.77, 129.18, 130.07, 131.21, 146.25, 159.19, 163.73, 195.42; IR (thin film) 3399s, 2934w, 2837w, 1672s, 1603s, 1508s, 1257s, 1170s, 1030m, 750m cm^{-1}; HRMS (ESI-TOF) *m/z* found 348.1594 $[(M+H)^+$; calcd. 348.1600 for $C_{22}H_{22}NO_3$]; $[\alpha]^{20}_D$ = +92.0° (c = 1.0, CH_2Cl_2) on 98% ee.

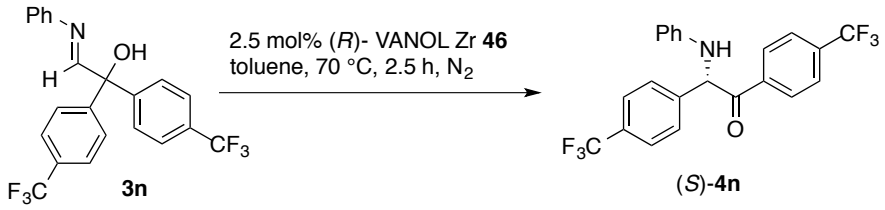
(*R*)-1,2-bis(4-fluorophenyl)-2-(phenylamino)ethan-1-one (4m)



Following procedure 4 with (*S*)-**46** and **3m** (0.0330 g, 0.102 mmol), this reaction afforded the product (*R*)-**4m** as a light yellow wax-like semi-solid (97%, 0.0320 g, 0.0991 mmol). The optical purity was determined to be >99% ee by Chiralcel OD-H column, 97:3 Hexane:*i*PrOH, 1 mL/min flow rate, 245 nm, 14.1 min for the major peak and 41.5 min for the minor peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*R*)-**4m**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.31 (br s, 1H), 5.97 (s, 1H), 6.65 (dd, *J* = 8.5, 1.0 Hz , 2H), 6.71 (td, *J* = 8.5, 1.0 Hz , 1H) 6.98 (td, *J* = 8.5, 2.0 Hz , 2H), 7.10-7.16 (m, 4H), 7.42 (ddt, *J* = 8.5, 5.5, 2.0 Hz, 2H), 8.03 (ddt, *J* = 8.5, 5.5, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 61.85, 113.49, 116.02 (d, *J* = 21.8 Hz) 116.11 (d, *J* = 21.8 Hz), 118.12, 129.29, 129.69 (d, *J* = 8.5 Hz), 131.46, 131.54, 133.36 (d, *J* = 8.5 Hz), 145.75, 162.38 (d, *J* = 246.3 Hz), 165.92 (d, *J* = 255.0 Hz), 195.29; ^{19}F NMR ($CDCl_3$, 470 MHz) δ –103.54, –113.37; IR (thin film) 3402s, 1684s, 1601s, 1508s, 1263s, 1155m, 995m, 837m, 798m, 750m cm^{-1}. HRMS (ESI-TOF) *m/z* found 324.1199 [$(M+H)^+$; calcd. 324.1200 for $C_{20}H_{16}NOF_2$]; $[\alpha]^{20}_D$ = –85.1° (c = 1.0, CH_2Cl_2) on >99% ee.

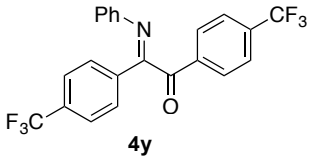
(*R*)-2-(phenylamino)-1,2-bis(4-(trifluoromethyl)phenyl)ethan-1-one (4n).



It was found necessary to perform the reaction of this substrate under an inert atmosphere. To a flame-dried Schlenk flask was added **3n** (0.0444 g, 0.104 mmol), catalyst (*R*)-**46** (0.2 mL in toluene, 10 mol%) and 0.1 mL toluene. The flask was sealed and cooled in liquid N_2 for 5 min, then, the flask was connected to vacuum for 5 min and then sealed again. The flask was allowed to warm up to room temperature, which completed one cycle. The mixture was treated to three freeze-pump-thaw cycles and after the final warming to room temperature, the flask was filled with N_2 gas and sealed. The reaction mixture was heated in a 70 °C oil bath for 2.5 h, and then cooled to room temperature. The crude product was directly purified by silica gel column chromatography with 2:1 hexanes: $CHCl_3$ as eluent. The reaction afforded the product (*S*)-**4n** as a yellow semi-solid (74%, 0.0329 g, 0.0773 mmol). The optical purity was determined to be 73% ee on a (R,R)-WHELK-O1 column, 99:1 Hexane:iPrOH, 0.5 mL/min flow rate, 245 nm, 26.7 min for the major peak and 29.0 min for the minor peak; R_f=0.85 in $CHCl_3$.

Spectral data for (*S*)-**4n**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.43 (br s, 1H), 6.08 (s, 1H), 6.65 (d, *J* = 7.5 Hz, 2H), 6.74 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 2H),

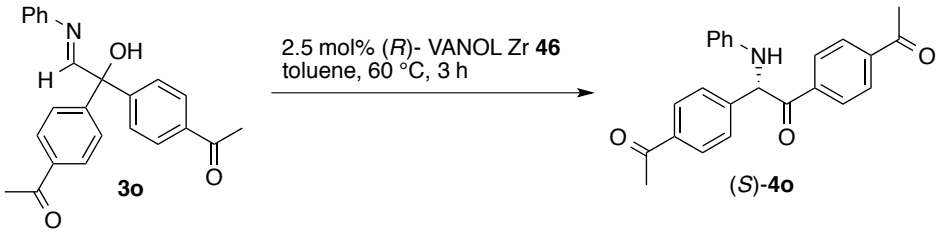
7.56 (s, 4H), 7.73 (d, *J* = 8.0 Hz, 2H), 8.07 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.71, 113.48, 118.54, 123.28 (q, *J* = 271.2 Hz), 123.69 (q, *J* = 270.2 Hz), 125.94 (q, *J* = 3.7 Hz), 126.22 (q, *J* = 3.7 Hz), 128.13, 129.13, 129.41, 130.61 (q, *J* = 33.1 Hz), 135.07 (q, *J* = 32.8 Hz), 137.45, 141.14, 145.29, 195.60; ^{19}F NMR ($CDCl_3$, 470 MHz) δ –63.30, –62.78; IR (thin film) 3402 br s, 3057m, 2928m, 1695s, 1604s, 1506s, 1325s, 1170s, 1128s, 1068s, 1018m cm^{-1}; HRMS (ESI-TOF) *m/z* found 424.1136 [(M+H)$^+$; calcd. 424.1136 for $C_{22}H_{16}NOF_6$]; $[\alpha]^{20}_D$ = +15.2° (c = 1.0, CH_2Cl_2) on 73% ee.



4y

Note: Exclusion of air is a must for this substrate because the product is sensitive to air under heat. If the reaction was performed with procedure 4, under air, an 18% yield of by-product **4y** was obtained as well as a 70% recovery of **3n**. The desired product **4n** was not observed.

(*R*)-1,1'-((1-oxo-2-(phenylamino)ethane-1,2-diyl)bis(4,1-phenylene))bis(ethan-1-one) (4o).

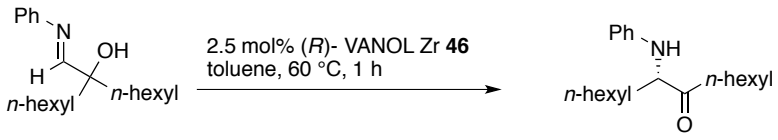


3o (*S*)-**4o**

The rearrangement of **3o** (0.0444 g, 0.120 mmol) was carried out with procedure 4 with the exception that 1 mL toluene was used due to the low solubility of the substrate **3o**, and the reaction time was 3 h. The product was purified by column chromatography on silica gel with 8:1 to 3:1 hexanes:EtOAc as eluent to afford the product (*S*)-**4o** as a yellow semi-solid (100%, 0.0444 g, 0.120 mmol). The optical purity was determined to be 97% ee by (R, R)-WHELK-O1 column, 70:30 Hexane:iPrOH, 2 mL/min flow rate, 254 nm, 24.2 min for the major peak and 31.5 min for the minor peak; R_f= 0.3 in 2:1 Hexanes:EtOAc.

Spectral data for (*S*)-**4o**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.52 (s, 3H), 2.62 (s, 3H), 5.54 (br s, 1H), 6.09 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.72 (t, *J* = 8.5 Hz, 1H), 7.15 (t, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 8.00 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.60, 26.87, 62.99, 113.55, 118.38, 128.34, 128.58, 129.02, 129.15, 129.36, 136.91, 138.03, 140.55, 142.46, 145.41, 195.96, 197.12, 197.32; IR (thin film) 3395 br s, 3053m, 2924s, 2855m, 1684s, 1603s, 1506s, 1311m, 1265s cm^{-1}. HRMS (ESI-TOF) *m/z* found 372.1603 [$(M+H)^+$; calcd. 372.1600 for $C_{24}H_{22}NO_3$]; $[\alpha]^{20}_D$ = +55.3° (c = 1.0, CH_2Cl_2) on 97% ee.

(*S*)-8-(phenylamino)tetradecan-7-one (4p).

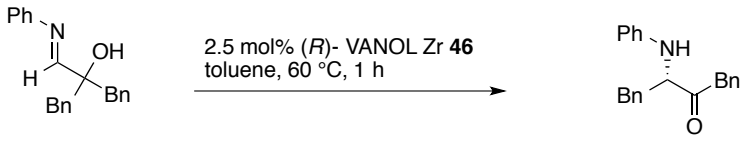


3p (*S*)-**4p**

Following procedure 4 with **3p** (0.0333 g, 0.110 mmol), this reaction afforded the product (*S*)-**4p** as a colorless liquid (95%, 0.0317 g, 0.105 mmol). The optical purity was determined to be 89% ee by Chiralcel OD-H column, 99:1 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 5.3 min for the minor peak and 8.3 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4p**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.5 Hz, 3H), 0.87 (t, *J* = 6.5 Hz, 3H), 1.24-1.38 (m, 14H), 1.55 (q, *J* = 7.5 Hz, 2H), 1.61-1.67 (m, 1H), 1.80-1.87 (m, 1H), 2.48 (t, *J* = 7.5 Hz, 2H), 3.99 (t, *J* = 7.0 Hz, 1H), 4.34 (br s, 1H), 6.56 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.70 (td, *J* = 7.5, 1.0 Hz, 1H), 7.16 (td, *J* = 8.5, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.02, 22.47, 22.54, 23.42, 25.26, 28.86, 29.17, 31.56, 31.59, 32.05, 38.72, 62.88, 113.00, 117.75, 129.35, 146.99, 212.50 (1 aliphatic carbon was not located); IR (neat) 3397s, 3053w, 2955s, 2930s, 2858s, 1713s, 1603s, 1506s, 1317m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 304.2642 [(M+H)$^+$; calcd. 304.2640 for $C_{20}H_{34}NO$]; $[\alpha]^{20}_D$ = +19.4° (c = 1.0, CH_2Cl_2) on 89% ee.

(*S*)-1,4-diphenyl-3-(phenylamino)butan-2-one (4q).

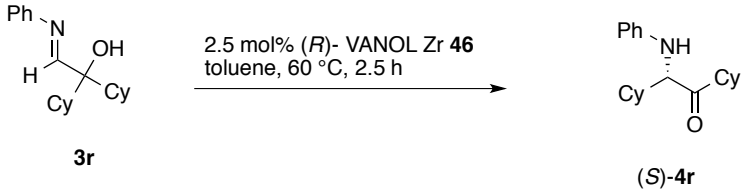


3q (*S*)-**4q**

Following procedure 4 with **3q** (0.0330 g, 0.105 mmol), this reaction afforded the product (*S*)-**4q** as a yellow liquid (98%, 0.0324 g, 0.103 mmol). The optical purity was determined to be >99% ee by (R, R)-WHELK-O1 column, 95:5 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 13.3 min for the minor peak and 17.2 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4q**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.01 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.11 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.66 (d, *J* = 16.0 Hz, 1H), 3.73 (d, *J* = 16.0 Hz, 1H), 4.24 (br s, 1H), 4.37 (t, *J* = 7.0 Hz, 1H), 6.51 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.74 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 7.14-7.19 (m, 4H), 7.25-7.33 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.09, 47.19, 63.04, 113.34, 118.35, 127.08, 128.62, 128.78, 129.21, 129.42, 129.50, 129.63, 133.34, 136.45, 146.28, 209.26; IR (neat) 3400br s, 3062m, 3028m, 2924m, 1716s, 1603s, 1500s, 1496s, 1437m, 1317m cm^{-1}; HRMS (ESI-TOF) *m/z* found 316.1699 [(M+H)$^+$; calcd. 316.1701 for $C_{22}H_{22}NO$]; $[\alpha]^{20}_D$ = +28.0° (c = 1.0, CH_2Cl_2) on >99% ee.

(*S*)-1,2-dicyclohexyl-2-(phenylamino)ethan-1-one (4r)

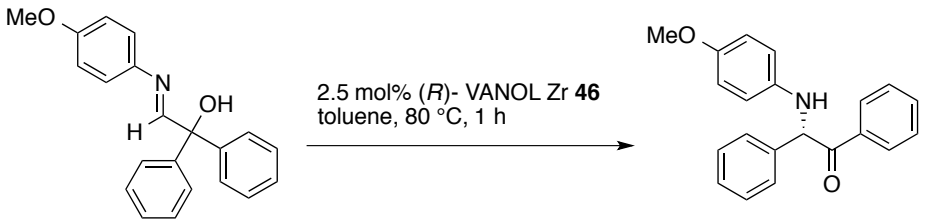


3r (*S*)-**4r**

Following procedure 4 with **3r** (0.0308 g, 0.103 mmol), this reaction afforded the product (*S*)-**4r** as a white solid (97%, 0.0299 g, 0.100 mmol); mp = 76-78 °C. The optical purity was determined to be 98% ee by Chiralcel OD-H column, 99.5:0.5 Hexane:iPrOH, 0.5 mL/min flow rate, 245 nm, 11.7 min for the minor peak and 15.6 min for the major peak; R_f=0.60 in $CHCl_3$.

Spectral data for (*S*)-**4r**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08-1.28 (m, 11H), 1.64-1.77 (m, 10H), 2.53-2.59 (m, 1H), 3.99 (d, *J* = 5.0 Hz, 1H), 4.41 (br s, 1H), 6.61 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.70 (td, *J* = 8.5, 1.0 Hz, 1H), 7.14 (td, *J* = 8.5, 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.36, 25.71, 25.90, 26.04, 26.15, 26.28, 27.74, 28.16, 29.21, 30.72, 40.66, 48.29, 66.77, 113.56, 117.68, 129.22, 148.05, 214.35; IR (thin film) 3395s, 2930s, 2855s, 1705s, 1603s, 1506s, 1450m, 1317m, 1255m, 748m cm^{-1}; HRMS (ESI-TOF) *m/z* found 300.2332 [(M+H)$^+$; calcd. 300.2327 for $C_{20}H_{30}NO$]; $[\alpha]^{20}_D$ = +33.8° (c = 1.0, CH_2Cl_2) on 98% ee.

(*S*)-2-((4-methoxyphenyl)amino)-1,2-diphenylethan-1-one (4s).

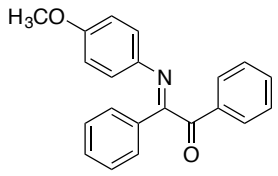


3s (*S*)-**4s**

The rearrangement of **3s** (0.0317 g, 0.10 mmol) was carried out following procedure 4 except that the reaction temperature was at 80 °C, and the eluent for column chromatography was 8:1 to 4:1 hexanes:EtOAc. The reaction afforded the product (*S*)-**4s** as a yellow solid (98%, 0.0311 g, 0.098 mmol). mp = 90-94 °C. The optical purity was determined to be 98% ee by (R, R)-WHELK-O1 column, 95:5 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 23.7 min for the major peak and 27.1 min for the minor peak; R_f=0.10 in $CHCl_3$.

Spectral data for (*S*)-**4s:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.71 (s, 3H), 5.14 (br s, 1H), 5.99 (s, 1H), 6.65 (dt, *J* = 9.0, 2.5 Hz, 2H), 6.74 (dt, *J* = 9.0, 2.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 4H), 7.54 (t, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.70, 63.77, 114.84, 115.03, 128.08, 128.12, 128.67, 128.83, 129.06, 133.47, 135.15, 137.85, 140.36, 152.36, 197.45; IR (thin film) 3397br s, 3062m, 2932m, 2833m, 1684s, 1514s, 1238s, 1176m, 1035m, 819m cm^{-1}. HRMS (ESI-TOF) *m/z* found 318.1507 [$(M+H)^+$; calcd. 318.1494 for $C_{21}H_{20}NO_2$]; $[\alpha]^{20}_D$ = +151.1° (c = 1.0, CH_2Cl_2) on 98% ee.

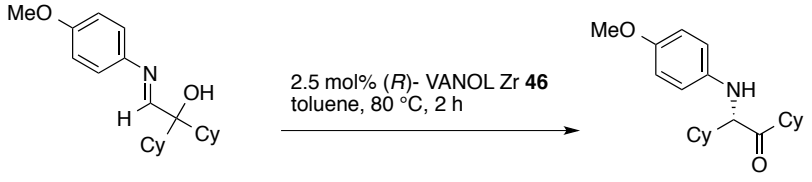
A second run on much larger scale (45x) was carried out under air at 80 °C for 2 h, with 1.5 mol% (*S*)-**46** in 14 mL toluene on a 1.42 gram scale (4.48 mmol) and produced the product (*R*)-**4s** as a yellow solid (1.22 g, 3.81 mmol, 85% yield); mp = 93-95 °C. The optical purity was determined to be 98% ee; $[\alpha]^{20}_{D} = -130.7°$ (c = 1.0, CH_2Cl_2) on 98% ee. A 7% yield of byproduct 2-((4-methoxyphenyl)imino)-1,2-diphenylethan-1-one was also isolated.



A third run on 41 times larger scale was carried out under N_2 atmosphere at 80 °C for 6 h, with 1 mol% (*R*)-**46** on a 1.30 gram scale (4.10 mmol) and produced the product (*S*)-**4s** as a yellow solid (1.22 g, 3.85 mmol, 94% yield) and the optical purity was determined to be 95% ee.

Notes: 1) A 7% yield of 2-((4-methoxyphenyl)imino)-1,2-diphenylethan--1-one was observed in this reaction as a by-product when air was present. 2) The product **4s** epimerized partially when it was left on the silica gel column over night: the ee dropped from 98% to 82%. 3) Recrystallization from 20:1 hexanes:EtOAc improved the ee from 95% to >99% with 82% recovery.

(*S*)-1,2-dicyclohexyl-2-((4-methoxyphenyl)amino)ethan-1-one (4t).

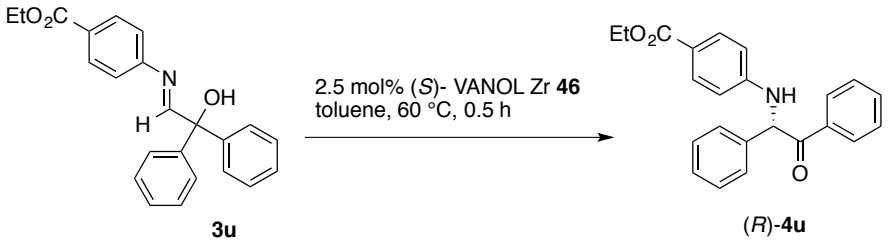


3t (*S*)-**4t**

The rearrangement of **3t** (0.0510 g, 0.154 mmol) was carried out with procedure 4 with the exception that the reaction temperature was 80 °C. After 2 h, the reaction afforded the product (*S*)-**4t** as a pale yellow solid (97%, 0.0495 g, 0.150 mmol); mp = 103-106 °C. The optical purity was determined to be 94% ee by Chiralcel OD-H column, 99:1 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 3.8 min for the minor peak and 4.2 min for the major peak; R_f=0.10 in $CHCl_3$.

Spectral data for (*S*)-**4t:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07-1.43 (m, 11H), 1.57-1.76 (m, 10H), 2.53 (tt, *J* = 11.0, 3.5 Hz, 1H), 3.72 (s, 3H), 3.85 (d, *J* = 5.0 Hz, 1H), 4.11 (br s, 1H), 6.57 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.35, 25.71, 25.90, 26.07, 26.17, 26.31, 27.68, 28.15, 29.08, 30.77, 40.54, 48.30, 55.70, 68.52, 114.74, 115.37, 142.39, 152.32, 215.02. IR (thin film) 3391br m, 2930s, 2855s, 1705s, 1512s, 1450m, 1238s, 1039m cm^{-1}. HRMS (ESI-TOF) *m/z* found 330.2436 $[(M+H)^+$; calcd. 330.2433 for $C_{21}H_{32}NO_2$]; $[\alpha]^{20}_D$ = +30.0° (c = 1.0, CH_2Cl_2) on 94% ee.

ethyl (*R*)-4-((2-oxo-1,2-diphenylethyl)amino)benzoate (4u).

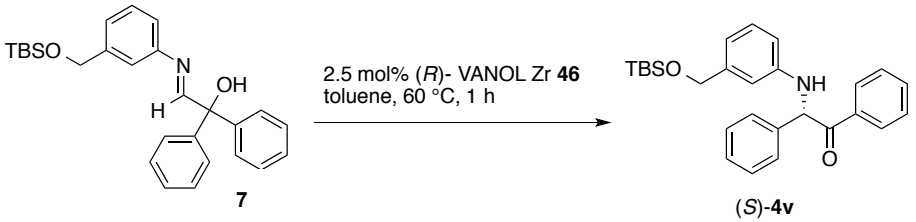


3u (*R*)-**4u**

Following procedure 4 with (*S*)-**46** and the imine **3u** (0.0448 g, 0.125 mmol) this reaction was complete in 30 min and afforded the product (*R*)-**4u** as a white solid (88%, 0.0394 g, 0.110 mmol); mp = 145-147 °C. The optical purity was determined to be 96% ee by Chiralcel OD-H column, 90:10 Hexane:iPrOH, 1 mL/min flow rate, 287 nm, 9.1 min for the minor peak and 31.3 min for the major peak.

Spectral data for (*R*)-**4u**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (t, *J* = 7.0 Hz, 3H), 4.30 (q, *J* = 7.0 Hz, 2H), 5.92 (br s, 1H), 6.08 (s, 1H), 6.65 (dt, *J* = 9.0, 2.5 Hz, 2H), 7.22 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.30 (tt, *J* = 7.5, 2.0 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 4H), 7.56 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.84 (dt, *J* = 8.5, 2.0 Hz, 2H), 8.02 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.43, 60.21, 61.96, 112.35, 119.33, 128.07, 128.36, 128.76, 128.93, 129.19, 131.43, 133.79, 134.57, 136.88, 149.53, 166.70, 196.02; IR (thin film) 3393br s, 3066m, 2926s, 1686s, 1606s, 1525s, 1448m, 1278s, 1174s, 1105s cm^{-1}; HRMS (ESI-TOF) *m/z* found 360.1606 [(M+H)$^{+}$; calcd. 360.1600 for $C_{23}H_{22}NO_3$]; $[\alpha]^{20}_{D}$ = –137.5° (c = 1.0, CH_2Cl_2) on 96% ee.

(*S*)-2-((3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)amino)-1,2-diphenyleth an-1-one (4v).

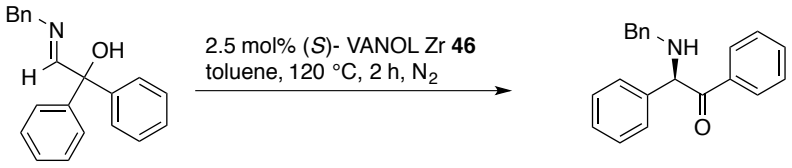


7 (*S*)-**4v**

Following procedure 4 with iminol **7** (0.0470 g, 0.1 mmol), this reaction afforded the product (*S*)-**4v** as a pale yellow liquid (91%, 0.0430 g, 0.09 mmol). The optical purity was determined to be 97% ee by (R, R)-WHELK-O1 column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 9.0 min for the major peak and 10.5 min for the minor peak.

Spectral data for (*S*)-**4v:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 6H), 0.94 (s, 9H), 4.64 (s, 2H), 5.42 (d, *J* = 6.0 Hz, 1H), 6.05 (d, *J* = 6.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.18-7.19 (m, 1H), 7.20-7.29 (m, 3H), 7.42-7.46 (m, 3H), 7.54 (t, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.23, 18.45, 26.01, 62.68, 64.99, 111.03, 112.09, 115.55, 128.05, 128.09, 128.67, 128.87, 129.02, 129.04, 133.49, 135.06, 137.74, 142.58, 146.18, 197.10; IR (neat) 3404s, 3061m, 2955s, 2928s, 2858s, 1688s, 1608s, 1491s, 1323m, 1253s, 1178m, 1101s, 1076s cm^{-1}; HRMS (ESI-TOF) *m/z* found 432.2362 [$(M+H)^+$; calcd. 432.2359 for $C_{27}H_{34}NO_2Si$]; $[\alpha]^{20}_D$ = +90.8° (c = 1.0, CH_2Cl_2) on 97% ee.

(*S*)-2-(benzylamino)-1,2-diphenylethan-1-one (4w)



3w (*R*)-**4w**

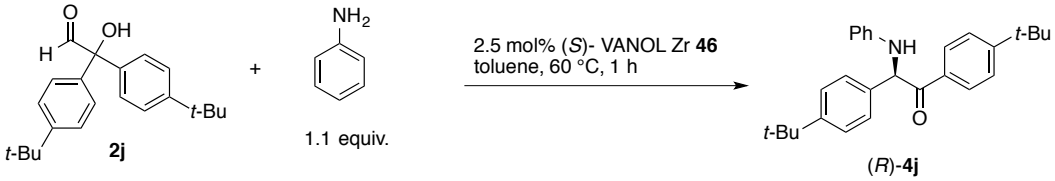
The rearrangement of **3w** (0.0300 g, 0.100 mmol) was performed following general procedure 4 with two exceptions: 1. The reaction conditions were 120 °C for 2 h under N_2 atmosphere (reaction was done in a Schlenk flask because the product was not stable at 120 °C in presence of air). 2. The workup and purification was as follows: hexanes (5 mL) was added to precipitate the catalyst after the reaction mixture was cooled to room temperature, and then the solid was removed by filtering through filter paper. The filtrate was concentrated by rotary vaporization and the residue was subjected to column chromatography with 8:1 to 4:1 hexane:EtOAc. The reaction afforded the product (*R*)-**4w** (0.0285 g, 0.095 mmol, 95%) as a white semi-solid. The optical purity was determined to be 10% ee with (R, R) WHELK-O1 column, 95:5 hexane:*i*PrOH, 1 mL/min, 245 nm, 16.2 min for the major peak and 18.0 min for the minor peak.

Spectral data for (*R*)-**4w:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.74 (br s, 1H), 3.76 (s, 2H), 5.31 (s, 1H), 7.26-7.28 (m, 2H), 7.32-7.39 (m, 10H), 7.49 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.01, 66.23, 127.07, 127.98, 128.24, 128.38, 128.42, 128.53, 128.69, 129.04, 133.16,

135.68, 138.24, 139.73, 198.92. $[\alpha]^{20}_D$ = –2.5° (c = 1.0, CH_2Cl_2) on 10% ee. These NMR data are in partial agreement with literature.[77]

Note: No rearrangement of **3w** was observed at 80 °C after 19 h. The ^{1}H NMR spectrum of the crude reaction mixture showed only the presence of the starting imine **3w** and the presence of aldehyde **2a** resulting from partial hydrolysis of **3w**. The presence of (*R*)-**4w** was detected.

5.3.5. Procedure for the a-Iminol rearrangement of in-situ generated Imines.



To a 20 mL vial was added aldehyde **2j** (0.0332 g, 0.102 mmol, 1 equiv), toluene 0.25 mL, (*S*)-**46** catalyst solution (0.5 mL) prepared in section 4 and aniline (10 µL, 0.11 mmol, 1.1 equiv). The vial was capped and heated under air in a 60 °C oil bath for 1 h. Thereafter, the solution was cooled to room temperature and subjected to column chromatography on silica gel with 2:1 $CHCl_3$:hexanes as eluent. The reaction afforded the product (*R*)-**4j** as a light yellow solid (0.0400 g, 0.100 mmol, 98% yield). mp = 132-135 °C; The optical purity was determined to be >99%. The Chiral HPCL conditions were identical to that described in section 5 for (*S*)-**4j**; ^{1}H NMR and ^{13}C NMR data were identical to that described in section 5 for (*S*)-**4j**; $[\alpha]^{20}_D$ = –84.0° (c = 1.0, CH_2Cl_2).

5.3.6. Determination of the stereochemistry of the product 4a.

Methyl-(R)-2-phenyl-2-(phenylamino)acetate (40)

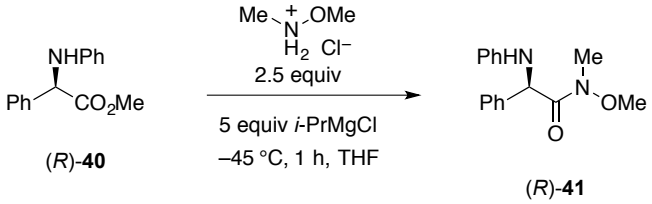
To a 20 mL vial was added (*R*)-2-phenylglycine methyl ester hydrochloride (2.01 g, 10.0 mmol, 1 equiv) and Na_2CO_3 solution (2M, 7.5 mL, 15 mmol, 1.5 equiv) and 5 mL ether. The resulting mixture was stirred at room temperature for 10 min. The aqueous layer was extracted with EtOAc (5 mL x 3), and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered through filter paper in a Büchner funnel and concentrated under rotary evaporation. The crude amino ester was used in the next step without purification.

To a three-necked round bottom flask equipped with a condenser was added copper(II) acetate monohydrate (0.11 g, 0.5 mmol, 10 mol%), 4 Å molecular sieves (3.05 g), $PhB(OH)_2$ (1.28 g, 10 mmol, 2 equiv.), and 40 mL CH_2Cl_2. The resulting mixture was stirred at room temperature for 5 min and then the crude amino ester (0.85 g, 5 mmol, 1 equiv.) was added. The two open necks were sealed by septa. A gentle air flow was introduced via a needle attached to one of the septa. The mixture was heated to reflux for 14h, then cooled to room temperature, filtered through filter paper in Büchner funnel. The filtrate was

concentrated under rotary evaporation. The product was purified by column chromatography on silica gel with 10:1 hexanes:EtOAc as eluent. The reaction afforded the product (*R*)-**40** as a white solid (23%, 0.29 g, 2.3 mmol); mp = 51-52 °C; R_f=0.45 in 4:1 hexanes:EtOAc.

Spectral data for (*R*)-**40**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.73 (s, 3H), 5.08 (s, 1H), 5.39 (br s, 1H), 6.59 (d, *J* = 7.5 Hz, 2H), 6.72 (t, *J* = 7.5 Hz, 1H), 7.12 (tt, *J* = 7.5, 2.0 Hz, 2H), 7.30 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.35 (tt, *J* = 7.5, 2.0 Hz, 2H), 7.49 (dt, *J* = 7.5, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.85, 60.74, 113.42, 118.14, 127.26, 128.33, 128.89, 129.25, 137.57, 145.87, 172.31; $[\alpha]^{20}_D$ = –93.8° (c = 1.0, $CHCl_3$), [lit.[78] –20.2° (c = 1.0, $CHCl_3$) on 30% ee, and lit.[9] +68.3° (c = 0.32, THF) on 98% ee for the (*S*)-enantiomer]. The ^{1}H NMR data are in agreement with the literature data.[78]

(R)-N-Methoxy-N-methyl-2-phenyl-2-(phenylamino)acetamide (41)



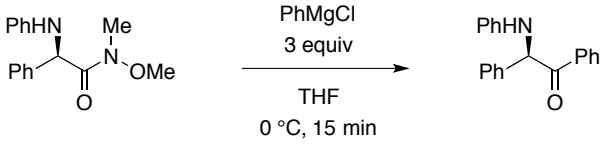
(*R*)-**40** (*R*)-**41**

To a 10 mL flame-dried round bottom flask was added N,O-dimethylhydroxylamine hydrochloride (0.10 g, 1.04 mmol, 2.5 equiv) and 2 mL THF at –45 °C in an acetonitrile dry ice bath for 5 min under a N_2 atmosphere. Then iPrMgCl (2M in THF, 1.04 mL, 2.08 mmol, 5 equiv) was added dropwise and

stirred at the same temperature for 10 min. Then methyl (*R*)-2-phenyl-2-(phenylamino)acetate **40** (0.10 g in 1 mL THF, 0.41 mmol, 1 equiv) was added dropwise via a syringe. The resulting mixture was kept at –45 °C for another 1 h before being quenched with saturated NH_4Cl solution. The solution was warmed up to room temperature, and extracted with EtOAc (5 mL x 3), dried over $MgSO_4$, filtered through filter paper in Büchner funnel and concentrated via rotary evaporation. The product was purified by column chromatography on silica gel with 4:1 to 2:1 hexanes:EtOAc as eluent. The reaction afforded the product (*R*)-41 as a yellow liquid (64%, 0.0722 g, 0.262 mmol); R_f=0.05 in 4:1 hexanes:EtOAc.

Spectral data for (*R*)-**41**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.21 (s, 3H), 3.52 (s, 3H), 5.33 (br s, 1H), 5.51 (s, 1H), 6.66-6.71 (m, 3H), 7.13 (tt, *J* = 7.5, 2.0 Hz, 2H), 7.28 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.35 (tt, *J* = 7.5, 2.0 Hz, 2H), 7.49 (dt, *J* = 7.5, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.49, 57.73, 61.19, 113.64, 117.91, 127.92, 127.99, 128.71, 129.19, 138.40, 146.15 (the amide carbon was not located); $[\alpha]^{20}_D$ = –151.8° (c = 0.71, CH_2Cl_2). These NMR data are in agreement with the literature data.[79]

(R)-1,2-diphenyl-2-(phenylamino)ethan-1-one (4a)

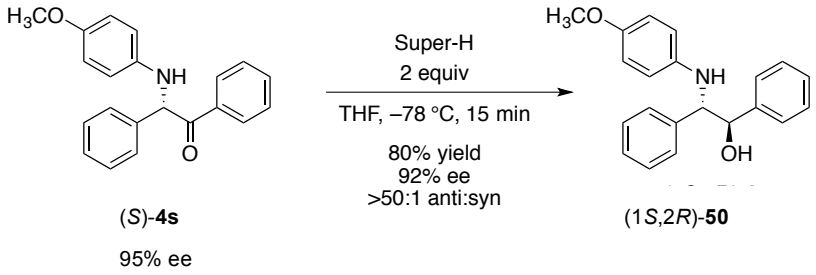


(*R*)-**41** (*R*)-**4a**

To a 10 mL flame-dried round bottom flask was added the Weinreb amide (*R*)-**41** prepared above (0.0581 g, 0.21 mmol, 1 equiv) and 1 mL THF. The resulting solution was cooled to 0 °C for 5 min in an ice bath and then PhMgCl (2M in THF, 0.31 mL, 0.63 mmol, 3 equiv.) was added dropwise via a syringe. The resulting mixture was kept at 0 °C for 15 min before being quenched with saturated NH_4Cl solution. The solution was warmed up to room temperature, and extracted with EtOAc (5 mL x 3), dried over $MgSO_4$, filtered through filter paper in Büchner funnel and concentrated under rotary evaporation. The crude product was purified by column chromatography on silica gel with 1:1 hexanes:$CHCl_3$ as eluent. The reaction afforded the product (*R*)-**4a** as a yellow solid (65%, 0.0402 g, 0.137 mmol); mp = 76-81 °C. The ^{1}H and ^{13}C NMR data were identical to the product (*S*)-**4a** from the rearrangement reaction of **3a** in section 5.4. The optical purity was determined to be 90% ee by Chiralcel OD-H column, 97:3 Hexane:iPrOH, 1 mL/min flow rate, 245 nm, 11.4 min for the major peak and 18.9 min for the minor peak; $[\alpha]^{20}_{D} = -116.8°$ (c = 1.0, CH_2Cl_2) on 90% ee. The configuration of this compound is opposite to that of the product **4a** obtained from the rearrangement using catalyst (*R*)-**46**.

5.3.7. Synthesis of amino alcohols from amino ketones.

(1S,2R)-2-((4-methoxyphenyl)amino-1,2-diphenylethan-1-ol (50)



(*S*)-**4s**

95% ee

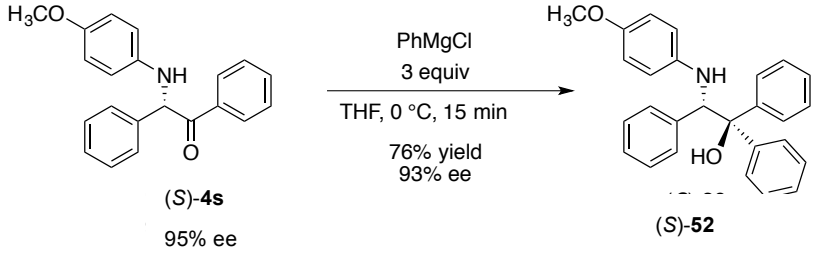
(1*S*,2*R*)-**50**

To a 10 mL flame-dried round bottom flask was added the amino ketone (*S*)-**4s** (0.0756 g, 0.24 mmol, 1 equiv, 95% ee) and 2 mL THF. The solution was cooled to –78 °C in dry ice/acetone bath for 5 min under a N_2 atmosphere and lithium triethylborohydride (0.48 mL, 1M in THF, 0.48 mmol, 2 equiv.) was added dropwise via a syringe. The resulting mixture was kept at –78 °C for 15 min before being quenched with saturated NH_4Cl solution. The solution was then gradually warmed up to room temperature and extracted with ether (5 mL x 3), dried over $MgSO_4$, filtered through filter paper in Büchner funnel and concentrated under rotary evaporation. The anti:syn ratio was greater than 50:1 by ^1H NMR analysis of the crude reaction mixture. The product was purified by flash column chromatography on silica gel with 8:1 to 4:1 hexanes:EtOAc as eluent to afford the product **50** as a light yellow solid (80%, 0.0605 g, 0.19 mmol); mp = 115-116 °C (lit[80] 121-124 °C). The optical purity was determined to be 92% ee by Chiralcel OD-H column, 95:5 Hexane:iPrOH, 1 mL/min flow rate, 220 nm, 19.3 min for the minor peak and 23.7 min for the major peak.

Spectral data for (*1S,2R*)-**50** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.51 (br s, 1H), 3.68 (s, 3H), 4.24 (br s, 1H), 4.61 (d, *J* = 4.5 Hz, 1H), 5.05 (d, *J* = 4.5 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 7.09-7.11 (m, 2H), 7.14-7.15 (m, 2H), 7.24-7.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.65, 64.65, 77.10, 114.67, 115.50, 126.58, 127.57, 127.90, 127.94, 128.19, 128.28, 138.67, 140.00, 140.71, 152.43; $[\alpha]^{20}_{D}$ = +50.7° (c = 1.0, $CHCl_3$) on 90% ee, [lit[80] +27.9°, c = 1.0, $CHCl_3$, on 93% ee]. The NMR data are in agreement with those in the literature.[80]

Note: The ee can be improved to >99% by crystallization from 10:1 hexanes:EtOAc with 87% recovery. Dissolution of 0.060 g product **50** (92% ee) in 1 mL EtOAc was followed by addition of 10 mL hexanes. The clear solution was cooled in freezer at –20 °C for 1h. The white crystals were collected to give 0.052 g of **50** (87% recovery) that was >99% ee.

(*S*)-2-((4-methoxyphenyl)amino)-1,1,2-triphenylethan-1-ol (52)



To a flame-dried 25 mL round bottom flask was added the amino ketone (*S*)-**4s** (0.0217 g, 0.068 mmol, 1 equiv, 95% ee) and 2 mL THF. The flask was sealed by a septum and a N_2 balloon was attached via a needle. The flask was

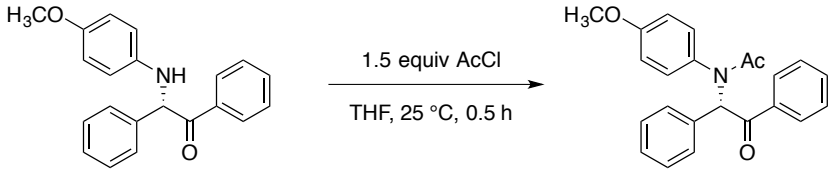
cooled to 0 °C in an ice bath for 5 min. PhMgCl (2M in THF, 0.1 mL, 0.2 mmol, 3 equiv.) was added dropwise via a syringe. The resulting mixture was kept at 0 °C for 15 min then quenched with 3 mL of saturated NH_4Cl solution. The mixture was warmed up to room temperature, extracted with ether (4 mL x 2), dried over $MgSO_4$, filtered through filter paper in Büchner funnel and concentrated under rotary evaporation. The product was purified by column chromatography on silica gel with 16:1 to 10:1 hexanes:EtOAc as eluent to afford the product **52** as a white solid (76%, 0.0206 g, 0.0517 mmol); mp = 181-183 °C (lit.[12] 175-176 °C). The optical purity was determined to be 93% ee by Chiralcel OD-H column, 99:1 Hexane:iPrOH, 1 mL/min flow rate, 220 nm, 10.0 min for the minor peak and 31.2 min for the major peak.

Spectral data for (*S*)-**52**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.82 (s, 1H), 3.67 (s, 3H), 4.36 (br s, 1H), 5.21 (s, 1H), 6.39 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 7.08-7.19 (m, 7H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.63, 65.07, 81.15, 114.68, 114.70, 125.90, 126.81, 126.91, 127.34, 127.39, 127.77, 127.91, 128.38, 128.72, 138.12, 140.85, 143.96, 144.72, 152.00; $[\alpha]^{20}_D$ = +196.1° (c = 1.0, CH_2Cl_2) on 93% ee. The NMR data are in agreement with those reported for the racemic compound.[81]

Note: The ee can be improved to >99% by crystallization from 10:1 hexanes:EtOAc with 82% recovery. A sample of **52** (0.0400 g, 93% ee) was

dissolved in 1 mL EtOAc followed by addition of 10 mL hexanes. The clear solution was cooled in freezer at –20 °C for 1 h. White crystals were collected to give 0.0328 g of **52** that was 82% recovery and >99% ee.

(*S*)-N-(4-methoxyphenyl)-N-(2-oxo-1,2-diphenylethyl)acetamide (51)



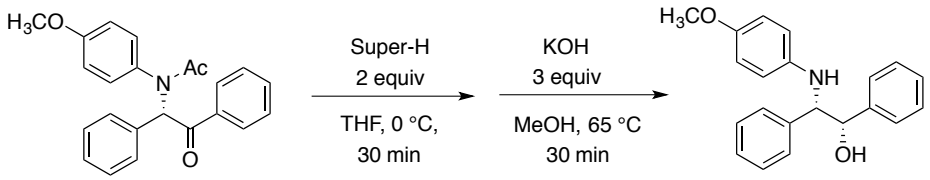
(*S*)-**4s**
95% ee

Acylated **4s**

To a flame-dried 25 mL round bottom flask was added the amino ketone (*S*)-**4s** (0.20 g, 0.64 mmol, 1 equiv, 95% ee) and 10 mL THF. The flask was sealed by a septum and a N_2 balloon was attached via a needle. Acetyl chloride (65 µL, 0.95 mmol, 1.5 equiv.) was added dropwise via a syringe. The mixture was stirred at room temperature for 30 min and then quenched with 3 mL saturated Na_2CO_3 solution. The aqueous layer was extracted with ether (5 mL x 2), and the combined organic layer was dried over $MgSO_4$, filtered through filter paper in Büchner funnel and concentrated by rotary evaporation. The product was purified by flash column chromatography on silica gel with 4:1 to 2:1 hexanes:EtOAc as eluent to afford the acylated **4s** product as a pale light yellow solid (75%, 0.17 g, 0.48 mmol); Rf = 0.05 in 4:1 hexanes:EtOAc; mp = 123-125 °C.

Spectral data for acylated **4s**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.89 (s, 3H), 3.73 (s, 3H), 6.66 (br s, 3H), 7.01-7.03 (m, 2H), 7.10-7.13 (m, 3H), 7.18 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 2H) (1 proton was not located); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.14, 55.28, 66.31, 113.67, 128.30, 128.43, 128.63, 128.84, 130.79, 131.84, 132.82, 132.91, 133.73, 135.57, 158.71, 171.39, 196.35; IR (thin film) 3063m, 2932m, 1695s, 1653s, 1516s, 1383m, 1248s, 1032m cm^{-1}; HRMS (ESI-TOF) *m/z* found 360.1510 [(M+H)$^{+}$; calcd. 360.1600 for $C_{23}H_{22}NO_3$]; $[\alpha]^{20}_{D}$ = +169.6° (c = 1.0, CH_2Cl_2).

(*1S,2S*)-2-((4-methoxyphenyl)amino)-1,2-diphenylethan-1-ol (51)



Acylated **4s** (*1S, 2S*)-**51**

To a flame-dried 10 mL round bottom flask was added the acylated amino ketone (0.17g, 0.47 mmol, 1 equiv) prepared above and 5 mL THF. The solution was cooled in an ice bath for 5 min under a N_2 atmosphere and lithium triethylborohydride (1.9 mL, 1M in THF, 1.90 mmol, 4 equiv) was added dropwise via a syringe. The resulting mixture was stirred in an ice bath for 30 min before being quenched with 4 mL saturated NH_4Cl solution. The solution was then gradually warmed up to room temperature, and extracted with ether (5 mL x 3),

dried over $MgSO_4$, filtered through filter paper in a Büchner funnel and concentrated under rotary evaporation. The product was subjected to the next step without purification. The crude product was transferred to a 25 mL Schlenk flask with 5 mL MeOH and KOH (0.078 g, 1.4 mmol, 3 equiv) was added. The flask was sealed and heated in a 65 °C oil bath for 30 min. Thereafter the solution was cooled to room temperature, which was followed by addition of 5 mL water. The mixture was extracted with ether (5 mL x 3). The syn:anti ratio was greater than 50:1 by ^{1}H NMR analysis of the crude reaction mixture. The combined ether layer was washed with brine and dried over $MgSO_4$, filtered through filter paper in a Büchner funnel and concentrated with rotary evaporation. The product was purified by silica gel column chromatography with 4:1 hexane:EtOAc as eluent to afford the product (*1S,2S*)-**51** as a white solid (70% over two steps, 0.10 g, 0.32 mmol). The optical purity was determined to be 92% ee by Chiralcel OD-H column, 95:5 Hexane:iPrOH, 1 mL/min flow rate, 220 nm, 18.7 min for the major peak and 22.6 min for the minor peak.

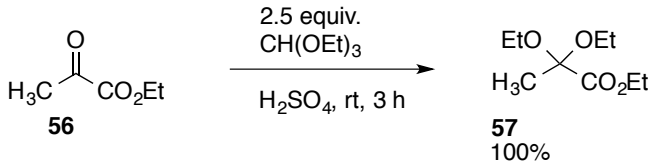
Spectral data for (*1S,2S*)-**51**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.90 (br s, 1H), 3.69 (s, 3H), 4.23 (br s, 1H), 4.42 (d, *J* = 7.0 Hz, 1H), 4.82 (d, *J* = 6.5 Hz, 1H), 6.53 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 7.17-7.18 (m, 2H), 7.22-7.28 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.70, 66.17, 78.13, 114.64, 115.75, 126.70, 127.35, 127.46, 127.83, 128.17, 128.47, 140.21, 140.58, 141.30, 152.49; $[\alpha]^{20}_D$ = –35.5° (c = 0.9, CH_2Cl_2) on 92% ee (lit[13] +30.7 (c=1, $CHCl_3$) on 78% ee

(*1R,2R*)-**51**). The NMR data are in agreement with those reported in the literature.[82]

Note: The ee can be improved to >99% by crystallization from 15:1 hexanes:EtOAc with 92% recovery. A sample of product **51** (92% ee, 0.10 g) was dissolved in 1 mL EtOAc and this was followed by addition of 15 mL hexanes. The clear solution was cooled in freezer at –20 °C for 1 h. White crystals were collected to give 0.092 g **51** that was a 92% recovery and >99% ee.

5.3.8. Attempt in iminol rearrangement with ketimine

ethyl 2,2-diethoxypropanoate (57)

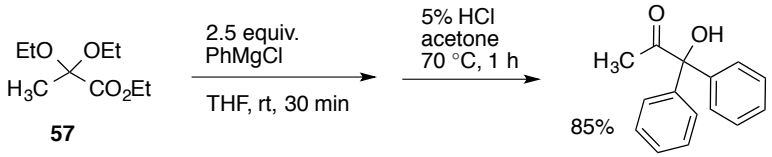


To a clean and dry 20 mL round bottom flask was added ethyl pyruvate **56** (1.00 g, 8.61 mmol, 1 equiv.) and triethyl orthoformate (3.20 g, 21.5 mmol, 2.5 equiv.). The flask was sealed with a septum with a N_2 balloon attached via a needle. To this stirring solution was added sulfuric acid (0.2 mL) dropwise. The resulting mixture was stirred at room temperature for 3 h and then diluted with 20 mL CH_2Cl_2. The reaction solution was successively washed with saturated Na_2CO_3 and brine, and dried over $MgSO_4$, filtered through a filter paper and concentrated on rotary vaporization. The residue was exposed to high vacuum in

60 °C oil bath for 30 min to remove the diethyl sulfate and no more further purification was performed. The reaction afforded the product **57** (1.64 g, 8.61 mmol, 100%) as a colorless oil.

Spectral data for **57**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.53 (s, 3H), 3.44-3.51 (m, 2H), 2.55-3.61 (m, 2H), 4.25 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.16, 15.21, 21.99, 57.93, 61.45, 99.57, 170.08. These NMR data are in agreement with the literature data.[83]

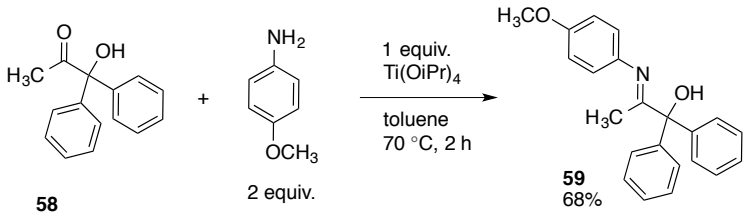
1-hydroxy-1,1-diphenylpropan-2-one (58)



The synthesis of **58** is identical to that of compound **2**. The reaction afforded **58** (0.97 g, 4.3 mmol, 85%) as a light yellow oil, which solidified in the freezer. mp. = 61-63 °C.

Spectral data for **58**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 3H), 4.87 (br s, 1H), 7.35-7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.21, 85.73, 128.07, 128.23, 128.48, 141.25, 208.61. These NMR data are in agreement with the literature data.[84]

2-((4-methoxyphenyl)imino)-1,1-diphenylpropan-1-ol (59)



58 2 equiv. **59** 68%

To a 20 mL screw cap vial was added ketone **58** (0.90 g, 4.0 mmol, 1 equiv.), 4-methoxyaniline (0.98 g, 8.0 mmol, 2 equiv.) and 2 mL toluene. To this stirring solution was added Ti(O*i*Pr)$_4$ (1.18 mL, 4.00 mmol, 1 equiv.) dropwise via a syringe. The vial was capped and heated in a 70 °C oil bath for 2 h. After the reaction solution was cooled to room temperature, 1 mL Et_3N and 10 mL CH_2Cl_2 were added. The resulting solution was successively washed with saturated Na_2CO_3 and brine, and dried over $MgSO_4$, filtered through a filter paper and concentrated on rotary vaporization. The residue was subjected to silica gel chromatography, a mixture of 8:1 hexane:EtOAc as the eluent, to afford the product **59** (0.90 g, 2.7 mmol, 68%) as an orange color oil.

Spectral data for **59**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (s 3H), 3.82 (s, 3H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 7.35 (tt, *J* = 7.0, 1.5 Hz, 2H), 7.39 (tt, *J* = 7.0, 1.5 Hz, 4H), 7.45 (dt, *J* = 7.0, 1.5 Hz, 4H), (the OH proton was not located); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.74, 55.49, 82.10, 114.36, 121.24, 127.64, 128.20, 128.38, 141.52, 143.54, 156.67, 172.79. IR (neat) 3285 br s, 2957 s, 1653 s, 1446 s, 1059 m cm^{-1}; HRMS (ESI+) calc. 332.1651 for $C_{22}H_{22}NO_2$ (M+H), found 332.1665.

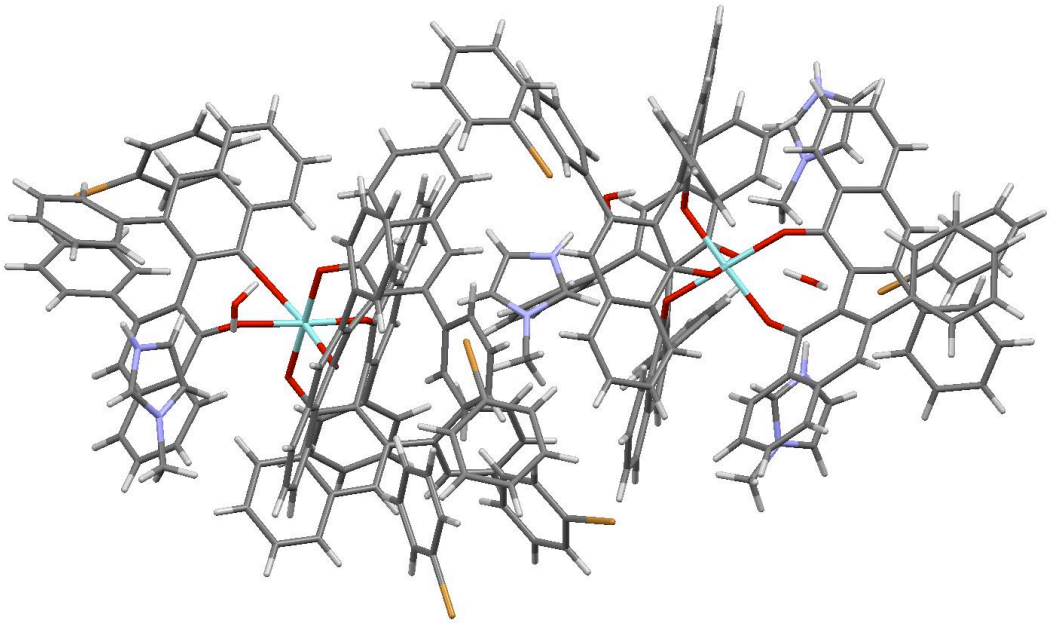
5.3.9. NMR study of crystals 61 in d^6-DMSO

5.3.9.1. Preparation and X-ray analysis of the crytals 61

A slurry of catalyst (*S*)-**46** was generated from a 1:2:1 mixture of Zr(O*i*Pr)$_4$(HO*i*Pr), (*S*)-VANOL and N-methylimidazole in toluene as described in section 5.3.4 and was subjected to high vacuum to remove all volatiles. Then 1 mL of bromobenzene was added and the mixture was heated in a 100 °C oil bath for 5-10 min to dissolve the solids. After all solids were dissolved, the solution was allowed to very slowly cool to room temperature and the crystals that formed were subjected to analysis. An X-ray diffraction study revealed the presence of a homoleptic zirconium atom with three VANOL ligands consisting of a six-coordinate dianionic zirconium hexa-aryloxide that was charged balanced with two protonated N-methylimidazoles. The unit cell contains two zirconium centers and seven molecules of the bromobenzene solvent (see Firgure 3.2 and 3.3). The ratio of zirconium:VANOL:NMI was 1:3:2 instead of 1:2:1 in the solution from which the crystals were grown. Therefore, a second sample of crystals was prepared from a 1:3:2 mixture of Zr(O*i*Pr)$_4$(HO*i*Pr), (*S*)-VANOL and N-methylimidazole and X-ray analysis gave an identical unit cell to that above. These crystals did not melt up to 300 °C. At around 220 °C the color started to darken from light yellow to brown, and at around 260 °C the color become black. The hydrogens on the protonated imidazolium were located but the hydrogens on the water molecules in the unit cell were not located and were added at

reasonable positions. In Figure 5.1 is a picture of one complete unit cell. For the detailed information of the crystal **61**, see the literature.[85]

Figure 5.1 One unit cell of crystal **61**



5.3.8.2. NMR results of crytals 61 in d^6-DMSO

NMR analysis of the crystal **61** was carried out in d^6-DMSO. However, if 1:3:2 Zr(O*i*Pr)$_4$(HO*i*Pr):(*S*)-VANOL:N-methylimidazole were mixed in d^6-DMSO at room temperature for 1 h, no catalyst assembly was observed, only free (*S*)-VANOL ligand and free N-methylimidazole were observed. By heating this solution in a 100 °C oil bath for 5 min, still no catalyst assembly was observed.

List of ^{1}H (500 Hz) and ^{13}C (125 Hz) NMR spectra (d^6-DMSO, 25 °C): 1. Crystal of the catalyst 1:3:2 Zr:(*S*)-VANOL:N-methylimidazole (NMI), the crystal was grown from bromobenzene. 2. Mixture of 1:3:2 Zr(O*i*Pr)$_4$(HO*i*Pr):(*S*)-VANOL:NMI made in d^6-DMSO at room temperature. 3. Mixture of 1:3:2

$Zr(OiPr)_4(HOiPr)$:(*S*)-VANOL:NMI made in d^6-DMSO heated to 100 °C for 5 min. 4. The catalyst of 1:3:2 Zr:(*S*)-VANOL:NMI slurry made in toluene, then volatiles removed. 5. NMI. 6. Mixture of 1:1 NMI:MsOH. 7. (*S*)-VANOL. 8. Bromobenzene. 9. Toluene.

Figure 5.2 ^{1}H NMR and ^{13}C NMR of Crystal **61**

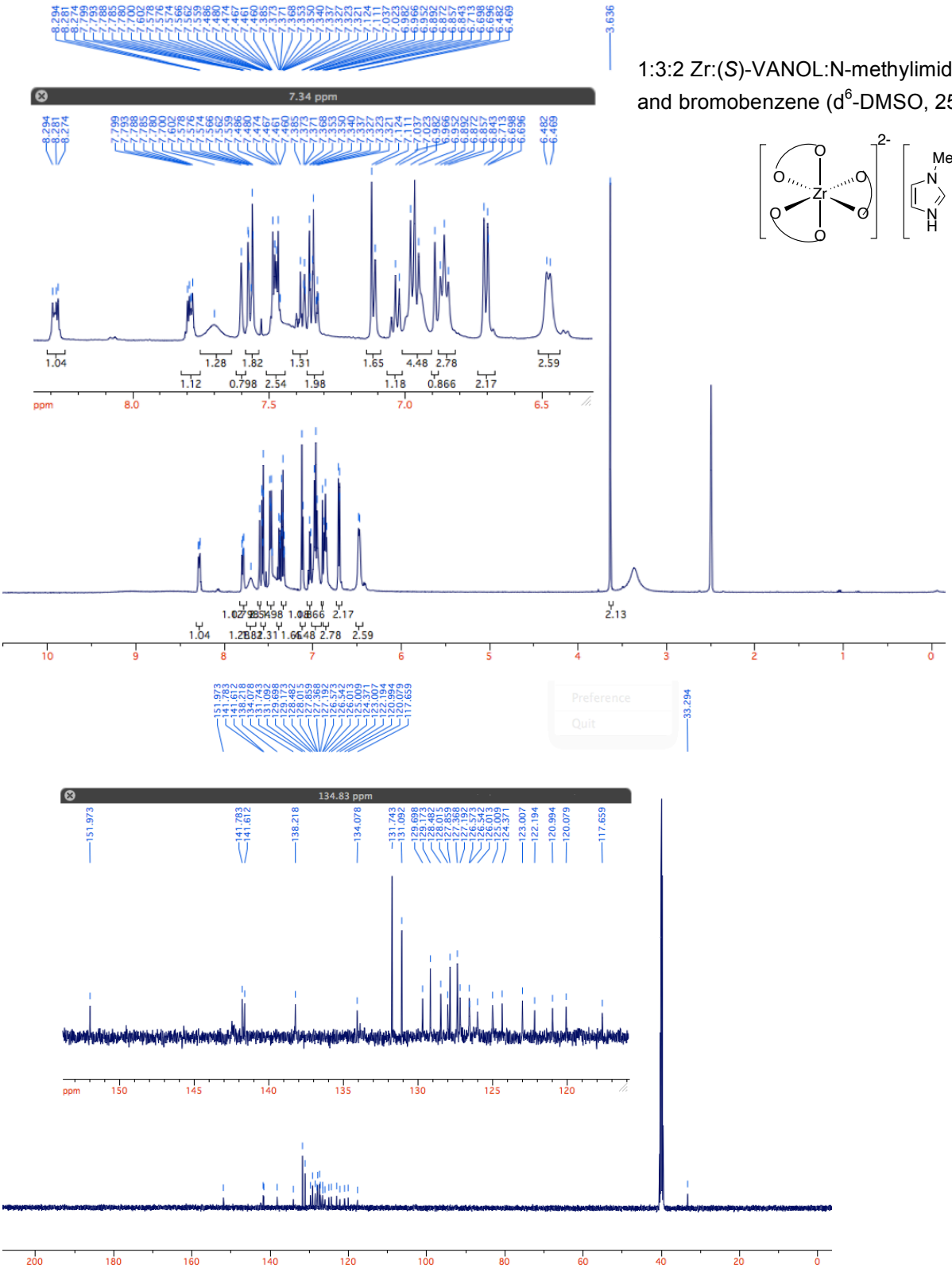


Figure 5.3 ^{1}H NMR and ^{13}C NMR of 1:3:2 Zr:VANOL:NMI made in d^{6}-DMSO

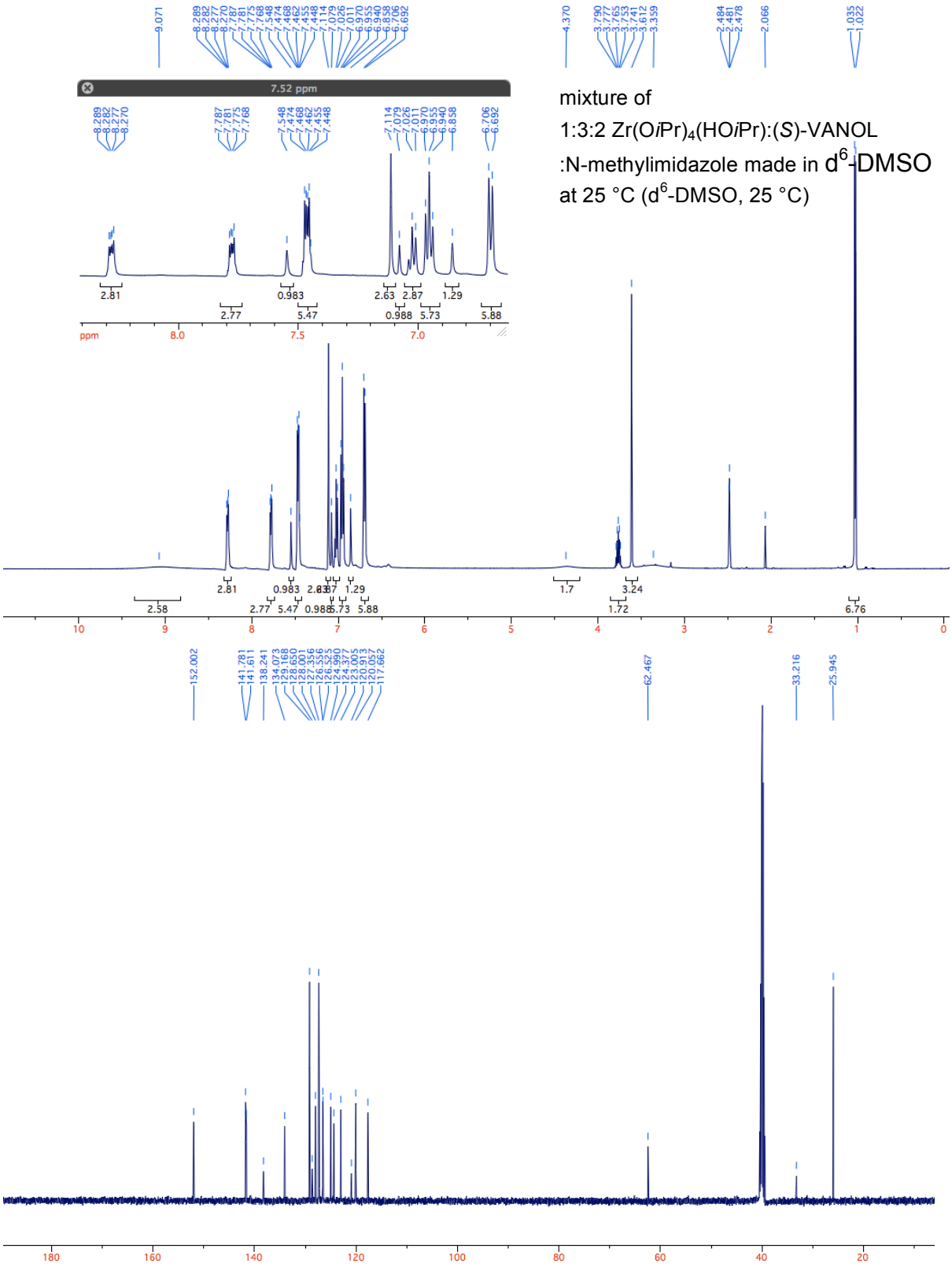


Figure 5.4 ^{1}H NMR and ^{13}C NMR of 1:3:2 Zr:VANOL:NMI heat to 100 °C

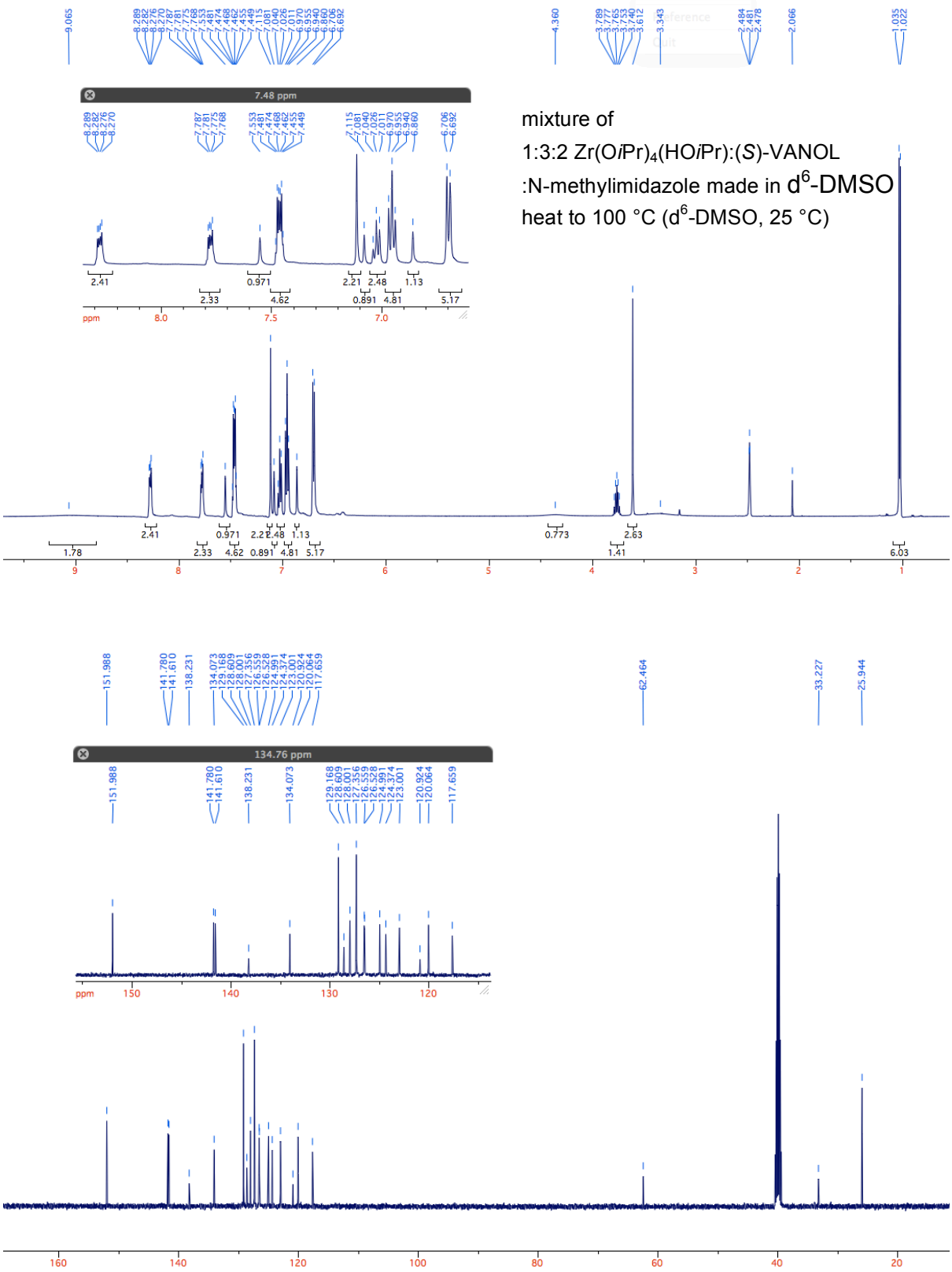
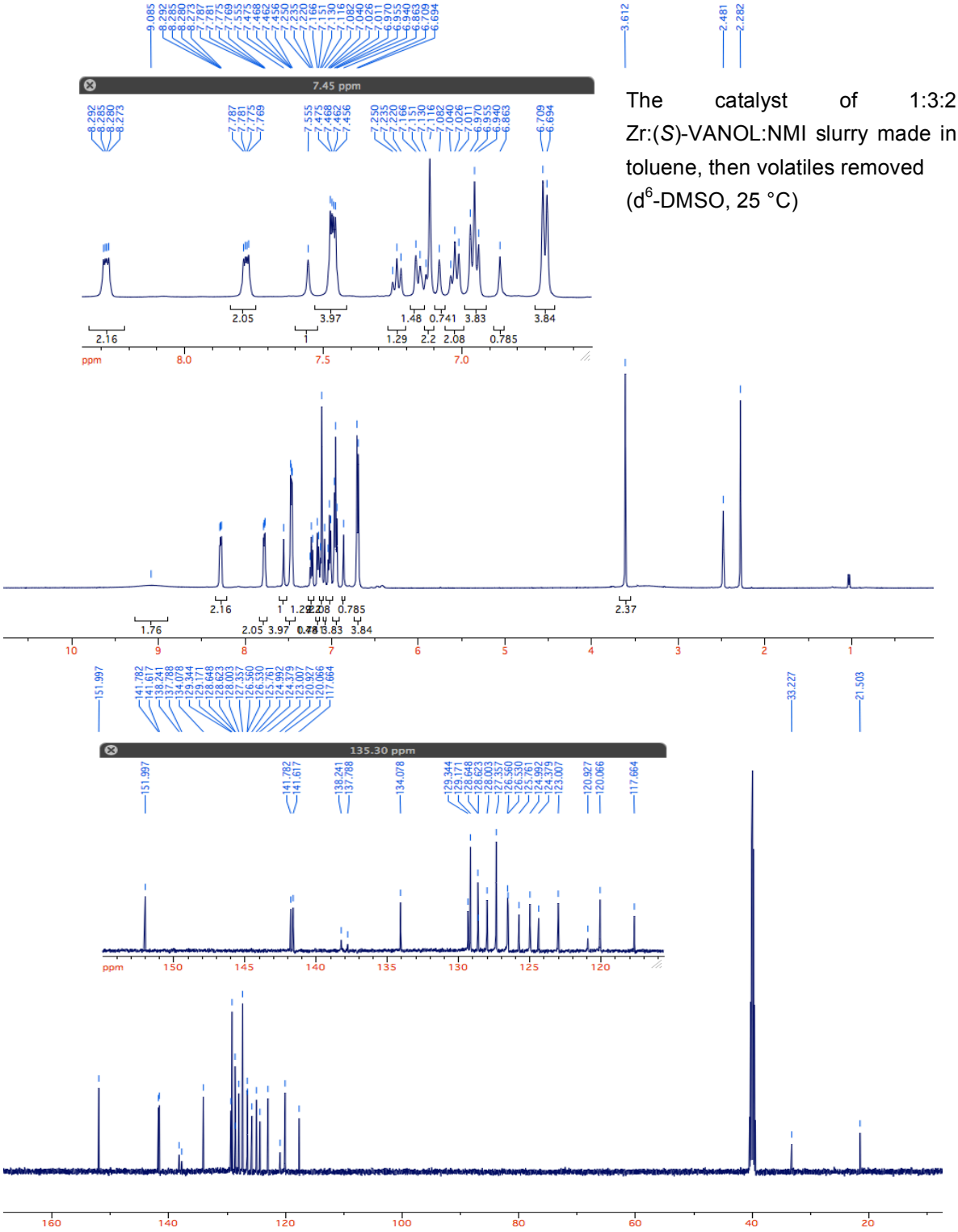


Figure 5.5 ^{1}H NMR and ^{13}C NMR of 1:3:2 Zr:VANOL:NMI made in toluene



The catalyst of 1:3:2 Zr:(*S*)-VANOL:NMI slurry made in toluene, then volatiles removed (d^6-DMSO, 25 °C)

Figure 5.6 ^{1}H NMR and ^{13}C NMR of NMI

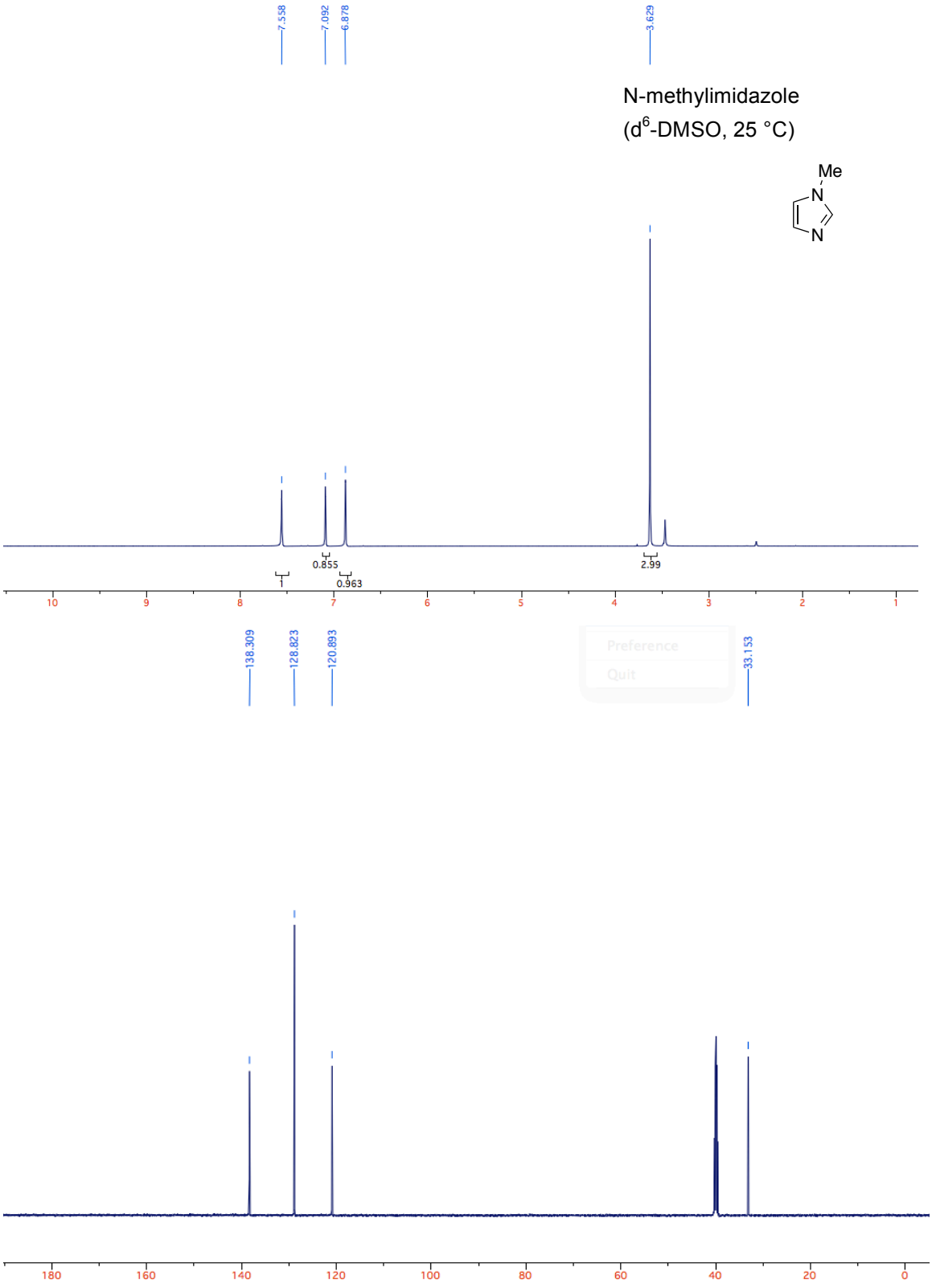


Figure 5.7 ^{1}H NMR and ^{13}C NMR of protonated NMI

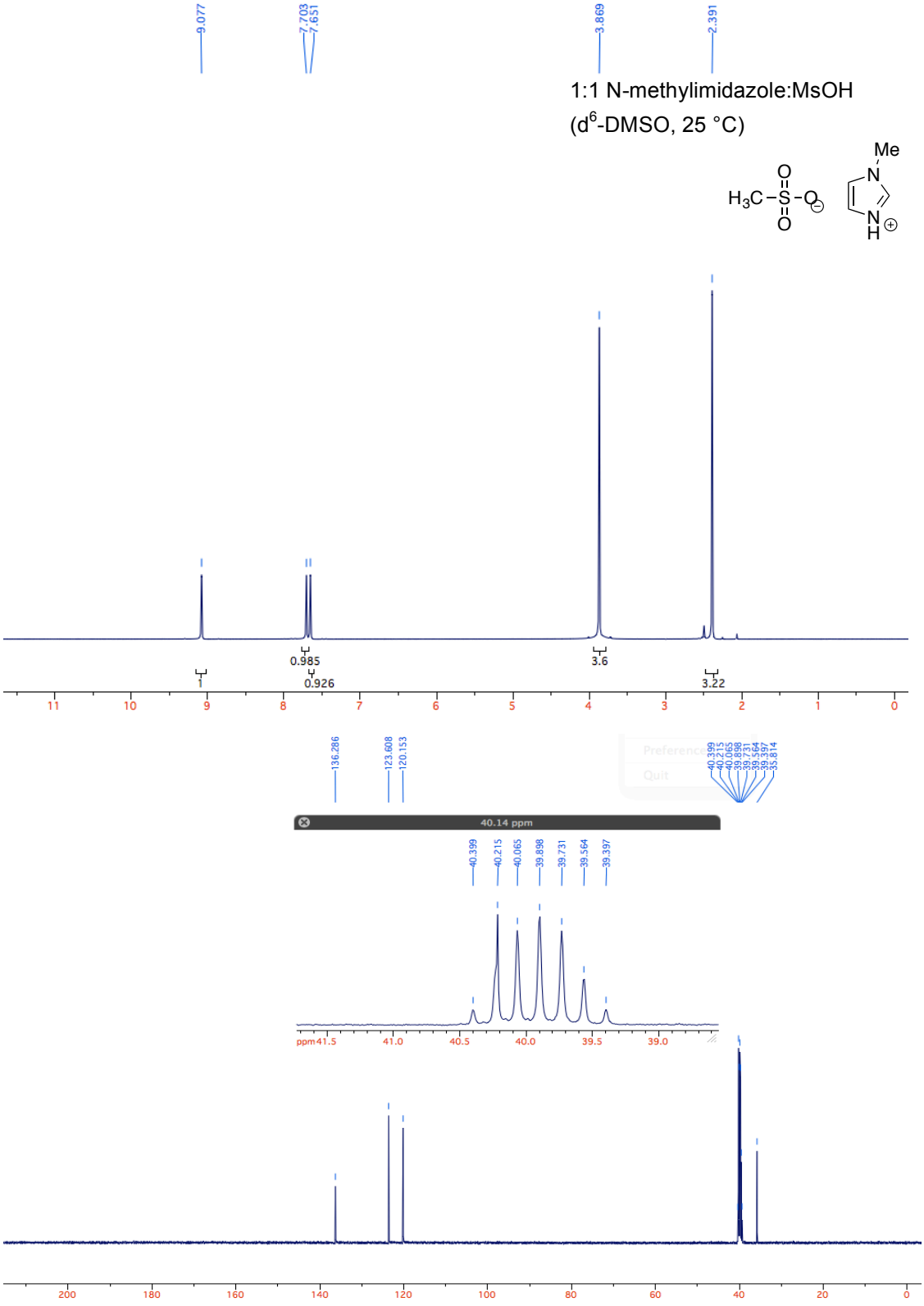


Figure 5.8 ^{1}H NMR and ^{13}C NMR of (*S*)-VANOL

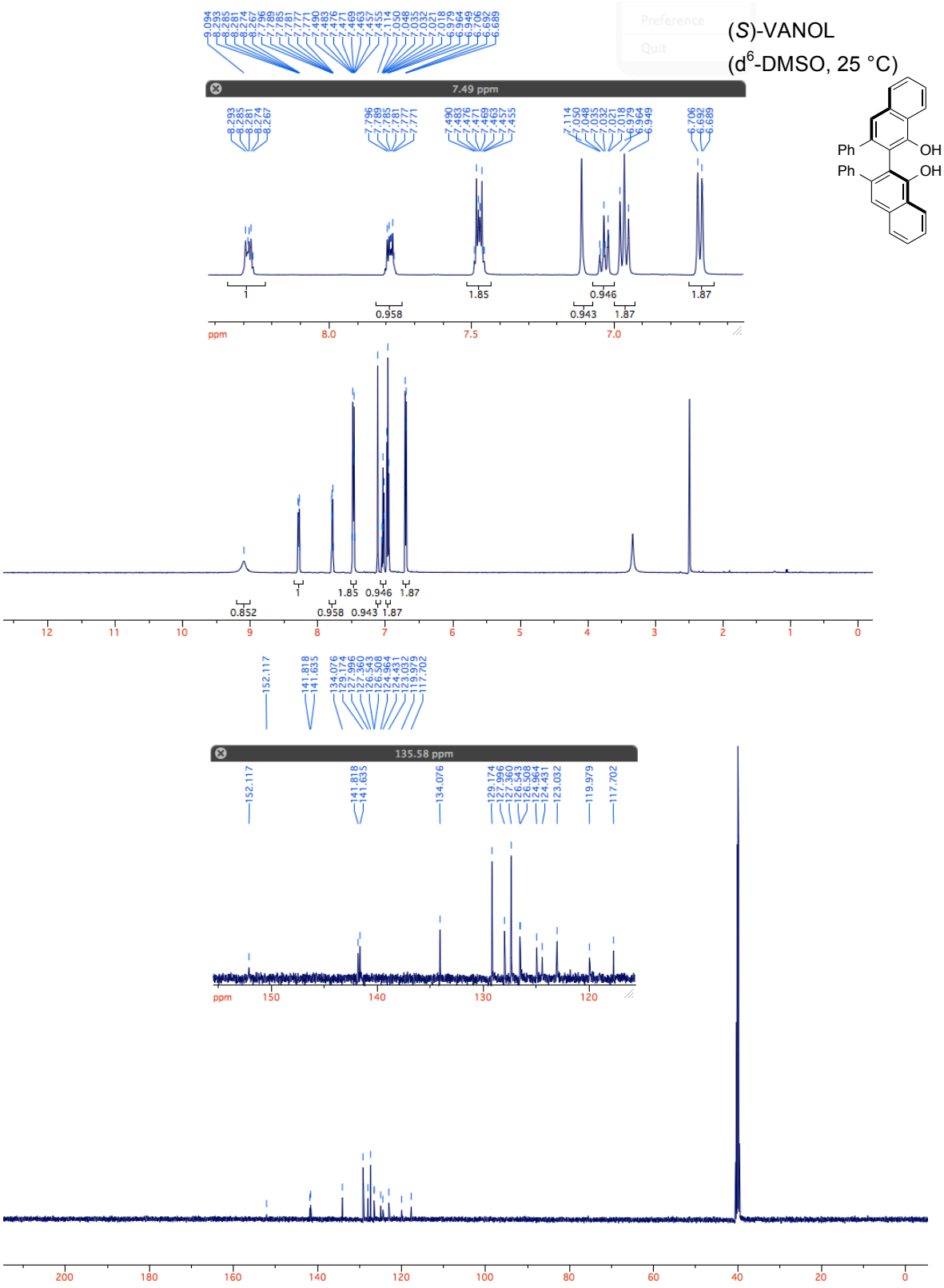


Figure 5.9 ^{1}H NMR and ^{13}C NMR of bromobenzene

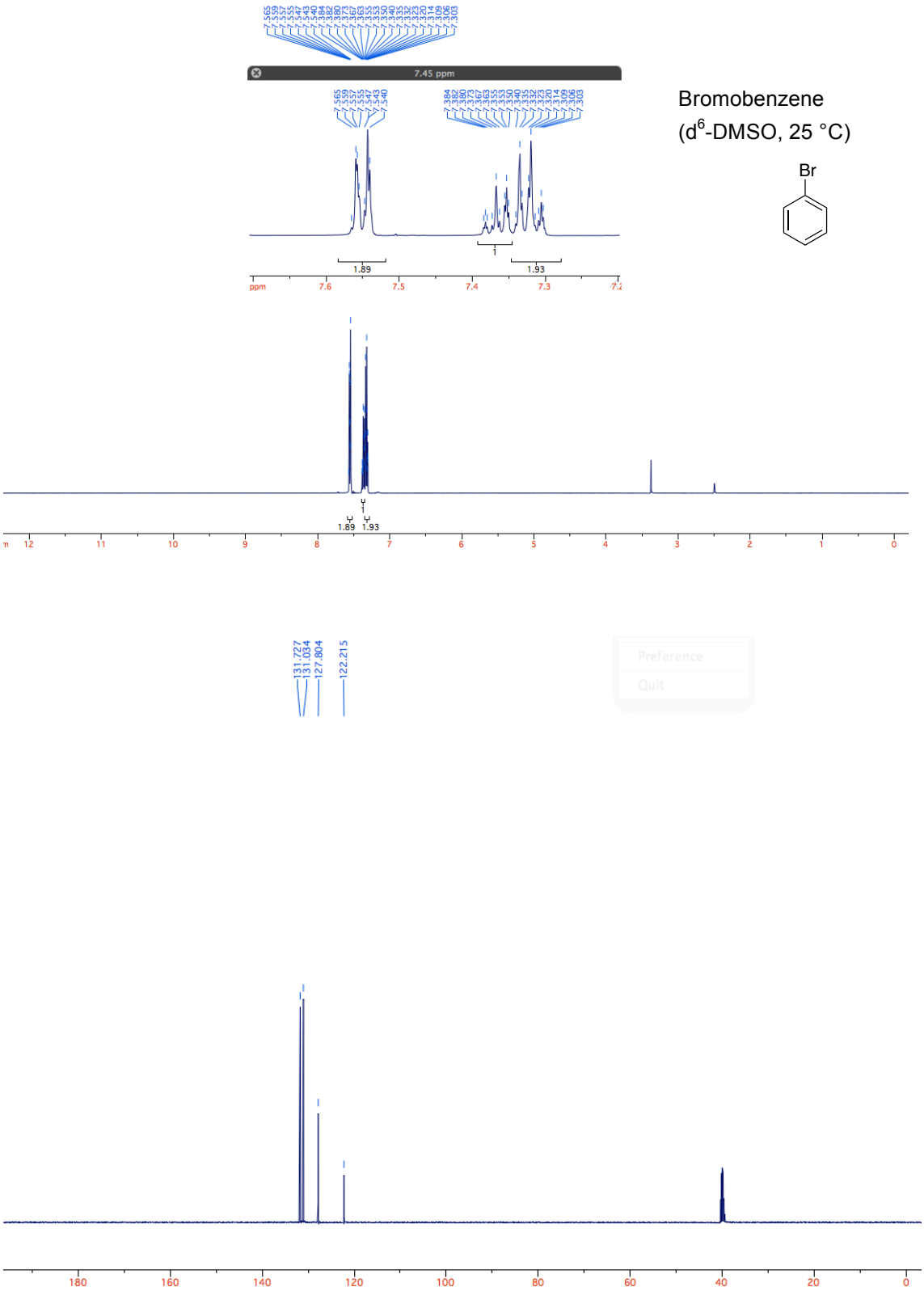


Figure 5.10 ^{1}H NMR and ^{13}C NMR of toluene

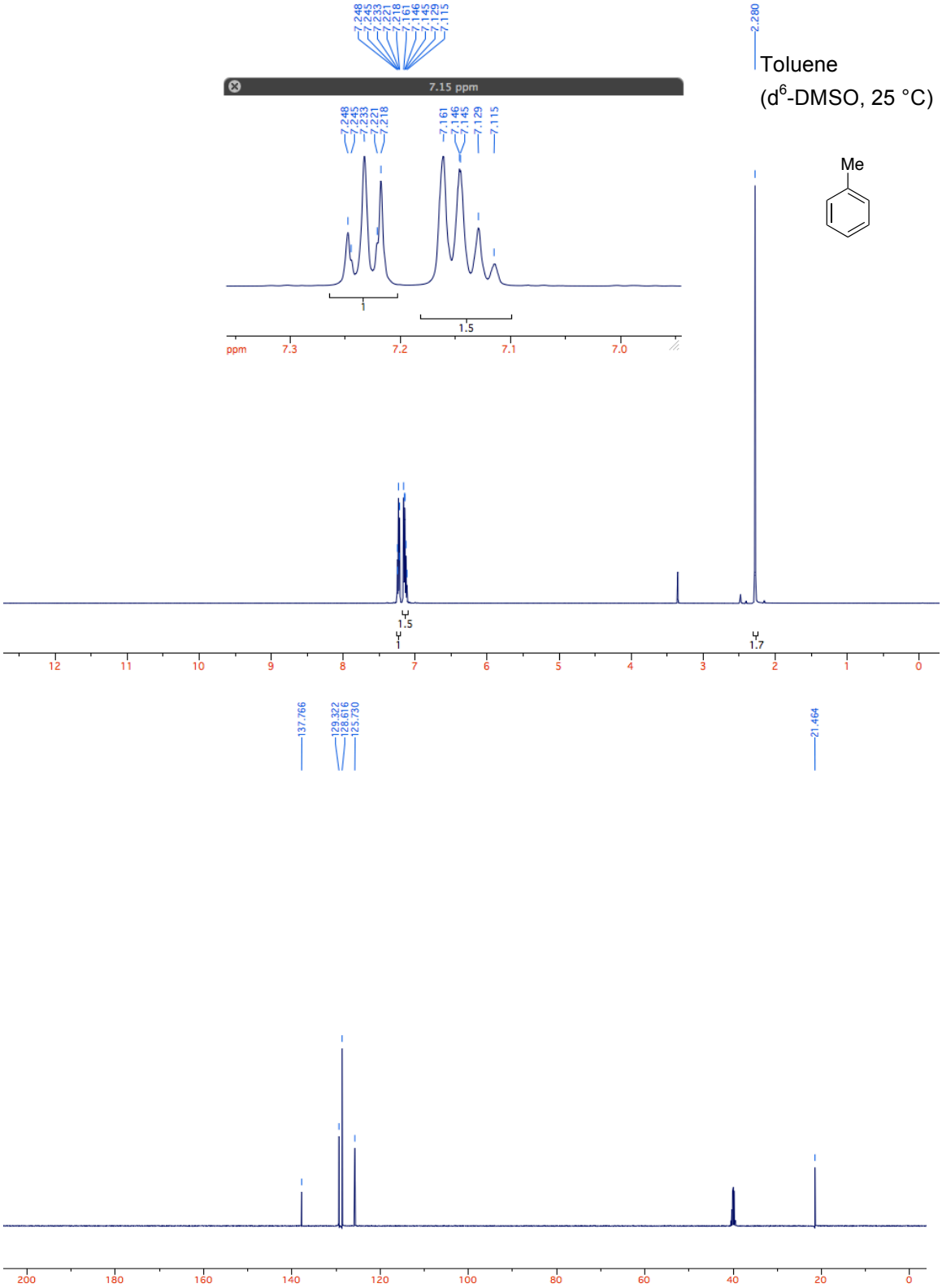
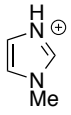
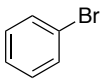
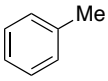


Table 5.1 Summary of the ^{13}C NMR data in the aromatic region

for crystal **61** studies

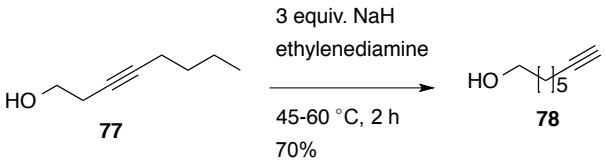
ppm	crystal **61** (Grown in Toluene)	crystal **61** (Grown in Bromobenzene)	*S*-VANOL				
	117.65	117.66	117.70 119.97				
	120.07 120.97	120.08 120.99		120.15	120.89		
		122.19				122.21	
	123.00	123.00	123.03	123.60			
	124.37	124.37	124.43 124.96				
	125.00 125.77	125.00					125.73
	126.01 126.53 126.56	126.01 126.54 126.57	126.50 126.54				
	127.19 127.36	127.19 127.36 127.85	127.36 127.99			127.80	
	128.01 128.53 128.66	128.01 128.48			128.82		128.61
	129.17 129.35 129.69	129.17 129.69	129.17				129.32
		131.09 131.74				131.03 131.72	
	134.07 137.79 138.21	134.07 138.21	134.07	136.28	138.30		137.76
	141.61 141.78	141.61 141.78	141.63 141.81				
	151.97	151.97	152.11				

All data were collected in d^6-DMSO at room temperature at 125 MHz.

5.4 Experimental procedures for chapter four

5.4.1. Experimental procedures for total synthesis of Rhizochalin C

Oct-7-yn-1-ol (78)

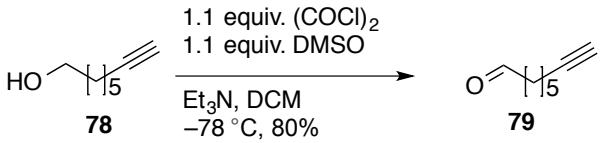


This procedure was adapted from literature for the same molecule.[86] To a flame-dried 500 mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added 150 mL of ethylenediamine. After addition, the flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. After cooling in an ice bath for 10 min, a dispersion of NaH (15.04 g, 376.5 mmol) in mineral oil (60 wt%) was added. The suspension was heated in an oil bath at 60 °C for 1h. After cooling to 45 °C, oct-3-yn-1-ol **77** (15.00 g, 119.3 mmol) was added via syringe. The resulting mixture was heated at 60 °C for 1h. Thereafter, it was cooled to room temperature and then further cooled in ice bath. The reaction was quenched with 10 mL of distilled water and with 6 M HCl solution until the solution became transparent. The crude mixture was extracted with ether (5 × 30 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After filtration through filter paper, the solvent was removed under rotary vaporization. The crude product was purified by silica gel column chromatography with a mixture of 4:1 hexane:EtOAc

as eluent (R_f = 0.14) to afford the titled compound (12.03 g, 83.51 mmol, 70%) as a yellow liquid.

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26-1.38 (m, 4H), 1.43-1.51 (m, 4H), 1.87 (t, 1H, *J* = 2.5 Hz), 2.11 (dt, 2H, *J* = 2.5 Hz, 7.0 Hz), 2.41 (s, 1H), 3.53 (t, 2H, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.16, 25.10, 28.23, 28.35, 32.37, 62.45, 68.11, 84.46; These NMR data are in agreement with the literature data.[86]

Oct-7-ynal (79)



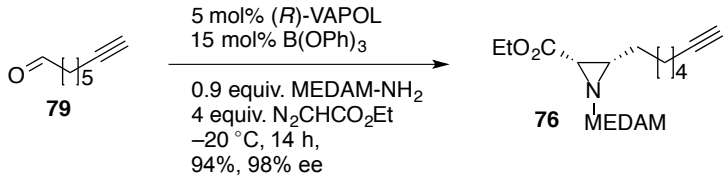
78 **79**

To a flame-dried 1000mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added 500mL CH_2Cl_2. After addition, the flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. The reaction flask was cooled in -78°C acetone dry ice bath. DMSO (5.5mL 60 mmol) and oxalyl chloride (5.5mL 60 mmol) were added via syringe and the resulting mixture was kept at -78 °C for 30 min, sequentially Oct-7-yn-1-ol **78** (6.51 g, 52 mmol) was then added to the flask via syringe. After it was stirred at -78 °C for 1h, 30 mL triethylamine was added to the flask. The solution was gradually warmed to room temperature. Then the reaction was quenched with aqueous NaOH (2.4 g, 60 mmol) solution (100mL). The aqueous

layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. After filtration, the filtrate was concentrated under rotary evaporation. Distillation of the crude product under vacuum (100 °C / 0.5 mmHg) afforded the title product (5.17 g, 80%) as a colorless liquid. R_f = 0.33 (4:1 hexane:EtOAc).

Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38-1.65 (m, 6H), 1.91 (t, 1H, *J* = 2.5 Hz), 2.17 (dt, 2H, *J* = 2.5, 7.0 Hz), 2.42 (dt, 2H, *J* = 1.8, 7.0 Hz), 9.74 (t, 1H, *J* = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.17, 21.51, 28.09, 28.14, 43.70, 68.40, 84.18, 202.49. These data match that reported for this compound.[87]

(2S,3S)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(hept-6-yn-1-yl)aziridine-2-carboxylate (76)



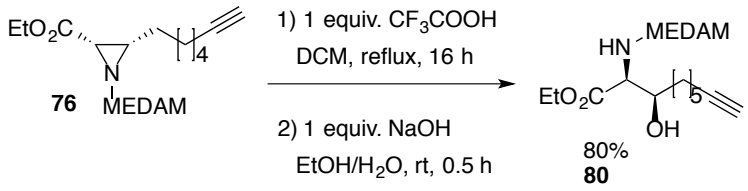
To a flame-dried 250mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added (*R*)-VAPOL (0.94g, 1.83mmol), $B(OPh)_3$ (1.47g, 5.51mmol), MEDAM-NH_2 (10.83g, 36.7mmol) and 70mL toluene. The flask was equipped with a condenser, sealed with a septum to which a nitrogen balloon was attached via a needle, and heated at 80°C for 0.5 h. Thereafter, the condenser was quickly removed and sealed with a septum to

which a nitrogen balloon was attached via a needle. The reaction mixture was cooled to -10°C by an immersion cooler. After cooling, 10.5 g 4Å powdered molecular sieve, oct-7-ynal **79** (5.00 g, 40.3 mmol) and ethyl diazoacetate (14 mL, 146.8 mmol, 4 equiv.) was successively added. The reaction mixture was kept at -20°C for 3h. Then it was diluted with 6 mL hexane, filtered through celite pad and the filtrate was concentrated under reduced pressure followed by exposure to high vacuum for 1h. The crude residue was purified by silica gel column chromatography, 4:1 hexane:EtOAc as eluent (R_f = 0.38), affording the product (16.79g, 94%) as a yellow oil. It was determined to be 98%ee by chiral HPLC analysis (CHIRAL OD-H column, 99:1 hexane:isopropanol at 222nm, flow rate: 0.7mL/min, retention time: R_t = 6.91 min as the major enantiomer and R_t = 4.87 min as the minor enantiomer). Specific Rotation: $[\alpha]_D^{20}$ = –64.4°(*c* 1.0, CH_2Cl_2) on 98%ee.

Spectral data for **76**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07-1.13 (m, 1H), 1.20 (q, 2H, *J* = 6.0 Hz), 1.23 (t, 3H, *J* = 6.0 Hz), 1.33 (q, 3H, *J* = 6.0 Hz), 1.42-1.54 (m, 2H), 1.88 (t, 1H, *J* = 3.0 Hz), 1.94 (q, 1H, *J* = 6.0 Hz), 2.04 (dt, 2H, *J* = 3.0 Hz, 6.0 Hz), 2.19 (d, 1H, *J* = 6.0 Hz), 2.16 (s, 6H), 2.22 (s, 6H), 3.38 (s, 1H), 3.65 (s, 3H), 3.66 (s, 3H), 4.13-4.22 (m, 2H), 6.99 (s, 2H), 7.07 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ14.18, 15.94, 15.97, 18.00, 26.54, 27.61, 28.01, 28.26, 43.40, 46.63, 59.34, 59.39, 60.47, 68.04, 77.23, 84.25, 127.24, 128.01, 130.28, 137.64,

138.10, 155.73, 156.09, 169.45 (one aromatic carbon was not located); IR (NaCl, thin film, cm^{-1}) 3287m, 2943s, 2858m, 2116w, 1742s, 1483s, 1457m, 1221s, 1183s, 1142m, 1014m; HRMS (ESI-TOF) calcd for $C_{31}H_{42}NO_4$ m/z $(M+H)^+$ 492.3114, meas 492.3106.

(2S,3R)-ethyl-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxydec-9-ynoate (80)

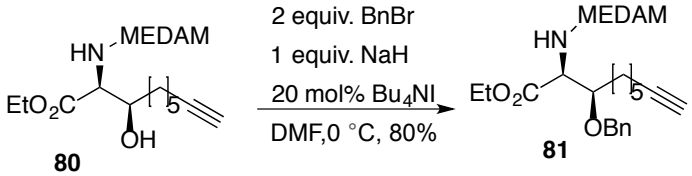


To a flame-dried 250mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added the aziridine **76** (14.55g 29.6mmol), 120mL CH_2Cl_2 and CF_3COOH (2.33mL 30.0mmol). The flask was equipped with a condenser, sealed with a septum to which a nitrogen balloon was attached via a needle, and heated at 45°C oil bath for 13h. After it was cooled down to room temperature, the volatile was removed under reduced pressure. 170mL 15:2 EtOH:H_2O solution with 1.12g NaOH was added to the flask and stirred at room temperature for 0.5h. Thereafter, ethanol was removed under reduced pressure. The residue was extracted with ethyl acetate (30mL×3), the combined organic layers were dried over $MgSO_4$. 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 (9.63g, 60%) as a colorless oil. Specific Rotation: $[\alpha]_D^{20}$=-25.8°(*c* 1.0, CH_2Cl_2).

Spectral data for **80** :^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.29 (m, 2H), 1.25 (t, 3H, *J* = 7.5 Hz), 1.34-1.39 (m, 2H), 1.44-1.52(m, 4H), 1.90 (t, 1H, *J* = 3.0 Hz), 2.15 (dt, 2H, *J* = 3.0 Hz, 7.5 Hz), 2.22 (s, 6H), 2.23 (s, 6H), 3.02 (d, 1H, *J* = 6.0 Hz), 3.60 (q, 1H, *J* = 6.0 Hz), 3.65 (s, 3H), 3.67 (s, 3H), 4.16(q, 2H, *J* = 7.5 Hz), 4.55 (s, 1H), 6.93 (s, 2H), 6.97 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.31, 16.18, 16.27, 18.30, 25.07, 28.35, 28.65, 33.57, 59.56, 59.59, 60.95, 63.71, 64.78, 68.16, 72.24, 84.55, 127.38, 127.81, 130.73, 130.81, 137.24, 139.13, 156.02, 156.06, 173.99; IR (NaCl, thin film, cm^{-1}) 3464m, 3290, 2938s, 2859m, 2116w, 1731s, 1483s, 1463s, 1189m, 1142s, 1016s. HRMS (ESI-TOF) calcd for $C_{31}H_{44}NO_5$ m/z $(M+H)^+$ 510.3219, meas 510.3226.

(2S,3R)-ethyl-3-(benzyloxy)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)dec-9-ynoate (81)



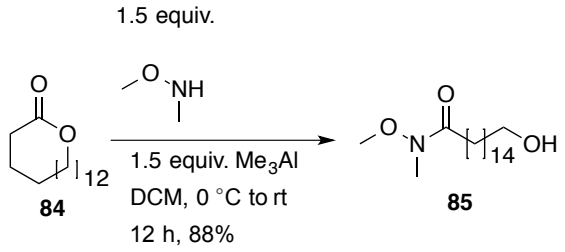
To a flame-dried 10mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added α-amino-β-alcohol ester **80** (0.2133g

0.4mmol), 1.5mL DMF, BnBr (0.1367g 0.8mmol) and Bu_4NI (0.0388g 0.08mmol). 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 (0.0166g 0.4mmol) suspended in 0.5mL DMF was added via syringe slowly. The reaction mixture was stirred for 18h (The ice melted and the temperature rose to room temperature in about 4 hours). Thereafter, the reaction was quenched with 5mL distilled water, and it was extracted with CH_2Cl_2 (10mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After silica gel column chromatography, 4:1 hexane:EtOAc as eluent (R_f =0.19), 0.1400g product was obtained as colorless oil in 50% yield and 0.08g starting material. Specific Rotation: $[\alpha]_D^{20}$= –26.2° (*c* 1.0 CH_2Cl_2).

Spectral data for **81**: ^{1}H NMR (500 MHz, $CDCl_3$) 1.09-1.19 (m, 1H), 1.22 (t, 2H, *J* = 6.0 Hz), 1.26-1.29 (m, 1H), 1.40 (q, 2H, *J* = 6.0 Hz), 1.50 (q, 2H, *J* = 6.0 Hz), 1.70-1.77 (m, 2H), 1.79-1.85 (m, 2H), 1.94 (t, 1H, *J* = 2.5 Hz), 2.16 (dt, 2H, *J* = 2.5 Hz, 7.5 Hz), 2.23 (s, 12H), 3.19 (s, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 4.08-4.17 (m, 2H), 4.46 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.64 (s, 1H), 7.04 (s, 2H), 7.05 (s, 2H), 7.21-7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.28, 16.17, 16.24, 18.35, 25.38, 28.42, 28.82, 30.82, 59.52, 59.56, 60.60, 61.07, 64.65, 68.22, 72.05, 80.71, 84.49, 127.46, 127.55, 127.83, 127.98, 128.22, 130.47, 130.55, 138.19, 138.32, 140.00, 155.86, 155.93, 174.07; IR (NaCl, thin film, cm^{-1}) 3290m,

2938s, 2860s, 2116m, 1735s, 1483s, 1455s, 1220s, 1144s, 1017s. HRMS (ESI-TOF) calcd for $C_{38}H_{50}NO_5$ m/z $(M+H)^+$ 600.3689, meas 600.3694.

16-hydroxy-N-methoxy-N-methylhexadecanamide (85)

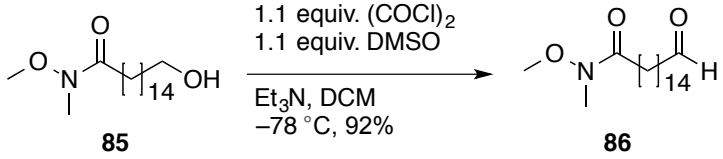


To a flame-dried 250mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added a solution of N,N,O-trimethylhydroxylammonium chloride (19.13g, 196mmol) in 200mL CH_2Cl_2. The flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. The resulting mixture was stirred in ice bath for 10min, then 98mL 2M trimethyl aluminum solution in toluene was added via syringe. It was stirred in ice bath for 30min. Thereafter, a solution of oxacyclohexadecan-2-one **84** (33.34g 131mmol) in 20mL CH_2Cl_2 was added to the flask. The reaction mixture was gradually warmed up to room temperature for 24h. Then the solution was diluted with 40mL CH_2Cl_2, cooled in ice bath to 0^oC. 0.1M HCl solution was added dropwise to quench the reaction. The resulting solution was filtered with a celite pad in a sintered glass funnel; the filtration was dried over $MgSO_4$ filtered, and concentrated under reduced

pressure and high vacuum. Recrystalization of the crude solid in hexane afforded 33.70 g product as a white solid in 81% yield. m. p. = 63-65°C.

Spectral data for **85**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21-1.29 (m, 20H), 1.51 (q, 2H, *J* = 7.2 Hz), 1.57 (q, 2H, *J* = 7.2 Hz), 1.73 (s, 1H), 2.36 (t, 2H, *J* = 7.2 Hz), 3.13 (s, 3H), 3.58 (t, 2H, *J* = 7.2 Hz), 3.63 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.60, 25.69, 29.35, 29.37, 29.38, 29.42, 29.50, 29.53, 29.55, 32.74, 61.12, 62.91, (one amide carbon and five aliphatic carbons not located); IR (KBr, thin film, cm^{-1}) 3443s, 3120br m, 2912s, 2849s, 1651s, 1471s, 1401s, 1193m, 1071m, 984m, 717m, 600m; HRMS (ESI-TOF) calcd for $C_{18}H_{36}NO_3$ m/z 316.2852 $(M+H)^+$ meas 316.2844.

N-methoxy-N-methyl-16-oxohexadecanamide (86)



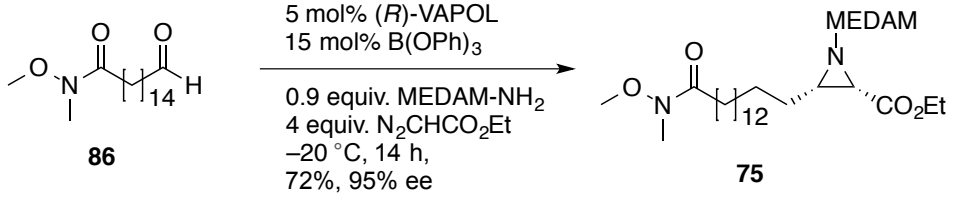
85 **86**

To a flame-dried 250mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added 150mL CH_2Cl_2. The flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. DMSO (1.85mL, 22mmol), and oxalyl chloride (1.85mL, 22mmol) was successively added to the flask via syringe. The resulting mixture was cooled in -78°C acetone dry ice bath for 30min, then a solution of

16-hydroxy-N-methoxy-N-methylhexadecanamide **85** (6.55g 20mmL) in 10mL CH_2Cl_2 was added to the flask via syringe. The reaction mixture was stirred at -78 °C for 1h. Thereafter, 9mL triethylamine was added via a syringe. After the addition, it was allowed to gradually warm up to room temperature for 30min. Then the reaction was quenched with 10mL H_2O, the aqueous layer was separated and extracted with 10mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated on reduced pressure and high vacuum. Recrystalization of the crude solid in hexane afforded 5.55g product as a white solid in 85% yield. m. p. = 34-36°C.

Spectral data for **86**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.28 (m, 18H), 1.58-1.61 (m, 4H), 2.37-2.40 (m, 4H), 3.15 (s, 3H), 3.65 (s, 3H), 9.73 (t, 1H, *J* = 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.05, 24.63, 25.70, 29.13, 29.31, 29.38, 29.40, 29.43, 29.47, 29.53, 29.57, 29.59, 43.89, 61.16, 202.97, one amide carbon and two aliphatic carbons not located; IR (KBr, thin film, cm^{-1}) 3433br m, 3129br m, 2914s, 2850s, 1722s, 1664s, 1472s, 1396s, 1180w, 993w, 716w; HRMS (ESI-TOF) calcd 314.2695 for $C_{18}H_{34}NO_3$ m/z $(M+H)^+$ meas 314.2694.

(2S,3S)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(15-(methoxy (methyl)amino)-15-oxopentadecyl)aziridine-2-carboxylate (75)



86 **75**

To a flame-dried 50mL Schlenk flask equipped with a magnetic stir bar and filled with nitrogen gas was added (R)-VAPOL (0.0155g, 0.02mmol, 5 mol%), $B(OPh)_3$ (0.0218g, 0.06mmol, 15 mol%) and MEDAM-NH_2 (0.1535g, 0.5mmol, 0.9 equiv.) and 1mL toluene. The flask was sealed. The resulting mixture was heated at 80°C for 1h. 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 0.15g 4Å molecular sieve, aldehyde **86** (0.1900g, 0.6mmol, 1 equiv.) and ethyl diazoacetate (0.2mL, 2mmol, 4 equiv.) was successively added at -10°C. The flask was sealed again. The resulting reaction mixture was stirred at -10°C for 16 h. Then it was warmed up to room temperature and diluted with 6mL 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, 1:1:2 Et_2O:CH_2Cl_2:hexane as eluent (R_f = 0.59 in 2:2:1 Et_2O:CH_2Cl_2:hexane),

affording the product (0.2540 g, 72%) 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 = 8.28min as the major enantiomer and R_t = 6.52min as the minor enantiomer.

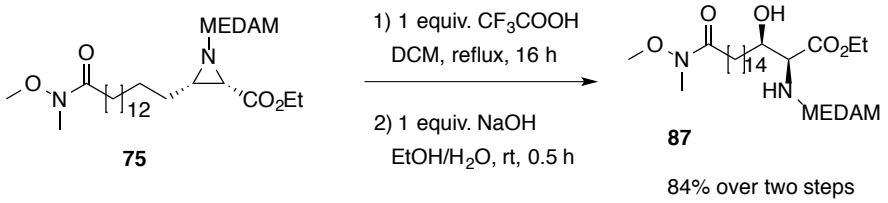
For a larger scale, the reaction needs longer time, and higher temperature. Starting with **86** (5.55 g, 17.7 mmol, 1 equiv.), the reaction was done at room temperature for 48 h, affording the product **75** (7.64 g, 11.7 mmol, 66%) as a yellow oil and the optical purity was determined to be 91% ee.

Spectral data for **75**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07-1.30 (m, 26H), 1.59 (q, 2H, *J* = 10.0 Hz), 1.93 (q, 2H, *J* =5.0 Hz), 2.16 (d, 1H, *J* = 5.0 Hz), 2.20 (s, 12H), 2.37 (t, 2H, *J* = 5.0 Hz), 3.13 (s, 3H), 3.37 (s, 1H), 3.631 (s, 3H), 3.636 (s, 3H), 3.64 (s, 3H), 4.10-4.19 (m, 2H), 6.97 (s, 2H), 7.06 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.22, 15.99, 16.03, 24.55, 27.12, 27.84, 29.05, 29.31, 29.34, 29.39, 29.43, 29.49, 29.50, 29.51, 29.53, 31.81, 43.44, 46.88, 59.42, 60.49, 61.04, 77.22, 127.29, 127.99, 130.27, 130.32, 137.68, 138.08, 155.71, 156.05, 169.55, one amide carbon and three aliphatic carbons not located; IR (NaCl, thin film, cm^{-1}) 2924s, 2853s, 1744s, 1668s, 1483s, 1221s, 1181s, 1142s, 1015s.

(2S,3R)-ethyl

2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxy-18-(metho

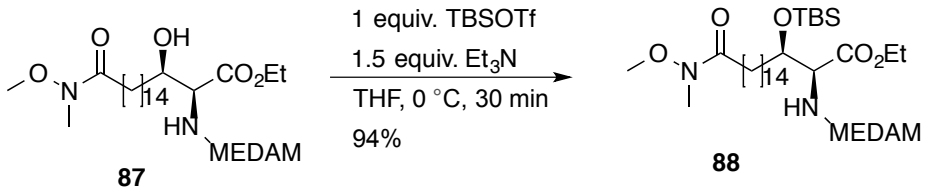
xy(methyl)amino)-18-oxooctadecanoate (87)



To a flame-dried 50mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added the aziridine **75** (0.93g 1.4mmol), 10mL CH_2Cl_2 and CF_3COOH (108μL 1.4mmol). 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 45°C for 16h. Then it was cooled to room temperature, the volatiles were removed under reduced pressure. A solution of 0.05g NaOH in 5mL 15:2 EtOH:H_2O was added to the flask containing the residue after removal of the volatile. It was stirred at room temperature for 0.5h, then ethanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (20mL×3), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography, 1:1:2 Et_2O:CH_2Cl_2:hexane as eluent (R_f = 0.51 in 2:2:1 Et_2O:CH_2Cl_2:hexane), affording the product (0.80g, 84%) as a colorless oil.

Spectral data for **87**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.14-1.30 (m, 25H), 1.46-1.50 (m, 2H), 1.57 (q, 2H, *J* = 7.5 Hz), 2.19 (s, 6H), 2.20 (s, 6H), 2.36 (t, 2H, *J* = 7.5 Hz), 3.02 (d, 1H, *J* = 6.0Hz), 3.11 (s, 3H), 3.61-3.63 (m, 10H), 4.13 (q, 2H, *J* = 7.5 Hz), 4.54 (s, 1H), 6.93 (s, 2H), 6.96 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.11, 15.97, 16.05, 24.45, 25.45, 29.23, 29.24, 29.31, 29.39, 29.42, 29.44, 31.67, 33.63, 59.31, 59.33, 60.64, 60.94, 63.38, 64.56, 72.26, 127.23, 127.65, 130.44, 130.51, 137.28, 139.15, 155.78, 155.81, 173.90, (one amide carbon and 5 aliphatic carbons not located).

(2S,3R)-ethyl-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-((tert-butyldimethylsilyl)oxy)-18-(methoxy(methyl)amino)-18-oxooctadecanoate (88)



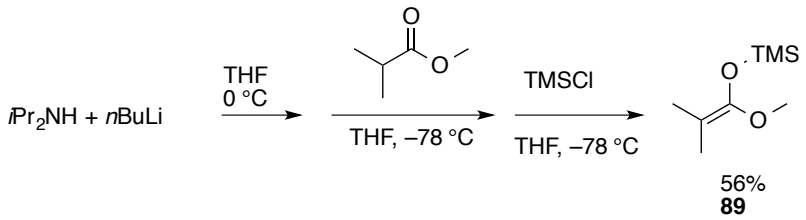
To a flame-dried 25mL round bottom flask equipped with a magnetic stir bar and filled with nitrogen gas was added a solution of compound **29** (0.90g, 1.1mmol) in 10mL THF. The flask was quickly sealed with a septum to which a nitrogen balloon was attached via a needle. It was then added TBSOTf (0.25mL, 1.2mmol) and Et_3N (0.2mL, 1.2mmol) 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, 1:1:2 Et_2O:CH_2Cl_2:hexane as eluent (R_f = 0.69 in 2:2:1 Et_2O:CH_2Cl_2:hexane). The product (0.34g, 36%) was obtained as colorless oil. Specific Rotation: $[\alpha]_D^{20}$= –20.0°(*c* 1.0, CH_2Cl_2).

Spectral data for **88**: ^{1}HNMR (500 MHz, $CDCl_3$) δ -0.96 (s, 3H), -0.01 (s, 3H), 0.81 (s, 9H), 1.23-1.40 (m, 27H), 1.61 (q, 2H, *J* = 7.0 Hz), 1.90-1.99 (m, 1H), 2.21 (s, 12H), 2.39 (t, 2H, *J* = 7.0 Hz), 3.08 (s, 1H), 3.15 (s, 3H), 3.651 (s, 3H), 3.653 (s, 3H), 3.66 (s, 3H), 3.89 (m, 1H), 4.13-4.17 (m, 2H), 4.63 (s, 1H), 7.00 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.06, -4.32, 14.26, 16.12, 16.14, 17.92, 24.61, 25.73, 25.78, 29.39, 29.42, 29.47, 29.56, 29.62, 29.68, 29.80, 31.89, 34.06, 59.47, 59.49, 60.34, 61.10, 61.87, 64.02, 74.48, 127.38, 128.15, 130.33, 130.45, 138.18, 140.31, 155.74, 155.92, 174.07, (one amide carbon and 4 aliphatic carbons not located); IR (NaCl, thin film, cm^{-1}) 3342m, 2927s, 2855s, 1738s, 1671s, 1463s, 1221s, 1150s, 1094s, 1018s, 940m, 836s, 776s; HRMS (ESI-TOF) calcd 813.5813 for $C_{47}H_{81}N_2O_7Si$ m/z $(M+H)^+$, meas 813.5831.

5.4.2. Experimental procedure for Mannich type reaction

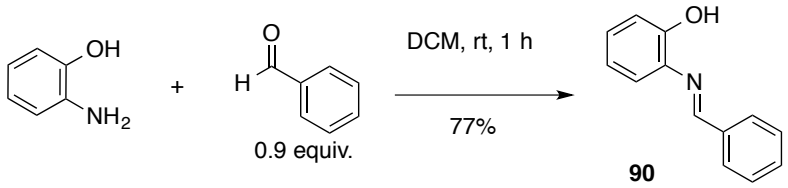
((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (89)



To a flame-dried 100 mL round bottom flask was added isopropylamine (7.0 mL, 50 mmol, 1 equiv.) and 30 mL THF, the flask was sealed with a septum with a N_2 balloon attached via a needle. The flask was cooled in an ice bath for 5 min, and then *n*-BuLi (2.5M in hexane, 20 mL, 50 mmol, 1 equiv.) was added dropwise. The resulting solution was stirred in the ice bath for another 30 min and followed by cooling to –78°C in an acetone dry ice bath for 5 min. Methyl isobutyrate (5.5 mL, 48 mmol, 0.95 equiv.) was added to the solution dropwise via a syringe. The resulting solution was stirred at –78 °C for 1 h before the slow addition of TMSCl (6.8 mL, 55 mmol, 1.1 equiv.). The flask was cooled at –78°C for another 30 min before warming up to room temperature. The mixture was filtered through celite pad and the filtrate was concentrated on rotary vaporization. The residue was subjected to partial vacuum distillation to afford the pure product **89** (4.60 g, 28.0 mmol, 56%) as a colorless oil.

Spectra data for **89**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 3H), 1.50 (s, 3H), 1.56 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.02, 16.07, 16.81, 56.47, 90.85, 149.27. These NMR data are in agreement with the literature data.[88]

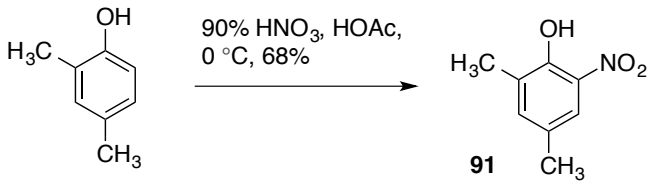
2-(benzylideneamino)phenol (90)



To a 20 mL round bottom flask was added 2-aminophenol (0.24 g, 2.2 mmol, 1.1 equiv.), 4 mL CH_2Cl_2, $MgSO_4$ (0.20 g) and benzaldehyde (0.20 mL, 2.0 mmol, 1 equiv.). The mixture was stirred at room temperature for 1 h, and filtered through filter paper, concentrated on rotary vaporization. The residue was subjected to flask column chromatography, a 4:1 mixture of hexane:EtOAc as the eluent, to afford the pure product **90** (0.30 g, 1.5 mmol, 77%) as a yellow solid. mp. = 88-89 °C.

Spectra data for **90**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (td, *J* = 8.0, 1.5 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.27 (br s, 1H), 7.31 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.48-7.51 (m, 3H), 7.93 (dd, *J* = 8.0, 1.5 Hz, 2H), 8.70 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.00, 115.84, 120.09, 128.81, 128.86, 128.94, 131.69, 135.43, 135.80, 152.31, 157.10. These NMR data are in agreement with literature data.[52]

2,4-dimethyl-6-nitrophenol (91)



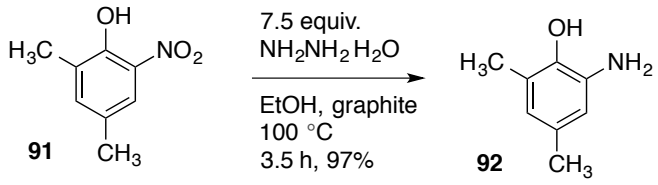
To a 250 mL Erlenmeyer flask was added a magnetic stir bar, 2,4-dimethylphenol (3.00 mL, 24.1 mmol) and acetic acid (30 mL). The flask was cooled in ice bath for 5 min. To another 50 mL Erlenmeyer flask was added acetic acid (10 mL) and HNO_3 (1.9 mL, c = 90%) and cooled in ice bath for 5 min. The HNO_3 solution was transferred to the dimethylphenol 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 mL x 4). The combined organic layer was successively washed with H_2O (20 mL) and brine (20 mL) and dried over $MgSO_4$. The solution was filtered through filter paper, and concentrated under rotary evaporation. The crude product was purified by silica gel column chromatography, with 8:1 hexanes:EtOAc as the eluent. The reaction afforded the product **91** as a yellow solid (2.73 g, 16.4 mmol, 68%). m. p. = 68-69 °C (lit.[89] 64-66 °C);

Spectra data for **91**: ^{1}H NMR (500M Hz, $CDCl_3$) δ 2.29 (s, 6H), 7.26 (s, 1H), 7.73 (s, 1H), 10.76 (s, 1H); ^{13}C NMR (125M Hz, $CDCl_3$) δ 15.77, 20.29, 121.87, 128.93, 128.99, 132.97, 139.54, 151.77; The ^{1}H NMR data was identical to that

reported in literature.[89]

Note: a second run was carried out on the same scale with 70% HNO_3, the yield dropped to 44%.

2-amino-4,6-dimethylphenol (92)

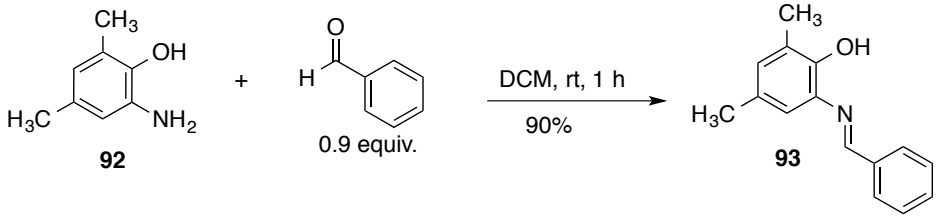


To a 100 mL RBF was added 4,6-dimethyl-2-nitrophenol **91** (1.76 g, 10.5 mmol), graphite (1.50 g), hydrazine monohydrate (1.28 mL, 26.3 mmol, 2.5 equiv.) and ethanol (30 mL). The flask was equipped with a condenser and the top was sealed by a septum with a needle attached to it. The flask was heated in a 100 °C oil bath for 3.5 h (another 5 equiv. of hydrazine monohydrate was added in two equal portions every other hour). The solution was allowed to cool to room temperature, and filtered though celite pad, the filter cake was washed by dichloromethane. The filtrate was concentrated under rotary evaporation and exposed to high vacuum to afford the pure product as a pale orange color solid (1.40 g, 10.1 mmol, 97%). m. p. = 130-132 °C (lit.[89] 127-129 °C);

Spectra data for **92**: ^{1}H NMR (500M Hz, d^{6}-DMSO) δ 2.03 (s, 6H), 4.42 (br s, 2H), 6.09 (s, 1H), 6.24 (s, 1H), 7.51 (br s, 1H); ^{13}C NMR (125M Hz, d^{6}-DMSO) δ 16.92, 20.95, 113.77, 119.46, 124.74, 128.50, 137.48, 139.68; and the NMR data

were also obtained in $CDCl_3$: ^1H NMR (500M Hz, $CDCl_3$) δ 2.17 (s, 3H), 2.18 (s, 3H), 3.63 (br s, 3H), 6.40 (s, 1H), 6.43 (s, 1H); ^{13}C NMR (125M Hz, $CDCl_3$) δ 15.98, 20.65, 115.38, 121.80, 124.55, 130.19, 134.92, 140.38; these NMR data obtained in d^6-DMSO were identical to those reported in literature.[89]

2-(benzylideneamino)-4,6-dimethylphenol (93)

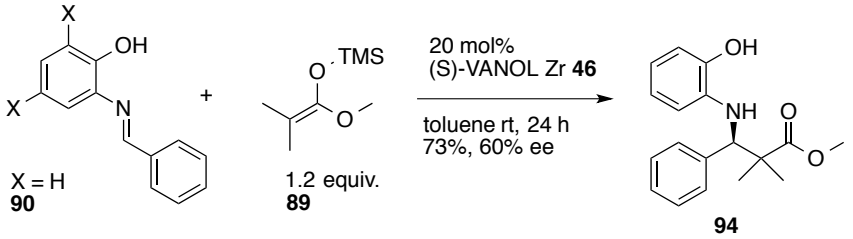


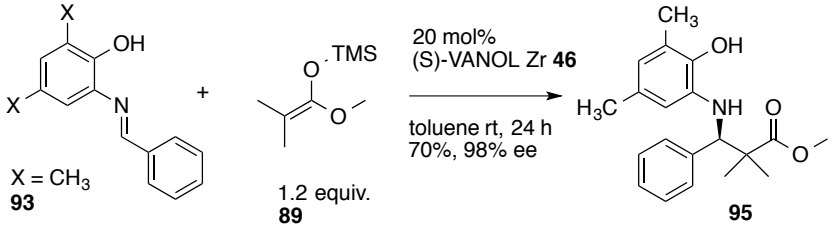
To a 20 mL round bottom flask was added 4,6-dimethyl-2-aminophenol **92** (0.30 g, 2.2 mmol, 1.1 equiv.), 4 mL CH_2Cl_2, $MgSO_4$ (0.20 g) and benzaldehyde (0.20 mL, 2.0 mmol, 1 equiv.). The mixture was stirred at room temperature for 1 h, and filtered through filter paper, concentrated on rotary vaporization. The residue was subjected to flask column chromatography, a 4:1 mixture of hexane:EtOAc as the eluent, and then recrystallized in hexane to afford the pure product **93** (0.40 g, 2.0 mmol, 90%) as a yellow solid. mp. = 70-72 °C.

Spectra data for **93**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.29 (s, 3H), 6.89 (s, 1H), 6.98 (s, 1H), 7.24 (br s, 1H), 7.47-7.49 (m, 3H), 7.90-7.92 (m, 2H), 8.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.65, 20.78, 113.58, 124.01, 128.44, 128.69, 128.82, 130.85, 131.47, 134.41, 135.97, 148.43, 156.43. These NMR

data are in agreement with literature data.[52]

methyl (*R*)-3-((2-hydroxyphenyl)amino)-2,2-dimethyl-3-phenylpropanoate (94) and methyl (*R*)-3-((2-hydroxy-3,5-dimethylphenyl)amino)-2,2-dimethyl-3-phenylpropanoate (95)





The experimental procedure for the Mannich type reaction in Tables 4.1 and 4.2 are similar to a literature procedure.[52] The catalyst **46** was prepared from a 2.2:1.0:1.2 mixture of (*S*)-VANOL : $Zr(O\textit{i}Pr)_4(HO\textit{i}Pr)$: N-methylimidazole according to section 5.3.4 procedure 4. To this catalyst **46** (20 mol%, in 0.5 mL toluene in a Schlenk flask) was added aldimine **90** or **93** (0.125 mmol, 1 equiv.) and 0.5 mL toluene and the solution was stirred for 5 min. Then the silyl ketene acetal 89 (0.15 mmol, 1.2 equiv.) was added via a syringe. The reaction mixture was stirred at room temperature for 24 h. Excess hexane was added to precipitate the catalyst and the solids were filtered off through a filter paper. The filtrate was

concentrated on rotary vaporization and the residue was diluted in 2 mL THF, and 1.5 N HCl 0.2 mL was added. The solution was allowed to stir at room temperature for 30 min. Then the reaction was quenched with saturated $NaHCO_3$ solution 5 mL. The aqueous phase was extracted with EtOAc (5 mL x 3) and the combined organic phase was washed with brine and dried over $MgSO_4$. The solids were filtered off through a filter paper. The filtrate was concentrated on rotary vaporization and the residue subjected to silica gel column chromatography, 1 mixture of 10:1 hexane:EtOAc as the eluent, to afford the product, for **94** (0.0273 g, 0.0912 mmol, 73%) as a a yellow oil and for **95** (0.0299 g, 0.0875 mmol, 70%) as a yellow solid.

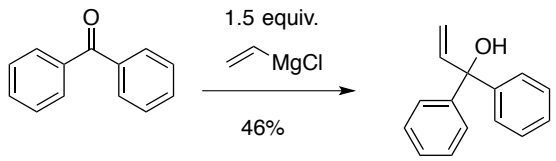
Data for **94**: The optical purity is 60% ee determined by Chirapak AD column, 90:10 hexane:HO*i*Pr, 1 mL/min, 9.5 min for the major peak and 12.7 min for the minor peak. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.23 (s, 3H), 3.67 (s, 3H), 4.53 (br s, 1H), 4.85 (br s, 1H), 5.29 (s, 1H), 6.37 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.52 (dt, *J* = 7.0, 1.0 Hz, 1H), 6.59 (dt, *J* = 8.0, 1.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 7.20-7.27 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.92, 24.24, 47.25, 52.43, 64.33, 133.23, 114.23, 117.54, 120.69, 127.22, 127.78, 128.15, 135.55, 138.90, 144.02, 178.10. These NMR data are in agreement with literature data.[52]

Data for **95**: m. p. = 124-126 °C. The optical purity is 98% ee determined by Chirapak AS column, 90:10 hexane:HO*i*Pr, 1 mL/min, 4.7 min for the minor peak and 5.8 min for the major peak. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.21 (s,

3H), 2.02 (s, 3H), 2.14 (s, 3H), 3.68 (s, 3H), 4.52 (s, 1H), 4.77 (br s, 1H), 4.97 (s, 1H), 6.01 (s, 1H), 6.27 (s, 1H), 7.16-7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.60, 19.92, 20.78, 24.33, 47.39, 52.10, 64.88, 113.69, 121.04, 122.44, 127.45, 127.90, 128.43, 129.66, 135.02, 139.19, 140.89, 177.70. These NMR data are in agreement with literature data.[52]

5.4.3. Experimental procedure for chloronium induced rearrangement of allylic alcohol

1,1-diphenylprop-2-en-1-ol (96)



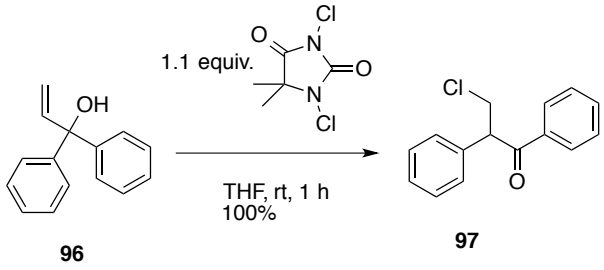
96

To a flame-dried 50 mL round bottom flask was added benzophenone (0.63 g, 3.5 mmol, 1 equiv.), 10 mL THF and the flask was sealed with septum with a N_2 balloon attached via a needle. Vinylmagnesium chloride (1M in THF, 5.0 mL, 5.0 mmol, 1.5 equiv.) was added dropwise via a syringe. The resulting mixture was allowed to stir at room temperature for 30 min. The reaction was quenched with 10 mL saturated NH_4Cl solution, and extracted with Et_2O (10 mL x 2). The combined organic phase was washed with brine, filtered through filter paper, concentrated on rotary vaporization. The residue was subjected to flash silica gel chromatography, a 20:1 mixture of hexane:EtOAc as the eluent, to afford the

product **96** (0.34 g, 1.6 mmol, 46%) as a colorless oil.

Spectra data for **96**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 1H), 5.32 (s, 1H), 5.35 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.50-6.55 (m, 1H), 7.28 (tt, *J* = 7.0, 1.5 Hz, 2H), 7.34 (tt, *J* = 7.5, 1.5 Hz, 4H), 7.40 (dt, *J* = 7.5, 1.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.39, 114.01, 126.86, 127.28, 128.16, 143.46, 145.72. These NMR data are in agreement with the literature data.[90]

3-chloro-1,2-diphenylpropan-1-one (97)



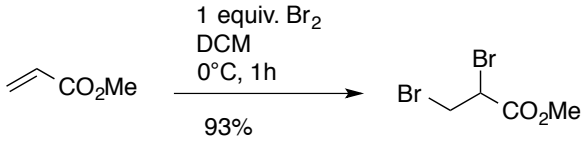
96 **97**

To a 20 mL screw cap vial was added allylic alcohol **96** (0.0420 g, 0.200 mmol, 1 equiv.) and 1 mL THF, to this stirring solution was slowly added the chlorine source 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (0.0400 g, 0.200 mmol, 1 equiv.). The vial was capped and allowed to stir at room temperature for 1 h. The reaction was quenched with 10 mL hexane. The resulting suspension was filtered through filter paper, concentrated on rotary vaporization. The residue was subjected to flash silica gel chromatography, a 16:1 mixture of hexane:EtOAc as the eluent, to afford the product **97** (0.0490 g, 0.200 mmol, 100%) as a colorless oil.

Spectra data for **97**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.33 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.95 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.26-7.30 (m, 1H), 7.34 (d, *J* = 4.5 Hz, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.98 (dd, *J* = 8.0, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.28, 56.16, 128.15, 128.27, 128.64, 128.78, 129.29, 133.37, 136.11, 136.16, 196.95. These NMR data are in agreement with the literature data.[91]

5.4.4. Experimental procedure for aziridinol rearrangement

methyl 2,3-dibromopropanoate (99)



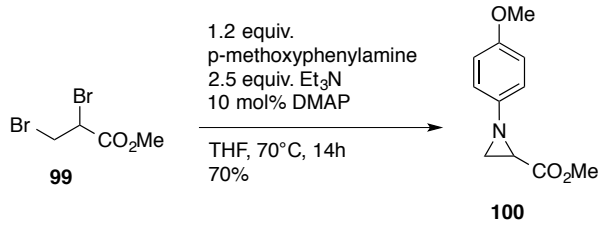
99

To a 20 mL round bottom flask was added methyl acrylate (2.0 mL, 22 mmol, 1 equiv.) and CH_2Cl_2 5mL, the flask was sealed with a septum with a N_2 balloon attached via a needle. The resulting mixture was cooled at 0 °C in an ice bath for 5 min. To this stirring solution was added Br_2 (1.2 mL, 22 mL, 1 equiv.) dropwise via a syringe. After stirring at 0 °C for 1 h, the solution was warmed up to room temperature and successively washed with 5 mL saturated $Na_2S_2O_3$, 5 mL saturated Na_2CO_3, and 5 mL brine, and then dried over $MgSO_4$, filtered through filter paper, concentrated on rotary vaporization and the residue was subjected to flash silica gel chromatography, a 10:1 mixture of hexane:EtOAc as the eluent, to

afford the product **99** (5.09 g, 20.5 mmol, 93%) as a colorless oil.

Spectra data for **99**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.85 (s, 3H), 3.94 (dd, *J* = 11.5, 10.0 Hz, 1H), 4.46 (dd, *J* = 11.5, 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.61, 40.71, 53.40, 168.04. These NMR data are in agreement with the literature data.[92]

Methyl-1-(4-methoxyphenyl)aziridine-2-carboxylate (100)

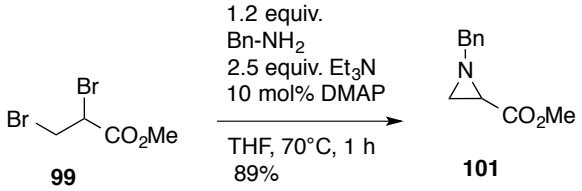


To a 50 mL round bottom flask was added the dibromo ester **99** (2.02 g, 8.13 mmol, 1 equiv.) and 30 mL THF, to this stirring solution was added a solution of Et_3N (2.81 mL, 20.3 mmol, 2.5 equiv.), p-methoxyphenylamine (1.20 g, 9.76 mmol, 1.2 equiv.) and 4-DMAP (0.099 g, 0.81 mmol, 10 mol%) in 10 mL THF. The flask was equipped with a water condenser and heated to 70 °C for 14 h. The flask was then cooled to room temperature, the solids were filtered off through a filter paper, and the filter cake was washed with ethyl ether (10 mL x 2). The filtrate was concentrated on rotary vaporization and the residue was subjected to flash silica gel chromatography, a 8:1 to 4:1 mixture of hexane:EtOAc as the eluent, to afford the product **100** (1.17 g, 5.69 mmol, 70%) as a yellow oil.

Spectra data for **100**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (dd, *J* = 6.0, 1.0 Hz,

1H), 2.63 (dd, *J* = 3.5, 1.0 Hz, 1H), 2.73 (dd, *J* = 6.0, 3.5 Hz, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.06, 37.76, 52.47, 55.48, 114.27, 121.40, 145.68, 155.71, 170.64. These ^{1}H NMR data are in agreement with the literature data.[93]

methyl 1-benzylaziridine-2-carboxylate (101)

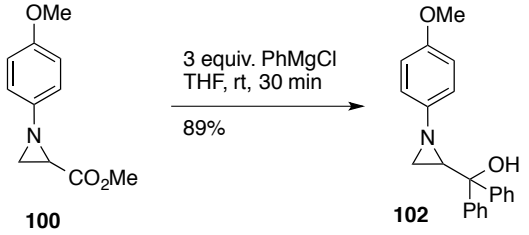


99 **101**

The procedure to synthesize **101** is identical to the synthesis of **100** above except benzyl amine was used and reaction was complete at 1 h. The reaction afforded **101** (1.01 g, 5.79 mmol, 89%) as a light yellow oil.

Spectra data for **101**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (dd, *J* = 6.5, 1.0 Hz, 1H), 2.21 (dd, *J* = 6.5, 3.5 Hz, 1H), 2.27 (dd, *J* = 3.5, 1.0 Hz, 1H), 3.55 (d, *J* = 4.5 Hz, 2H), 3.72 (s, 3H), 7.26-7.29 (m, 1H), 7.33-7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.57, 37.34, 52.25, 63.91, 127.36, 128.06, 128.44, 137.67, 171.17. These ^{1}H NMR data are in agreement with the literature data.[94]

(1-(4-methoxyphenyl)aziridin-2-yl)diphenylmethanol (102)



100 **102**

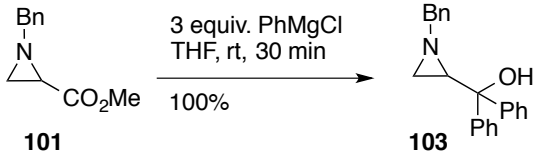
To a flame-dried 20 mL round bottom flask was added the aziridine ester **100** (0.30 g, 1.45 mmol, 1 equiv.) and 10 mL THF. The flask was sealed with a septum with a N_2 balloon attached via a needle. To this stirring solution was added PhMgCl (2M in THF, 2.2 mL, 4.4 mmol, 3 equiv.) dropwise. The resulting solution was stirred at room temperature for 30 min and then quenched with saturated NH_4Cl solution 10 mL. The aqueous phase was extracted with ethyl ether (10 mL x 2), and the combined organic phase was washed with brine 10 mL, dried over $MgSO_4$, filtered through filter paper, concentrated on rotary vaporization and the residue was dissolved in 5 mL hot hexane, then placed in the freezer for 30 min, the solid collected from the solution was washed with hexane until the solid is white. The reaction afforded the product **102** (0.45 g, 1.3 mmol, 89%) as a white solid. mp. = 112-113 °C.

A second run with (*R*)-**100** gave (*R*)-**102** (0.0850 g, 0.259 mmol, 69%) as a yellow solid. The optical purity of (*R*)-**102** was determined to be 99% ee by Chiralcel OD-H, 99:1 hexane:*i*-PrOH, 238 nm, 1 mL/min, 14.3 min for the minor enantiomer and 15.0 min for the major enantiomer.

Spectra data for (*R*)-**102**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (d, *J* = 6.5 Hz,

1H), 2.53 (d, *J* = 3.5 Hz, 1H), 2.98 (dd, *J* = 6.5, 3.5 Hz, 1H), 3.72 (s, 3H), 3.79 (s, 1H), 6.52 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 7.29 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.33 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.16, 47.84, 55.50, 74.31, 114.20, 121.22, 125.96, 126.62, 127.10, 127.45, 128.28, 128.34, 144.15, 146.09, 147.35, 155.45. IR (thin film) 3427 br m, 2928 m, 1508 s, 1448 m, 1242 s, 1033 m cm^{-1}; HRMS (ESI-TOF) calcd 332.1651 for $C_{22}H_{22}NO_2$ m/z $(M+H)^+$, found . $[\alpha]_D^{20}$= +57.5° (*c* 1.0, CH_2Cl_2) on 99% ee.

(1-benzylaziridin-2-yl)diphenylmethanol (103)



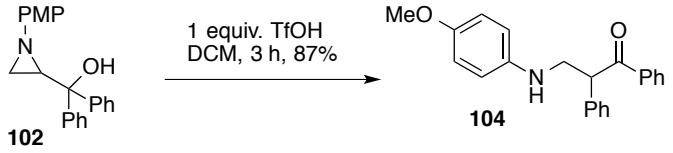
101 **103**

The procedure to synthesize **103** is identical to the synthesis of **102** above except the starting material is **101**. The reaction afforded **103** (0.49 g, 1.6 mmol, 100%) as a white solid. mp. = 101-102 °C.

Spectra data for **103**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (d, *J* = 6.5 Hz, 1H), 2.05 (d, *J* = 3.5 Hz, 1H), 2.57 (dd, *J* = 6.5, 3.5 Hz, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 13.5 Hz, 1H), 3.87 (s, 1H), 7.20-7.30 (m, 8H), 7.32-7.37 (m, 4H), 7.44 (dt, *J* = 8.0, 1.5 Hz, 2H), 1 aromatic proton was not located; ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.54, 46.13, 63.05, 74.13, 125.80, 126.32, 126.34, 126.82, 127.04, 127.24, 128.04, 128.16, 128.35, 138.32, 144.93, 147.51. These NMR data are in

partial agreement with the literature data.[95]

3-((4-methoxyphenyl)amino)-1,2-diphenylpropan-1-one (104)



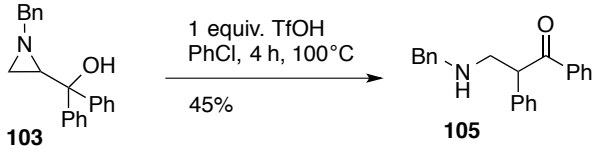
To a flame-dried 10 mL round bottom flask was added aziridinol **102** (0.0331 g, 0.100 mmol, 1 equiv.) and 0.3 mL CH_2Cl_2. The flask was sealed with a septum with a N_2 balloon attached via a needle. To this stirring solution was slowly added TfOH (9.24 µL, 0.105 mmol, 1.05 equiv.). The resulting orange color solution was allowed to stir at room temperature for 3 h (due to volatility of CH_2Cl_2, 0.1 mL CH_2Cl_2 was added to the reaction mixture every 1 h). The reaction was quenched with 1 drop of Et_3N. The solvent was removed on rotary vaporization and the residue was subjected to silica gel chromatography, a 8:1 mixture of hexane:EtOAc as the eluent, to afford the product **104** (0.0287 g, 0.0879 mmol, 87%) as a yellow oil.

A second run with 99% ee (*R*)-**102** gave (*S*)-**104** (0.0310 g, 0.0941 mmol, 94%) as a yellow oil. The optical purity of (*S*)-**104** was determined to be 96% ee by Chiralcel OD-H, 97:3 hexane:*i*-PrOH, 245 nm, 1 mL/min, 12.8 min for the minor enantiomer and 15.8 min for the major enantiomer.

Spectra data for (*S*)-**104**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (dd, *J* = 13.5, 6.0 Hz, 1H), 3.73 (br s, 1H), 3.76 (s, 3H), 3.95 (dd, *J* = 13.5, 8.0 Hz, 1H), 4.91 (dd, *J* =

8.0, 6.0 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 7.26 (tt, *J* = 7.0, 2.0 Hz, 1H), 7.30-7.33 (m, 3H), 7.36 (t, *J* = 8.0 Hz, 3H), 7.47 (tt, *J* = 7.0, 1.0 Hz, 1H), 7.91 (dt, *J* = 7.0, 1.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.15, 52.95, 55.77, 114.57, 115.00, 127.55, 128.24, 128.53, 128.79, 129.27, 133.10, 136.39, 137.45, 141.54, 152.27, 199.20. IR (neat) 3399 br m, 2928 m, 1676 s, 1514 s, 1236 s, 1037 m cm^{-1}; HRMS (ESI-TOF) calcd 332.1651 for $C_{22}H_{22}NO_2$ m/z $(M+H)^+$, found . $[\alpha]_D^{20}$= –110.2°(*c* 1.0, CH_2Cl_2) on 96% ee.

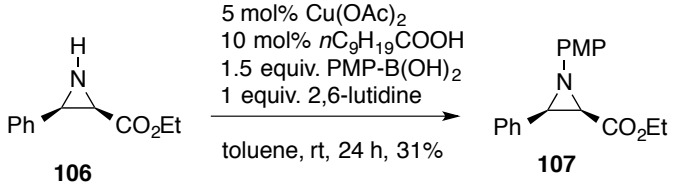
3-(benzylamino)-1,2-diphenylpropan-1-one (105)



The synthesis procedure for **105** is similar to that of **104** above, except **103** was the starting material, solvent was PhCl and heated to 100 °C for 4 h with a water condenser. The reaction did not proceed at a lower temperature, i. e. 70 °C for 1 h. The reaction afforded **105** (0.0138 g, 0.0438 mmol, 45%) as a yellow oil.

Spectra data for **105**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (br s, 1H), 2.97 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.45 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.79 (d, *J* = 13.5 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 4.85 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.20-7.32 (m, 10H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.82, 54.04, 54.41, 126.93, 127.37, 128.04, 128.28, 128.40, 128.49, 128.78, 129.09, 133.00, 136.50, 137.79, 140.06, 199.30

ethyl (2*R*,3*R*)-1-(4-methoxyphenyl)-3-phenylaziridine-2-carboxylate (107)



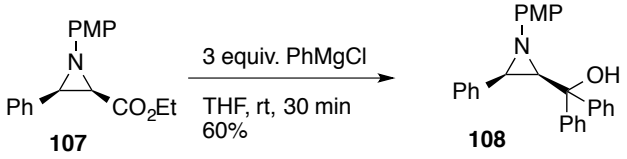
PMP = p-methoxylphenyl

Compound **106** was synthesized according to a literature procedure. This reaction procedure is the same to the literature.[68] To a 20 mL flame-dried round bottom flask was added copper (II) acetate (0.0094 g, 0.052 mmol, 5 mol%), *n*-$C_9H_{18}COOH$ (0.0172 g, 0.100 mmol, 10 mol%), 4-methoxyphenylboronic acid (0.22 g, 1.4 mmol, 1.5 equiv.) and toluene 2 mL. The resulting suspension was stirred slowly and 2,6-lutidine (0.11 mL, 0.95 mmol, 1 equiv.) was added via a syringe. After a few minutes, NH aziridine 106 (0.18 g, 0.95 mmol, 1 equiv.) was added and the resulting mixture was stirred vigorously at room temperature under air for 24 h. The reaction mixture was then diluted with 10 mL hexane, and the solids are filtered off through a filter paper. The filtrate was concentrated on rotary vaporization and the residue was subjected to silica gel chromatography, a 10:1 mixture of hexane:EtOAc as the eluent, to afford the product **107** (0.0862 g, 0.294 mmol, 31%) as a yellow oil.

Spectra data for **107**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.5 Hz, 3H), 3.15 (d, *J* = 7.0 Hz, 1H), 3.53 (d, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.99 (dq, *J* = 9.5, 7.0 Hz, 1H), 4.07 (dq, *J* = 9.5, 7.0 Hz, 1H), 6.82 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.00 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.30 (tt, *J* = 7.0, 1.5 Hz, 1H), 7.35 (tt, *J* = 7.0. 1.5 Hz, 2H),

7.51 (dt, *J* = 7.0, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.94, 45.83, 47.46, 55.51, 61.00, 114.41, 120.81, 127.68, 127.82, 128.07, 134.73, 145.73, 155.83, 167.82. These NMR data are in partial agreement with the literature data. [93]

((2*R*,3*R*)-1-(4-methoxyphenyl)-3-phenylaziridin-2-yl)diphenylmethanol (108)

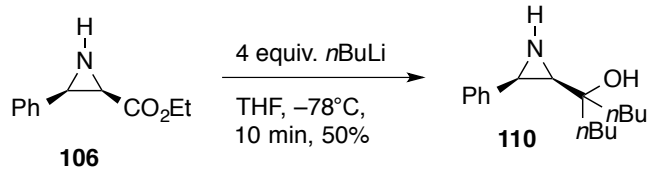


107 **108**

The synthesis procedure of **108** is identical to **102** except it was purified with silica gel column, a 2:1 to 1:1 mixture of hexane:CH_2Cl_2 as the eluent. The reaction gave **108** (0.10 g, 0.27 mmol, 60%) as a white solid product. mp. = 155-156 °C.

Spectra data for **108**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 1H), 3.34 (d, *J* = 6.0 Hz, 1H), 3.56 (d, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 6.59 (dt, *J* = 9.0, 2.0 Hz, 2H), 6.69 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.17-7.21 (m, 5H), 7.24-7.31 (m, 4H), 7.38 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.45 (dt, *J* = 7.0, 1.5 Hz, 2H), 7.53 (dt, *J* = 7.0, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.79, 54.84, 55.54, 75.04, 114.30, 120.64, 125.64, 126.24, 126.97, 127.00, 127.03, 127.53, 127.87, 128.02, 128.32, 135.75, 144.33, 146.64, 147.99, 155.67.

5-((2*R*,3*R*)-3-phenylaziridin-2-yl)nonan-5-ol (110)

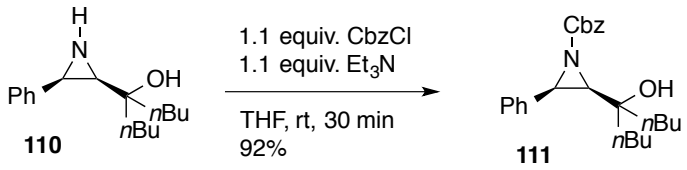


To a flame-dried 10 mL round bottom flask was added 0.5 mL THF and *n*-BuLi (2M in hexane, 0.60 mL, 1.2 mmol, 4 equiv.). The flask was sealed with a septum with a N_2 balloon attached via a needle. The flask was cooled to –78 °C in a dry ice acetone bath for 5 min. The a solution of NH aziridine **106** (0.0620 g, 0.321 mmol, 1 equiv.) in 0.5 mL THF was added to the flask dropwise via a syringe. The resulting mixture was stirred at the same temperature for 10 min and then quenched with saturated NH_4Cl solution. The aqueous phase was extracted with diethyl ether (10 mL x 2), washed with brine and dried over $MgSO_4$. the solids are filtered off through a filter paper. The filtrate was concentrated on rotary vaporization and the residue was subjected to silica gel chromatography, a 10:1 mixture of hexane:EtOAc as the eluent, to afford the product **110** (0.0418 g, 0.160 mmol, 50%) as a white solid. mp. = 101-102 °C.

Spectra data for **110**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H), 1.21-1.41 (m, 11H), 1.50-1.53 (m, 2H), 2.12 (br s, 1H), 2.35 (d, *J* = 6.5 Hz, 1H), 3.29 (d, *J* = 6.5 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.03, 14.18, 23.32, 23.34, 25.30, 25.92, 36.81, 36.87, 40.60, 43.28, 71.85, 126.71, 127.69,

128.00, 137.25.

Benzyl (2*R*,3*R*)-2-(5-hydroxynonan-5-yl)-3-phenylaziridine-1-carboxylate (111)

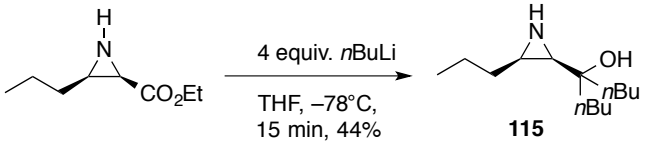


To a 20 mL screw cap vial was added NH aziridine **110** (0.0400 g, 0.152 mmol, 1 equiv.), THF 1 mL and Et_3N (0.025 mL, 0.18 mmol, 1.2 equiv.), while stirring, CbzCl (0.025 mL, 0.18 mmol, 1.2 equiv.) was added dropwise to the solution. The vial was capped and the resulting mixture was stirred at room temperature for 30 min. The solids are filtered off through a filter paper. The filter cake was thoroughly washed with diethyl ether. The filtrate was concentrated on rotary vaporization and the residue was subjected to silica gel chromatography, a 15:1 mixture of hexane:EtOAc as the eluent, to afford the product **111** (0.0559 g, 0.141 mmol, 92%) as a white solid. mp. = 80-82 °C.

Spectra data for **111**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85-0.89 (m, 6H), 1.13 (s, 1H), 1.27-1.42 (m, 10H), 1.56-1.66 (m, 2H), 2.80 (d, *J* = 6.5 Hz, 1H), 3.74 (d, *J* = 6.5 Hz, 1H), 5.20 (d, *J* = 6.5 Hz, 2H), 7.26 (t, *J* = 7.0 Hz, 1H), 7.31-7.38 (m, 7H), 7.43 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.98, 14.06, 23.17, 23.25, 25.01, 25.63, 36.02, 39.35, 43.83, 50.72, 68.44, 72.82, 127.40, 127.48, 128.11,

128.28, 128.37, 128.58, 134.83, 135.59, 163.70.

5-((2*R*,3*R*)-3-propylaziridin-2-yl)nonan-5-ol (115)

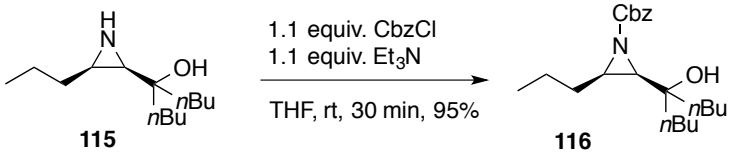


114 **115**

Compound **114** was synthesized according to a literature procedure. The synthesis procedure for **115** is identical to that of **110**. The reaction gave **115** (0.10 g, 0.44 mmol, 44%) as a light yellow solid product. mp. = 60-61 °C.

Spectra data for **115**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89-0.97 (m, 9H), 1.25-1.63 (m, 17H), 1.99-2.03 (m, 2H), 2.90 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.04, 14.08, 14.19, 21.86, 23.38, 23.49, 25.49, 25.97, 30.52, 35.20, 37.62, 40.17, 41.36, 70.59.

benzyl (2*R*,3*R*)-2-(5-hydroxynonan-5-yl)-3-propylaziridine-1-carboxylate (116)



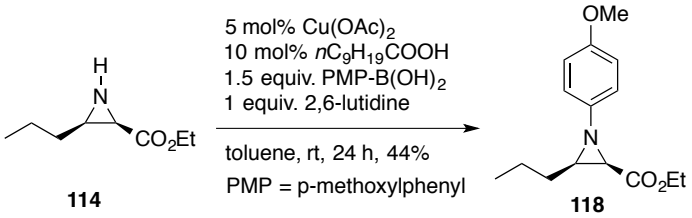
115 **116**

The synthesis procedure of **116** is identical to that of **111**. The reaction gave **116** (0.0880g, 0.243 mmol, 95%) as a white wax-like solid. mp. = 52-53 °C.

Spectra data for **116**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H),

0.92 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.0 Hz, 3H), 1.25-1.36 (m, 8H), 1.41-1.71 (m, 9H), 1.71-1.80 (m, 1H), 1.89 (s, 1H), 2.45-2.49 (m, 2H), 5.13 (s, 2H), 7.32-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.82, 14.02, 14.06, 21.48, 23.19, 23.37, 25.18, 25.71, 29.67, 35.92, 40.52, 43.65, 48.43, 68.20, 71.79, 127.94, 128.26, 128.53, 135.73, 163.99.

ethyl (2*R*,3*R*)-1-(4-methoxyphenyl)-3-propylaziridine-2-carboxylate (118)

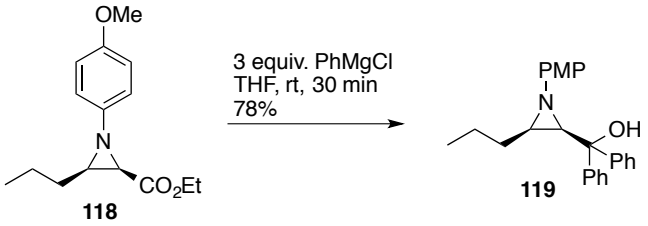


114 **118**

The synthesis procedure of **118** is identical to that of **107**. The reaction gave **118** (0.22 g, 0.84 mmol, 44%) as a yellow oil.

Spectra data for **118**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.50-1.58 (m, 1H), 1.59-1.70 (m, 2H), 1.72-1.80 (m, 1H), 2.38 (dt, *J* = 7.0, 5.0 Hz, 1H), 2.78 (d, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 4.24-4.32 (m, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.91, 14.35, 20.92, 30.18, 42.88, 46.28, 55.46, 61.20, 114.19, 120.96, 146.29, 155.51, 169.42.

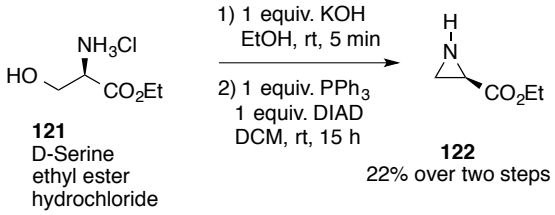
((2*R*,3*R*)-1-(4-methoxyphenyl)-3-propylaziridin-2-yl)diphenylmethanol (119)



The synthesis procedure of **119** is identical to that of **102** and **108**, except it was purified with silica gel column, a 15:1 mixture of hexane:EtOAc as the eluent. The reaction gave **119** (0.0624 g, 0.156 mmol, 78%) as a white solid product. mp. = 145-147 °C.

Spectra data for **119**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.0 Hz, 3H), 1.44-1.51 (m, 2H), 1.57-1.72 (m, 2H), 2.40-2.44 (m, 1H), 2.98 (d, *J* = 6.5 Hz, 1H), 3.72 (s, 3H), 4.31 (s, 1H), 6.51 (d, *J* = 9.0 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 7.29 (td, *J* = 7.5, 1.5 Hz, 2H), 7.35-7.39 (m, 4H), 7.53 (d, *J* = 7.0 Hz, 2H), 7.56 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.08, 21.91, 29.98, 46.41, 53.03, 55.50, 74.23, 114.18, 120.97, 125.97, 126.38, 126.80, 127.12, 128.11, 128.29, 144.82, 146.81, 149.13, 155.46.

ethyl (*R*)-aziridine-2-carboxylate (122)

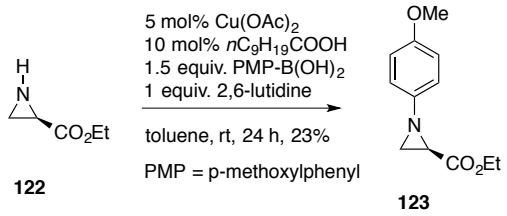


The synthesis of **122** is adapted from a literature procedure.[69] To a 10 mL round bottom flask was added D-serine ethyl ester hydrochloride **121** (1.69 g, 10.0 mmol. 1 equiv.) and 5 mL EtOH, while stirring, a solution of KOH (0.56 g, 10 mmol, 1 equiv.) in 5 mL EtOH was added dropwise and the flask was sealed with a septum with a N_2 balloon attached via a needle. The solution was allowed to stir at room temperature for 10 min. The solids were filtered through a filter paper and the filter cake was thoroughly washed with EtOH. The filtrate was concentrated on rotary vaporization. To the residue was added 10 mL CH_2Cl_2, and cooled in an ice bath for 5 min. PPh_3 (2.63 g, 10.0 mmol, 1 equiv.) was added slowly to the stirring solution in several portions. After addition of PPh_3, DIAD (2.0 mL, 10 mmol, 1 equiv.) was added dropwise via a syringe. Then the solution was allowed to warm to room temperature and stirred for 15 h. The solvent was removed on rotary vaporization. The residue was treated with a mixture of 1:1 Et_2O:hexane 20 mL, and cooled in the freezer for 30 min to precipitate the phosphine oxide. The solids were filtered through a filter paper and the filter cake was thoroughly washed with a mixture of 1:1 Et_2O:hexane. The filtrate was concentrated on rotary vaporization. The treatment with a mixture of 1:1 Et_2O:hexane was repeated until no more solid formed after the treatment. The final residue was subjected to silica gel chromatography, a mixture of 1:1 Et_2O:hexane as the eluent, to afford the product **122** (0.25 g, 2.2 mmol, 22%) as a yellow oil. The low yield was due to the high volatility of the product. A butyl ester or benzyl ester of D-Serine may improve the

yield.[69]

Spectra data for **122**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (br s, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.86 (dd, *J* = 5.5, 1.5 Hz, 1H), 2.00 (dd, *J* = 3.0, 1.5 Hz, 1H), 2.51 (dd, *J* = 5.5, 3.0 Hz, 1H), 4.17-4.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.16, 27.21, 28.94, 61.58, 172.99. These ^{1}H NMR data are in agreement with literature data.[96]

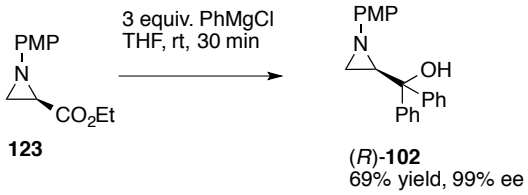
ethyl (*R*)-1-(4-methoxyphenyl)aziridine-2-carboxylate (123)



The procedure for the synthesis of **123** is identical to that of **107** and **118**. The reaction afforded **123** (0.11 g, 0.50 mmol, 23%) as a yellow oil.

Spectra data for **123**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.0 Hz, 3H), 2.26 (dd, *J* = 6.0, 1.0 Hz, 1H), 2.62 (dd, *J* = 3.0, 1.0 Hz, 1H), 2.71 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.75 (s, 3H), 4.20-4.31 (m, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.18, 34.00, 37.95, 55.47, 61.46, 114.24, 121.45, 145.72, 155.68, 170.17. These NMR data are in agreement with literature data.[97]

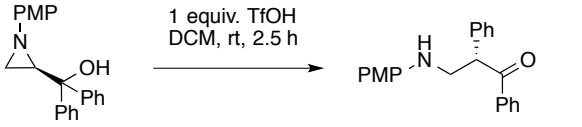
(*R*)-(1-(4-methoxyphenyl)aziridin-2-yl)diphenylmethanol (*R*-102)



The synthesis procedure of (*R*)-**102** is identical to that of **102**. The reaction gave the product (*R*)-**102** (0.0850 g, 0.256 mmol, 69%) as a white solid. mp. = 112-113 °C. The optical purity of (*R*)-**102** was determined to be 99% ee by Chiralcel OD-H, 99:1 hexane:*i*-PrOH, 238 nm, 1 mL/min, 14.3 min for the minor enantiomer and 15.0 min for the major enantiomer.

Spectra data for (*R*)-**102**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (d, *J* = 6.5 Hz, 1H), 2.53 (d, *J* = 3.5 Hz, 1H), 2.98 (dd, *J* = 6.5, 3.5 Hz, 1H), 3.72 (s, 3H), 3.79 (s, 1H), 6.52 (d, *J* = 9.0 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 2H), 7.29 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.33 (tt, *J* = 7.5, 2.0 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.16, 47.84, 55.50, 74.31, 114.20, 121.22, 125.96, 126.62, 127.10, 127.45, 128.28, 128.34, 144.15, 146.09, 147.35, 155.45. IR (thin film) 3427 br m, 2928 m, 1508 s, 1448 m, 1242 s, 1033 m cm^{-1}; HRMS (ESI-TOF) calcd 332.1651 for $C_{22}H_{22}NO_2$ m/z $(M+H)^+$, found 332.1699. $[\alpha]_D^{20}$= +57.5° (*c* 1.0, CH_2Cl_2) on 99% ee.

(*S*)-3-((4-methoxyphenyl)amino)-1,2-diphenylpropan-1-one (*S*-104)



(*R*)-**102**
69% yield, 99% ee

(*S*)-**104**
95% yield, 96% ee

The synthesis procedure of (*S*)-**104** is identical to that of **104**. To a flame-dried 10 mL round bottom flask was added aziridinol (*R*)-**102** (0.0331 g, 0.100 mmol, 1 equiv.) and 0.3 mL CH_2Cl_2. The flask was sealed with a septum with a N_2 balloon attached via a needle. To this stirring solution was slowly added TfOH (9.24 µL, 0.105 mmol, 1.05 equiv.) via a syringe. The resulting orange color solution was allowed to stir at room temperature for 2.5 h (the reaction progress was monitored with ^{1}HNMR, and due to volatility of CH_2Cl_2, 0.1 mL CH_2Cl_2 was added to the reaction mixture every 1 h). The reaction was quenched with 1 drop of Et_3N. The solvent was removed on rotary vaporization and the residue was subjected to silica gel chromatography, a 8:1 mixture of hexane:EtOAc as the eluent, to afford the product (*S*)-**104** (0.0310 g, 0.0941 mmol, 94%) as a yellow oil. The optical purity of (*S*)-**104** was determined to be 96% ee by Chiralcel OD-H, 97:3 hexane:*i*-PrOH, 245 nm, 1 mL/min, 12.8 min for the minor enantiomer and 15.8 min for the major enantiomer.

Spectra data for (*S*)-**104**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (dd, *J* = 13.5, 6.0 Hz, 1H), 3.73 (br s, 1H), 3.76 (s, 3H), 3.95 (dd, *J* = 13.5, 8.0 Hz, 1H), 4.91 (dd, *J* = 8.0, 6.0 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H),

7.26 (tt, *J* = 7.0, 2.0 Hz, 1H), 7.30-7.33 (m, 3H), 7.36 (t, *J* = 8.0 Hz, 3H), 7.47 (tt, *J* = 7.0, 1.0 Hz, 1H), 7.91 (dt, *J* = 7.0, 1.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.15, 52.95, 55.77, 114.57, 115.00, 127.55, 128.24, 128.53, 128.79, 129.27, 133.10, 136.39, 137.45, 141.54, 152.27, 199.20. IR (neat) 3399 br m, 2928 m, 1676 s, 1514 s, 1236 s, 1037 m cm^{-1}; HRMS (ESI-TOF) calcd 332.1651 for $C_{22}H_{22}NO_2$ m/z $(M+H)^+$, found 332.1521. $[\alpha]_D^{20}$= –110.2°(*c* 1.0, CH_2Cl_2) on 96% ee.

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