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ASYMMETRIC SYNTHESIS WITH VAPOL DERIVATIVES
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ASYMMETRIC SYNTHESIS WITH VAPOL DERIVATIVES AND NOVEL CHIRAL THIOUREA ORGANOCATALYSTS

By

Konstantinos Rampalakos

A DISSERTATION

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

2008

ABSTRACT

ASYMMETRIC SYNTHESIS WITH VAPOL DERIVATIVES AND NOVEL CHIRAL THIOUREA ORGANOCATALYSTS

By

Konstantinos Rampalakos

This thesis describes the investigation of the catalytic asymmetric imino-aldol reaction using VAPOL-derived catalysts, and the development of novel chiral thiourea catalysts for asymmetric transformations, specifically for the aza-Henry reaction and for the Michael-type addition of nitroalkanes to nitroolefins.

Concerning the first project (Chapters 1 and 2), a derivative of the VAPOL ligand, 7,7'-dimethylVAPOL, was synthesized according to the method developed in our laboratories for vaulted biaryls based on the Snieckus phenol synthesis. The new ligand was designed based on CPK models for the suspected intermediates of the iminoaldol reaction between imines with ketene silyl acetals catalyzed by a Zr-VAPOL catalyst. Attempts to try the new ligand in reactions where VAPOL wasn't very efficient afforded a significant improvement on the enantioselectivities. These results not only demonstrate the efficiency of the new ligand but also confirm the model that we proposed for the reaction.

The rest of the Thesis, and the major amount of work described in this disertation, concerns the design, synthesis and application of novel chiral thiourea catalysts for asymmetric synthesis. Concerning the aza-Henry reaction (Chapters 3 and 4) we evaluated new potential catalysts with two thiourea moieties for simultaneous activation of both reaction components via H-bonding. We identified a new promising catalyst based on BINAM as chiral schaffold. Optimization of the reaction conditions for the aza-Henry reaction led to the development of an efficient protocol for the reaction of N-Boc imines

with nitroalkanes. The yields for a variety of substituted imines were modest to good, and the asymmetric inductions were high. To account for the enantioselective reaction of N-Boc imines with nitroalkanes we proposed an intermediate where one thiourea moiety of the catalyst is bound to the imine while the other one is hydrogen bonding to nitromethane.

Chapter 5 describes the application of another novel thiourea catalyst to the addition of nitroalkanes to nitroolefins. First, the unasymmetric addition was studied with simple achiral aromatic thioureas as promoters. As a result, we developed the first efficient protocol for diastereoselective synthesis of unasymmetric syn 1,3-dinitro compounds. Subsequently, the asymmetric variant of the reaction was investigated. A novel thiourea/DMAP bifunctional catalyst was made, based again on binaphthyl diamine. The conjugate addition using this catalyst followed a unique selectivity trend according to which, the less catalyst used, the higher the enantioselectivity of the reaction. Investigation of this trend with a series of studies showed that the nitroalkane/catalyst ratio is the determining factor for the selectivities. Optimization of the reaction conditions led to the first highly efficient protocol for the organocatalytic direct conjugate addition of nitroalkanes to nitroolefines with only 2% catalyst loading and ee's in the mid-90's for a range of electron deficient and rich nitrostyrenes.

Finally, the last chapter (Chapter 6) discusses some efforts towards the synthesis of new biaryl-based thiourea catalysts using vaulted biaryls as schaffolds, in an effort to extend the scope and applicability of the thiourea catalysts that were described in the previous chapters.

ACKNOWLEDGMENTS

I would like to thank Prof. Wulff for being a great advisor. His broad knowledge and his valuable advice helped a lot in carrying out the reaserch presented herein.

It was very exciting to have Prof. Borhan around too. He is a very fun guy and has provided a lot of help and support (despite the centuries-old Greek-Persian conflict).

I was lucky to meet great people in the group all these years. Manish Rawat and Billy Mitchell were gret labmates who didn't only gave valuable help in the beginning, but also made life in the lab very amusing. The same is true for Glenn Phillips as well, and for Zhengsheng Ding. Ding is probably one the funniest guys I've met, and also a very good friend. Aman, Victor, Alex, and other people created nice atmosphere to work in.

I am also greatfull to my friends outside the lab; Kyoungsoo, Ninneta, Chryssoula, Justas and Kit have been my dearest friends during the last five years, and I will miss their great friendship.

Finally, I am greatfull to my family and my beloved fiancée for their love and continous support.

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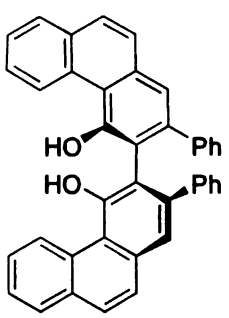
CHAPTER 1

THE CATALYTIC ASYMMETRIC IMINO ALDOL REACTION USING VAPOL-DERIVED CATALYSTS

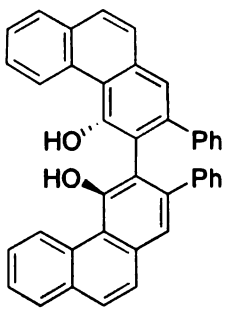
1.1 INTRODUCTION

The development of stereoselective transformations for the creation of functionalized optically active molecules is one of the ultimate goals in chemistry, and hence the design of highly efficient catalytic asymmetric reactions has been a major focus of organic synthesis during the last years.[1] Consequently, the design and synthesis of new effective ligands has been a great challenge in this field. The C_2-symmetric vaulted biaryl ligand VAPOL[2] (2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol, Figure 1) developed in our laboratories has proven to be an excellent ligand for various important catalytic asymmetric reactions, such as Diels Alder reactions[3], aziridination reactions[4] and imino aldol reactions[5].

Figure 1. The VAPOL chiral ligand



(S)-1 VAPOL

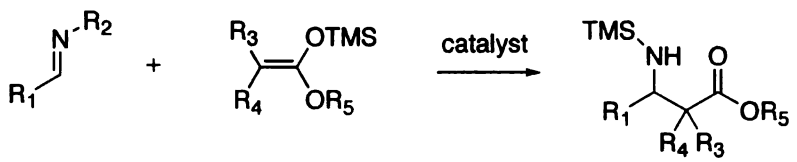


(R)-1 VAPOL

The catalytic asymmetric imino aldol rection[6] (Figure 2) is one of the most important carbon-carbon-bond forming reactions since it provides access to chiral β-amino ketones or esters, which are versatile chiral building blocks for the synthesis of many nitrogen containing biologically important compounds including β-amino acids and lactams.[7] In 1997 Kobayashi reported the first asymmetric Manich type reaction between an aldimine and a ketene silyl acetal using substoichiometric amounts of a Zr-BINOL species as catalyst.[8] Their method involves a catalyst generated from zirconium(IV) tert-butoxide and two equivalents of (R)-6,6'-dibromo BINOL (BINOL=1,1'-binaphth-2-ol).

In 2001 we developed an unusually robust Zr-VAPOL catalyst[5] that could provide even higher selectivities, and and which retained its selectivity over a range of temperatures from 25 to 100°C, resulting in one of the most efficient protocols for the name reaction to date.

Figure 2. Iminoaldol reaction between an imine and a ketene silyl acetal

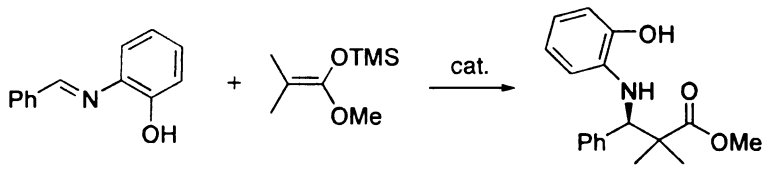


1.2 THE IMINO ALDOL REACTION USING Zr-VAPOL CATALYST

Our interest in the synthesis of chiral amines led us to investigate the use of VAPOL-derived catalysts[2] (see Figure 1) for this reaction. The catalyst was prepared by reaction of the ligand with 0.5 eq of zirconium tetraalkoxide in the presence of 0.6 eq of N-methyl imidazole at room temperature for one hour. It was found that VAPOL and 6,6'-

dibromo BINOL are superior to BINOL at –45°C[5]. When the reaction was performed at room temperature, the asymmetric induction for VAPOL remained unchanged, while that for dibromo BINOL and BINOL decreased (Table 1).

Table 1. Reactions of Imine **2** with ketene acetal **3a** using various catalysts



2 **3a** **4**

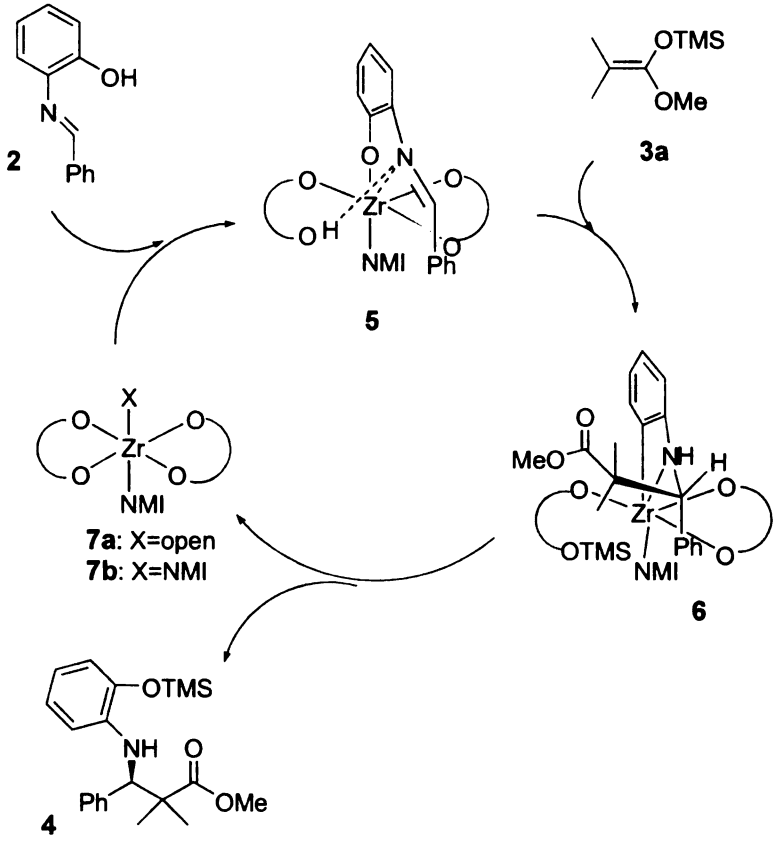
entry	ligand	mol% cat	T(°C)	t(h)	solvent	yield%	ee%
1	S-VAPOL	20	-45	20	toluene	92	91
2	S-VAPOL	20	25	15	toluene	94	89
3	R-BINOL	20	-45	19	DCM	80	36
4	R-BINOL	20	25	4	DCM	100	28
5	R-6,6'-Br_2-BINOL	10	-45	19	DCM	87	86
6	R-6,6'-Br_2-BINOL	10	25	4	DCM	87	48

Catalyst prepared from $Zr(OiPr)_4$/*i*-PrOH, chiral ligand (2.2 eq) and 1.1 eq of N-methyl imidazole (NMI) in DCM or toluene at 25°C for 1 h. Reactions were performed with 1.2 eq of ketene acetal and 0.125M in imine. (entry 2: 0.5M in imine)

The mechanism we proposed for the catalytic cycle involves a catalyst bearing two VAPOL ligands on one zirconium and the coordination of the *o*-hydroxyphenylimine to the zirconium as a bidentate ligand[8]. It is clear from the examination of spacefilling CPK models that it is possible to bind two VAPOL ligands to one zirconium atom only with a

facial arrangement of the four oxygen atoms as is illustratred by structure **7a** in Scheme 1. This is supported by ^{1}H-NMR experiments on a catalyst generated from zirconium tetraisopropoxide and VAPOL in the presence of two equivalents of N-methyl imidiazole. A clean spectrum is only observed with two equivalents of VAPOL relative to zirconium and the spectrum is consistent with a single C2-symmetrical species which is tentatively identified as structure **7b** bearing mutually *trans* NMI ligands bound to the zirconium.[9,10] An approach of imine **2** to the open apical position in intermediate **7a** is proposed to lead to intermediate **5** in which a phenol exchange has occurred.

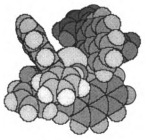
Scheme 1. Proposed Mechanism for the Imino Aldol Reaction Using Zr-VAPOL catalyst



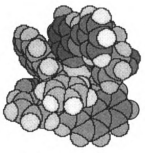
Reaction of species **5** with the ketene acetal would give intermediate **6** and then release of the product would regenerate the unsaturated species **7a** and complete the cycle.

A space-filling CPK model of intermediate **7a** is shown in Figure 3 and illustrates the binding cleft that is available for docking with imine **2**. When imine **2** is bound to zirconium un the cleft, CPK models reveal that there is some freedom of movement up and down in the cleft. The figure depicts the imine rotated up and out of the cleft as far as possible. This conformation should lead to reduced selectivity. The model in Figure 3 predicts that the *re*-face will be the more shielded face of the imine and this is consistent with our observations. The CPK model indicates that imine **8** with a methyl group *ortho* to the phenol function should be sufficient to push the imine down into the cleft, thus increasing the selectivity of the reaction.

Figure 3. CPK models of Intermediate **7a** and of two imines complexed with it

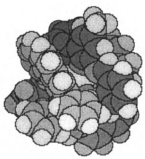


Intermediate **7a**

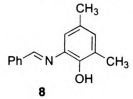


Intermediate **7a** with

2



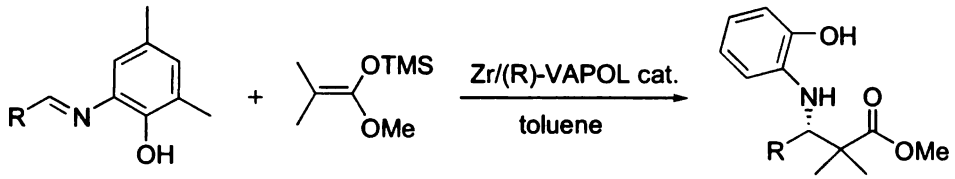
Intermediate **7a** with



8

Indeed, when the *ortho* position was methylated there was a profound increase in the asymmetric induction.[5] The rate of the reaction of imines with ketene acetals with the VAPOL catalyst is slower with imines generated from substituted aminophenols, however, as indicated in Table 2, this effect can be offset by performing the reaction at a higher temperature where greater turnover numbers are observed. The induction with imine **8a** (R=phenyl) shows absolutely no temperature dependence over the range of 25 to 100°C.

Table 2. Temperature dependence of the asymmetric induction in **10**



8 **3a** **10**

entry	R	mol% cat.	T(C°)	yield%	ee%
1	Ph	20	25	100	98
2	Ph	20	65	93	98
3	Ph	20	85	94	98
4	Ph	20	100	91	98
5	Ph	2	100	95	98
6	4-Cl-Ph	2	100	90	95
7	4-MeO-Ph	2	100	85	>99
8	3,4-$(MeO)_2$	2	100	85	96
9	1-Naphthyl	2	100	83	93

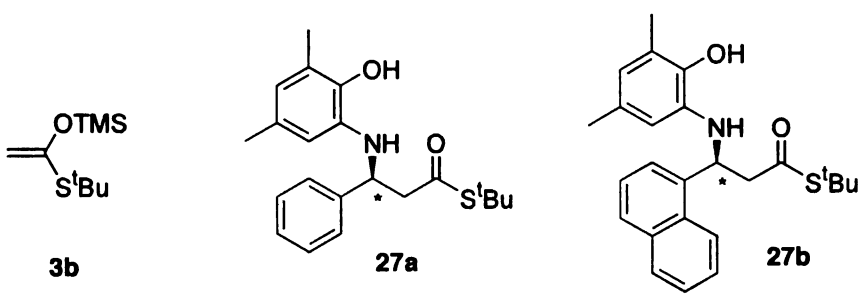
Reaction time: 2-3 h. (Entry 1: Reaction time 15 h, entry 5: 5h, entries 6, 7, 8, 9: reaction time 24h)

Furthermore, the reaction at 100°C can be performed with an order of magnitude change in catalyst loading with no loss in induction. The electronic nature of the imine has a small effect on the induction at this temperature with a slight increase noted for a p-methoxy substituent and a slight decrease for a p-chloro substituent.

1.3 CAN A MODIFICATION ON THE CATALYST STRUCTURE EXPAND THE SCOPE OF THE IMINO ALDOL REACTION AND PROBE ITS MECHANISM?

For imine **2**, that bears the non-substituted arene ring, selectivities are lower than for imines **8**. Additionally, the corresponding reactions with the unsubstituted ketene acetal **3b** derived from t-butyl thioacetate (Figure 4) mediated by the same catalyst are slower and do not display the same temperature independence[5]. For example, it was reported that the reaction of imine **8** when R=1-naphthyl with **3b** gives **27b** in 91% enantiomeric excess at 25°C (20 mol% catalyst) and in 76% enantiomeric excess at 100°C (5 mol% catalyst). Similarly, the reaction of imine **8** when R=Ph with **3a** gives **27a** in 71% ee at 25°C (20 mol% catalyst) and 60% ee at 100°C (2 mol% catalyst).[5]

Figure 4. Structure of ketene acetal **3b** and products **27a**, **27b**.

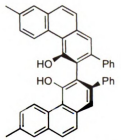


3b **27a** **27b**

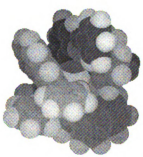
To improve the selectivities of these reactions, a slight modification on the catalyst structure was envisaged. As it was described aboved (Figure 3), the source of selectivity is the shielding of the re-face of the imine by the phenanthrene unit of the ligand, so that the *si*-face is exposed for attack by the ketene silyl acetal. This model predicts that any modification that would make the phenanthrene unit bulkier would result in more efficient shelding and thus in higher selectivities. Accordingly, a methyl group on the 7 position of the phenanthrene skeleton would increase the size of the phenanthrene unit and serve to test this model. Figure 5 shows the space-filling CPK model of the complexes between the

imines **2** and **8** and the 7,7'-dimethylVAPOL (**11**) catalyst. The CPK model suggests that there is a significant increase in the steric shielding provided by the phenenthrol of 7,7'-dimethylVAPOL (7-methyl shown in black-red color) compared to that of VAPOL for both imines **2** and **8**, and that such a derivative of VAPOL would be expected to increase the selectivities for the above transformations.

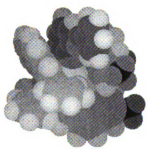
Figure 5. CPK models of complexes of VAPOL and 7,7'-dimethyl VAPOL derived catalysts with imines **2** and **8**



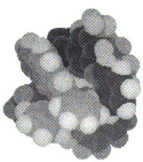
11 (S)-7,7'-dimethyl VAPOL



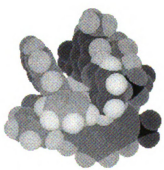
Intermediate **7a** with imine **2**



dimethylVAPOL catalyst with imine **2**



Intermediate **7a** with imine **8**



dimethylVAPOL catalyst with imine **8**

The next chapter details the synthesis of 7,7'-dimethylVAPOL **11** and its evaluation in the asymmetric imino aldol reaction. Specifically, a comparison between VAPOL and 7,7'-dimethylVAPOL is described for the reactions between imine **2** and acetal **3a**, and between imines **8** and a ketene acetal **3b** derived from t-butyl thioacetate. The ultimate purpose of this project is on one hand the expansion of the scope and synthetic utility of these reactions and on the other hand the justification of our model and the proposed mechanism for the reaction.

CHAPTER 2

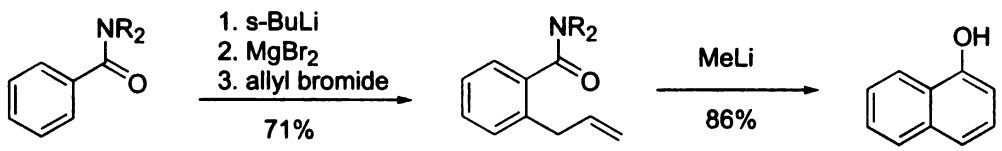
SYNTHESIS OF (S)-7,7'-DIMETHYL VAPOL AND EVALUATION OF THE LIGAND IN THE IMINO ALDOL REACTION

2.1 SYNTHESIS OF (S)-7,7'-DIMETHYL VAPOL

2.1.1 Synthesis of 6-methyl-2-phenyl-phenanthrol

In 1986, Snieckus and his coworkers reported that *o*-allylbenzamides undewent MeLi induced cyclization to give 1-naphthols[11]. *o*-Allylbenzamides were prepared by the directed *ortho*-metallation of tertiary benzamides followed by the reactions with allyl bromide[12] (Scheme 2). This chemistry has subsequently been used to prepare various substituted naphthols[13].

Scheme 2. Synthesis of naphthols through annelation of *o*-allyl benzamides



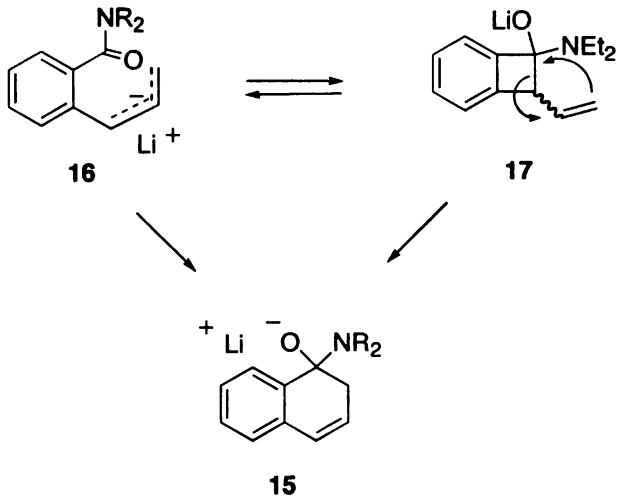
12 **13** **14**

The precursor **13** of the annelation product was synthesized using the extensively reported directed *ortho* metallation methodology developed by Snieckus' group. According to that method – which is focused on tertiary amides as effective *ortho* metallation directors[14] – lithiation of aromatic benzamide **12** is directed *ortho* to the amide group and subsequent reaction with $MgBr_2$ affords an arylmagnesium bromide species as the transmetallation reaction product. The lithium to magnesium transmetallation in the

first step of the sequence is necessary for the successful *ortho* allylation, since the lithiated species failed to give the *ortho* substituted product[12].

A mechanistic rational for the transformation is illustrated in Scheme 3. Formation of the naphthol **14** may occur via intermediate **15** by two pathways. The first involves direct cyclization from anion **16**, while the second involves formation of benzocyclobutane **17** followed by a [1,3]-sigmatropic rearrangement[11].

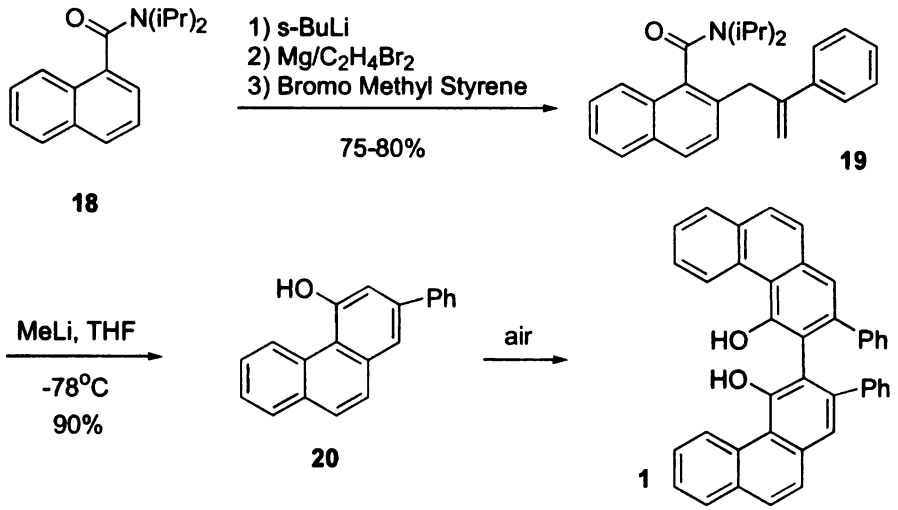
Scheme 3. A tentative mechanistic rationalization for the anionic benzannelation.



A few years ago, Dr Su Yu from our group developed a new strategy for the synthesis of VAPOL that was inspired by the Snieckus' naphthol synthesis. The synthesis of 2-phenyl-4-phenanthrol **20** (the precursor to VAPOL) was realized from a MeLi induced cyclization of diisopropyl 6-methyl-2-(2-phenylallyl)naphthamide **19**, which was obtained by a directed *o*-allylation of 1-naphthamide **18** (Scheme 4). This unprecedented synthesis of a 4-phenanthrol using the Snieckus method established a new efficient method for the synthesis of vaulted biphenanthrols.

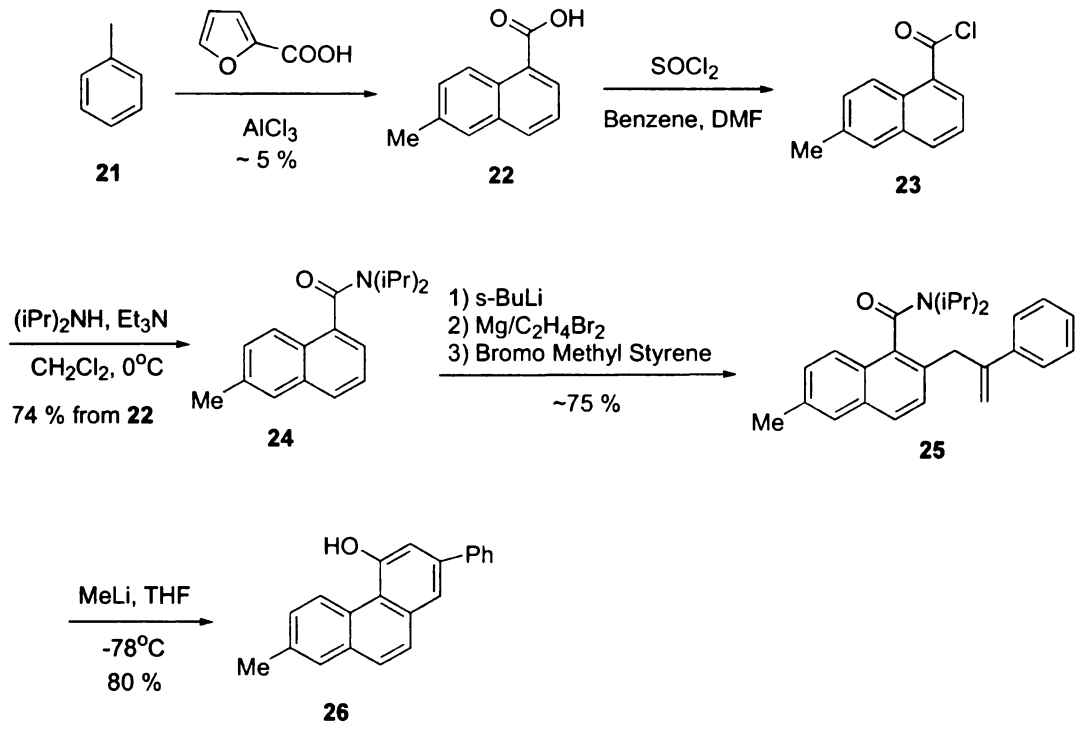
The method Dr. Yu developed has a few modifications from Snieckus' original protocol. For the synthesis of naphthols, Snieckus used diethyl-benzamide, TMEDA as an additive, and commercially available $MgBr_2$. Dr Su Yu found that, for the synthesis of the 4-phenanthrol **20**, diisopropyl naphthamide works better than diethyl naphthamide, TMEDA is not necessary, and $MgBr_2$ has to be prepared in situ in order for the transformation to be most efficient. The in situ preparation of $MgBr_2$ can be achieved by reacting Mg turnings with 1,2-dibromoethane in Et_2O. In this way higher and more reproducible yields of compound **19** can be obtained.

Scheme 4. The synthesis of VAPOL using an anionic benzannelation as a key step



Su Yu's method for the synthesis of 2-phenyl-4-phenanthrol **20** was applied to the synthesis of 7-Methyl-2-phenyl-4-phenanthrol **26**, the precursor to 7,7'-dimethyl VAPOL. The synthesis of this new phenanthrol is outlined below (Scheme 5).

Scheme 5. The Synthesis of 7-methyl-2-phenyl-4-phenanthrol **26**



The first step involves a formal Diels Alder reaction between toluene and furoic acid to furnish 6-methylnaphthoic acid **22**. The product was obtained in ~5% yield. The majority of the mass balance for this reaction (as was described in the original protocol by Price et al.) is a mixture of high molecular weight acids of complex structure, formed by the condensation of two or three molecules of toluene with one of furoic acid[15]. The larger acids could be separated by extraction of the reaction mixture with aqueous sodium bicarbonate (the high molecular weigh acids could not be extracted with this method). The 6-methylnaphthoic acid was obtained from the resulting mixture with barium hydroxide, since the barium naphthoate of **22** (and furoate) dissolved in hot water while the high

molecular weigh acids formed an insoluble barium salt. Finally, after crystallization from ethyl acetate, 8 grams of quite pure product were available for the next step.

Compound **22** was then treated with 1.1 eq of $SOCl_2$ and 0.44 eq of DMF in benzene to afford 6-methylnaphthoyl chloride **23**. Assuming that the transformation was quantitative, the crude product was taken on to the next step, where it was treated with 1.2 eq of $(i\text{-Pr})_2NH$ and 1.2 eq of Et_3N in DCM to give diisopropyl-6-methyl naphthamide **24** in 74% yield from the naphthoic acid, which is consistent with the parent ligand synthesis.

The stage was set for the key step of the sequence, the *ortho*-allylation / cyclization reactions that would give the desired phenanthrol. Accordingly, following the modified procedure of Dr. Yu, the 6-methyl naphthamide **24** was treated with 1.1 eq of *s*-BuLi, 3 eq of freshly prepared $MgBr_2$ and 2 eq of *a*-bromomethyl styrene to furnish diisopropyl 6-methyl-2-(2-phenylallyl)naphthamide **25** in 75% yield.

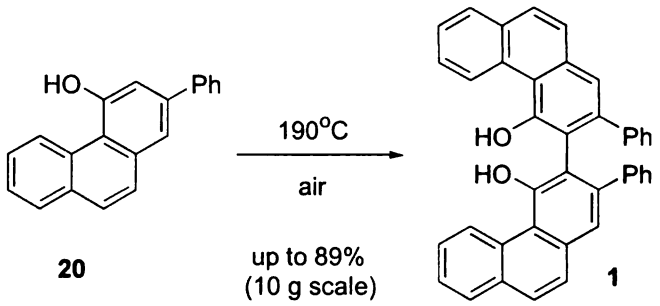
Finally, the cyclization of the *o*-allyl naphthamide **25** proceeded smoothly upon treatment with MeLi in THF at –78°C to afford the desired 7-methyl-2-phenyl-4-phenanthrol **26** in 80 % yield.

2.1.2 Oxidative coupling of 6-methyl-2-phenyl phenanthrol and deracemization of 7,7'-dimethyl VAPOL.

In 1996 we showed that racemic VAPOL can be prepared efficiently on a 10 g scale by oxidative dimerization of 2-phenyl-4-phenanthrol **20**, simply by heating the neat solid at 190°C in a beaker for ~24h, provided that efficient stirring is supplied in order to maintain sufficient contact of the solid with air[2]. With this method, up to 89% yield of

VAPOL can be obtained after a simple extraction of the reaction mixture with ethyl acetate (Scheme 6).

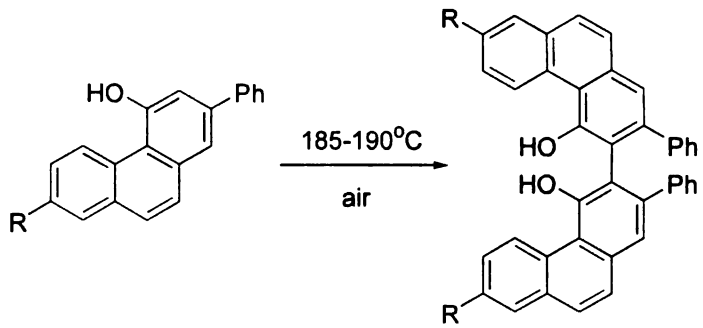
Scheme 6. Oxidative dimerization of phenanthrol **20** for the preparation of VAPOL



20 **1**

Since the synthesis of compound **26** that was described in Scheme 5 afforded only a few hundreds of milligrams of desired product, the oxidative coupling for the synthesis of racemic 7,7'-dimethyl VAPOL had to be performed on a very small scale. Following the procedure described by Bao, oxidative coupling of 2-phenyl-4-phenanthrol **20** and 7-methyl-2-phenyl-4-phenanthrol **26** was examined on small scales (~0.3-0.5 g). The preliminary results are shown below in Table 3.

Table 3. Small scale oxidative dimerization of **20** and **26**

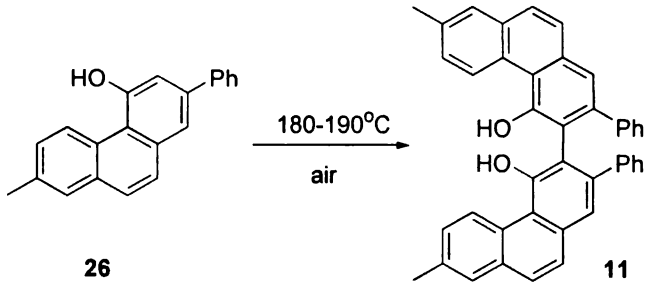


R	scale	t (h)	yield %
H (**20**)	300 mg	39	48
Me (**26**)	490 mg	46	33

It was found that the dimerization of 2-phenyl-4-phenanthrol on a 300 mg scale gave a yield of 86% after extraction of the reaction mixture with EtOAc. Although the ^{1}H-NMR was clean, TLC analysis showed some minor byproduct spots and baseline material, probably polymeric products. The isolated yield after column chromatography was only 48% (Table 3, entry 1), indicating that the dimerization on 300 mg scale behaves differently than on 10 g scale. This is probably due to insufficient stirring. As the phenanthrol was slowly oxidized to VAPOL, the reaction mixture solidified and finally the stirring stopped due to the high melting point of VAPOL(~250°C) and the small amount of material that was present. In a similar fashion, the dimerization of 7-methyl-2-phenyl-4-phenanthrol gave 33% of 7,7'dimethyl VAPOL after 46 h of heating.

Since the oxidative dimerization of the phenanthrols gave a significant amount of byproducts, various reaction times were examined for the reaction of 7-methyl-2-phenyl-4-phenanthrol in an effort to increase the yield. The results are summarized in the following table.

Table 4. Examination of various reaction times for the oxidative coupling of **26**



26 **11**

entry	t (h)	dimer/monomer	%yield **11**
1	36	7/1	30
2	19	2.7/1	40
3	10	2.3/1	40
4	11	1.5/1	51
5	8	1.1/1	45
6*	10	nd	55
7**	10	nd	67***

*Reaction performed in an Erlemeyer flask in order to increase the reactive surface. **Reaction repeated using the recovered starting material from entry 6. ***Total yield from entries 6 and 7.

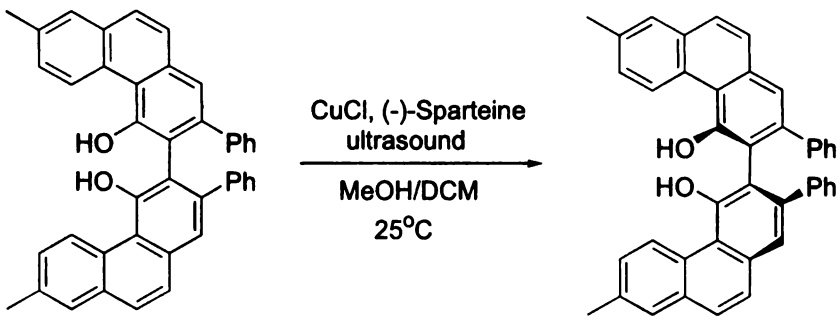
It is obvious that by decreasing the time of the reaction, the yield of the desired product increases. It was found that for heating times of >10 h a major byproduct with R_f very similar to that of the desired product was formed (entries 1 and 2) and that compound (not characterized) probably comes from decomposition of 7,7'-dimethyl VAPOL. By decreasing the time of heating to 10-11 h, the decomposition can be prevented, and even if the conversions are lower, the isolated yields are higher. The starting material for these reactions can be recovered and used again. For example, as it is shown in entry 7, an

isolated yield of 67% can be obtained based on the recovery of starting material and re-subjection in the reaction conditions.

Recently Yu et al. found that the deracemization of VAPOL can be readily achieved in the presence of a copper complex of (-)-sparteine[16]. The optimal procedure involves the in situ generation of copper(II) and leads to the formation of (S)-VAPOL in >99% ee from the racemate.

Yu's conditions were used to deracemize 7,7'-dimethyl VAPOL. The results are shown in the table below.

Table 5. Deracemization of 7,7'-dimethyl VAPOL



11 (S)-**11**

entry	purity of **11**	yield%	%ee
1	purified once	65	97.8
2	purified twice*	80	99.0

*A second column chromatography was performed before the reaction to ensure that all yellow impurities were removed.

It was apparent from the above results that the purity of the ligand to be deracemized is of crucial importance in order for the reaction to afford enantiopure product (>99%ee).

It was also found that the enantioselectivity of the chiral ligand could be further enriched by crystallization from methylene chloride/hexanes. Starting from material of 97.8% ee, the first crop of crystals (~50%) were found to have 99.6% ee, indicating that the (S)-compound is less soluble than the racemic, in contrast to VAPOL.

2.2 EVALUATION OF 7,7'-DIMETHYL VAPOL IN THE IMINO ALDOL REACTION AND COMPARISON WITH THE PARENT LIGAND

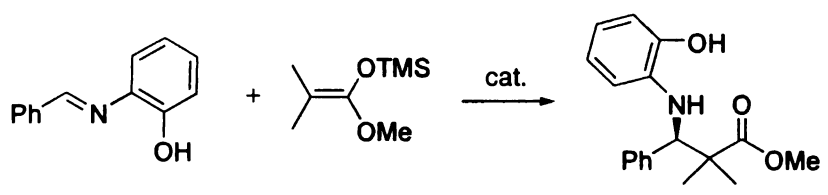
As was mentioned on chapter 1 (Figure 4), the purpose of synthesizing and studying 7,7'-dimethyl VAPOL in the imino aldol reaction was to test weather the methyl substitution on the 7 and 7' positions can enhance the asymmetric induction of substrates that didn't afford excellent selectivities when VAPOL was used as a ligand.

The reactions that were chosen as models for the comparison were: (i) Reactions of the ketene acetal **3a** with the unsubstituted imine **2** derived from 2-aminonaphthol (Table 6), and (ii) Reactions using the acetal **3b** derived from *t*-butyl thioacetate with imines **8** derived from 2-amino-4,6-dimethyl phenol (Tables 7 and 8).

2.2.1 Reactions using the unsubstituted imine 2

With (S)-7,7'-dimethyl VAPOL in hand, experiments for the comparison of the new ligand with (S)-VAPOL were conducted for the reaction of imine **2** using ketene acetal **3a**. The results for the comparison of the two ligands at r.t. and at -45°C are summarized Table 6.

Table 6. Comparison of the efficiency of (S)-VAPOL and (S)-7,7'-dimethyl VAPOL in the asymmetric induction in compound **4**. (a)



2 **3a** **4**

entry	ligand	conditions	yield% (b)	ee% (c)
1	(S)-VAPOL	rt, 0.5M, Toluene	93	89
2	(S)-MeVAPOL	rt, 0.5M, Toluene[d]	94	75
3	(S)-MeVAPOL	rt, 0.5M, DCM	100	52
4	(S)-VAPOL	rt, 0.125M, Toluene	95	89
5	(S)-MeVAPOL	rt, 0.125M, Toluene	97	86
6	(S)-VAPOL	-45°C, 0.125M, Toluene	92	91
7	(S)-MeVAPOL	-45°C, 0.125M, Toluene	90	91

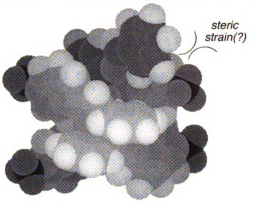
(a) Catalyst prepared from $Zr(O\textit{i}Pr)_4/\textit{i}$-PrOH, chiral ligand (2.2 eq) and 1.1 eq of N-methyl imidazole (NMI) in DCM or toluene at 25°C for 1 h. Reactions were performed with 1.2 eq of ketene acetal and were run for 24h. (b) Isolated yield after column chromatography. (c) Determined throuh chiral HPLC analysis. (d) The ligand was not completely soluble for the given conditions.

In the first attempt to compare the two ligands at r.t., it was found that 7,7'-dimethyl VAPOL was not completely soluble in toluene when the reaction was performed at 0.5M in imine (entry 2), and presumably that's the reason for the significant drop in the ee (75%). The reaction in DCM removed the problem of solubility of the new ligand (entry 3) but the reaction was probably too fast (considering that some evaporation of the volatile solvent may took place) to be selective, affording an even bigger decrease in the selectivity (entry 3, 52% ee).

It was then realized that high concentrations are not necessary for the reaction to go to completion in toluene and that lower concentrations should allow the new catalyst to dissolve completely, allowing for an accurate comparison with VAPOL. The optimum conditions for the reactions – concerning catalyst solubility and reaction rate – were met when 0.125M imine was used in toluene. The new catalyst was completely soluble in 0.125M toluene, but, as shown in entries 4 and 5, the enantiomeric excess was slightly lower than that obtained using (S)-VAPOL. Finally, when the temperature was decreased to –45°C, the stereochemical outcome of the two ligands was essentially the same (entries 6, 7).

This preliminary comparison shows that the new ligand can be as efficient as (S)-VAPOL at low temperatures for this particular reaction, but at room temperature the asymmetric induction was slightly lower. This is contrary to expectations since the design of the ligand anticipated greater shielding of the imine and greater inductions (Chapter 1, Figure 4). One possible explanation for this outcome is that, the methyl substituent at the 7 position of the phenanthrene ring is bulky enough to make close contacts with the imine, preventing it from properly fitting down into the chiral pocket. In other words, steric hindrance between the phenyl group of the imine and the 7-methyl group of the ligand might be responsible for failure of the imine from properly binding with the catalyst with the result that there is an increase in the exposure of the *re*-face of the C-N double bond to attack by the ketene acetal leading to decreased selectivity.

Figure 6. Steric strain between imine **2** and the 7-Me of dimethylVAPOL as a possible explanation for the stereochemical outcome of the reactions in Table 6.



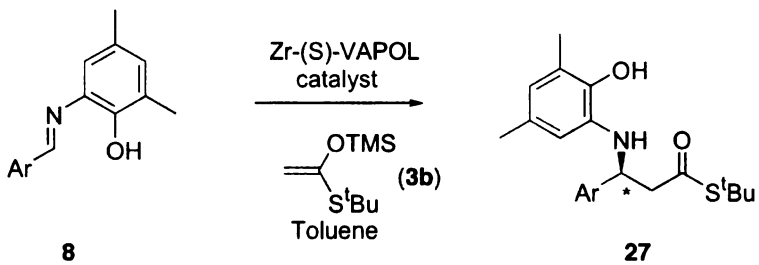
If the above arguments are true, then reactions with imine **8** should not encounter this complication, since CPK models show that the methyl substituent *ortho* to the hydroxyl group of the imine should push the imine down into the chiral pocket of the catalyst. In this way, the *o*-methyl group of the imine **8** should be expected to overcome any problem of steric repulsion between the imine and the ligand. Thus, the rections with imine **8** were chosen for evaluation with the new ligand. The ketene acetal **3b** was chosen because this substrate gave less than desired results with the VAPOL ligand.[5]

2.2.2 Reactions using the ketene acetal 3b

Despite the high efficiency of the Zr-VAPOL catalyst for the imino aldol reactions using ketene acetal **3a** (Table 6), the corresponding reactions with the unsubstituted ketene acetal **3b** mediated by the same catalyst were slower and did not display the same temperature independence. The reactions with imines **8a** and **8b** with ketene acetal **3b** with the Zr-(S)-VAPOL catalyst have been reported[5] and were reexamined in the present work as control experiments and the data in Table 7 are similar to those reported. The imine **8c** was also examined since it gave lower induction with ketene acetal **3** (Chapter 1, Table 2). For imine **8a**, in contrast wth the excellent enantioselection observed with ketene

acetal **3a** at room temperature (98% ee, Chapter 1, Table 2) the reaction with **3b** affords only 83% ee (entry 1), while a slight drop is observed at 100°C (entry 2, 80% ee). For imines **8b** and **8c** the enantioselectivites are also not very high at room temperature (88 % ee and 81% ee respectively) and their decrease at high temperatures is even more significant (80 % ee and 66 % ee, entries 4 and 6).

Table 7. Temperature dependence on the asymmetric induction of **27** using Zr-VAPOL catalyst (a)



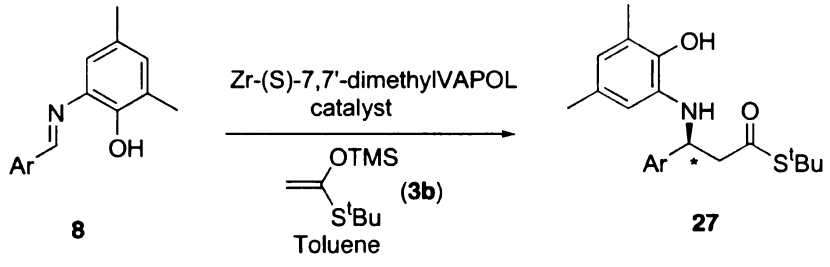
8 **27**

entry	series	Ar	T°(C)	% cat.	%yield(b)	% s.m. recovered	%ee(c)
1	**a**	Ph	25	20	65	23	83
2	**a**	Ph	100	10	70	22	80
3	**b**	1-Naphthyl	25	20	50	35	88
4	**b**	1-Naphthyl	100	10	60	30	80
5	**c**	4-Cl-C_6H_4	25	20	55	33	81
6	**c**	4-Cl-C_6H_4	100	10	60	30	66

(a) Catalyst prepared from Zr(O*i*Pr)$_4$/*i*-PrOH, chiral ligand (2.2 eq) and 1.1 eq of N-methyl imidazole (NMI) in toluene at 25°C for 1 h. Reactions were performed with 1.2 eq of ketene acetal and 0.125M in imine and were run for 24 hours. (b) Isolated yield. (c) Determined by HPLC analysis.

The corresponding set of reactions using the catalyst obtained from 7,7'-dimethylVAPOL is shown in Table 8.

Table 8. Temperature dependence in the asymmetric induction of **27** using Zr-7,7'-dimethylVAPOL catalyst (a)



8 **27**

entry	series	Ar	T°(C)	% cat.	%yield (b)	%s.m. recovered	%ee (c)
1	**a**	Ph	25	20	65	23	90
2	**a**	Ph	100	10	70	22	84
3	**b**	1-Naphthyl	25	20	49	35	96
4	**b**	1-Naphthyl	100	10	60	30	88
5	**c**	4-Cl-C_6H_4	25	20	56	32	91
6	**c**	4-Cl-C_6H_4	100	10	60	30	76

(a) See Table 7. (b) Isolated yield based on recovery of the starting material. (c) Determined by HPLC analysis.

The very first attempts to evaluate the new ligand in the iminoaldol reaction of ketene acetal **27** showed that there is a significant improvement in the enantioselectivity compared to VAPOL. For imine **8a** where Ar is phenyl the ee rises from 83% [(S)-VAPOL] to 90% [(S)-7,7'-dimethyl VAPOL]. When the reaction is performed at 100°C (Table 8, entry 2) the induction drops a little bit (84%), but it is still higher than that afforded with (S)-VAPOL (80%, Table 5, entry 2). For the other imines these

improvements were even greater: For the naphthyl-substituted imine 7,7'-dimethylVAPOL affords 8% higher ee than VAPOL both at rt and at 100°C (entries 3 and 4) while when R is 4-chlorophenyl the increase in the induction is 10% higher at both temperatures (entries 5, 6).

2.3 CONCLUSION

It is obvious that the catalyst derived from 7,7'-dimethylVAPOL is quite efficient for the imino aldol reaction with regard to the asymmetric inductions observed with both the ketene acetals **3a** and **3b**.

In the first case where imine **2** was used the reason that dimethylVAPOL does not afford higher selectivities than VAPOL is not very clear, although it is suspected that steric strain between the imine and the 7-methyl group of the ligand may destabilize the normal conformation of the imine in the complex.

The reactions of imines **8a-c** with acetal **3b** turned out to be less temperature independent than the corresponding reactions with ketene acetal **3a** (Chapter 1, Table 2), even when 7,7'-dimethylVAPOL was employed (Table 6), nonetheless it is exciting though to observe that a modification on the ligand structure as small as a methyl group can induce a remarkable enhancement in the enantioselectivity of these transformations. Additionally, these results not only demonstrate the efficiency of the ligand but also help to confirm the proposed model for the reaction. The enhancement of selectivities achieved both through the modification of the imine (Chapter 1) and the modification of the catalyst (Chapter 2) agree with our proposed catalyst structure and its mechanism.

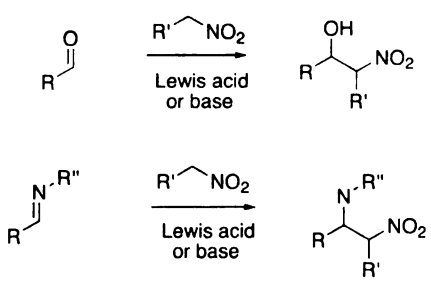
CHAPTER 3

THE CATALYTIC ASYMMETRIC AZA-HENRY REACTION

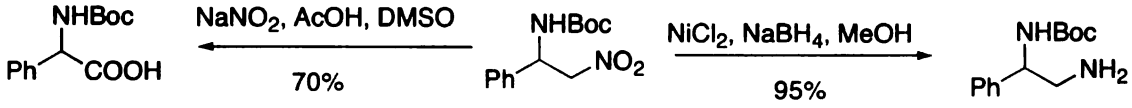
3.1 INTRODUCTION

The development of stereoselective carbon–carbon bond forming reactions that create contiguous stereogenic centers bearing heteroatom functionality can provide valuable building blocks for organic synthesis. The aza-Henry (nitro-Mannich) reaction, that is, nucleophilic addition of nitroalkanes to imines (Scheme 7), is such a useful carbon–carbon bond-forming process. The resulting β-nitroamines can be transformed into valuable compounds such as vicinal diamines and α-amino acids by reduction[17] and Nef reactions[18] of the nitro moiety (Scheme 8), respectively. Vicinal diamines are of particular interest owing to their broad utility in the synthesis of biologically active natural products and drug candidates, and also more recently, as chiral ligands for asymmetric reactions[19]. Although a variety of synthetic procedures have been devised to carry out the Mannich reaction enantioselectively, until quite recently the enantioselective aza-Henry reaction was unknown. Therefore, as an unsolved problem, considerable effort has been directed toward the development of catalytic asymmetric aza-Henry reactions over the past several years.

Scheme 7. The Henry and the Aza-Henry reaction



Scheme 8. Useful transformations of β-nitroamines

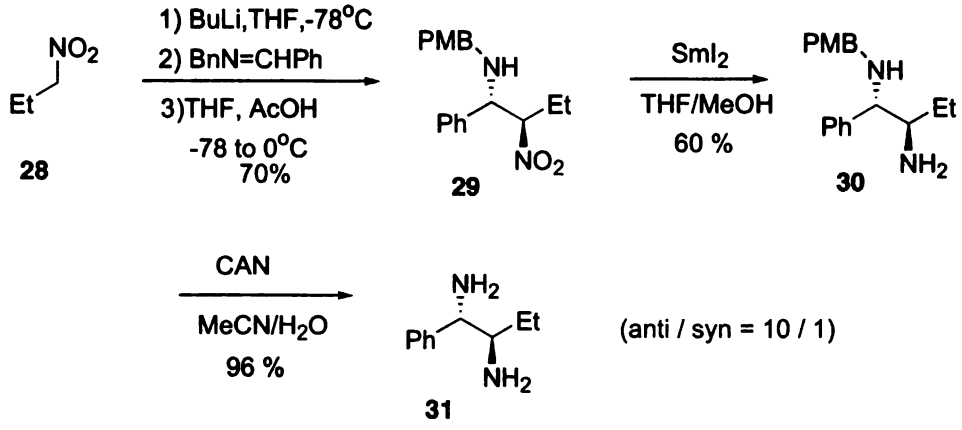


This chapter is a review of the available methods that have been developed so far for the catalystic asymmetric aza-Henry reaction, from the early metal-catalyzed examples to the organocatalytic protocols that have appeared more recently.

3.2 METAL CATALYZED PROTOCOLS

To the best of our knowledge the first example of a stereoselective (although non-asymmetric) aza-Henry reaction appeared in 1998 by Anderson's group[20]. The method they reported was an interesting synthesis of 1,2-diamines, through an addition of lithium nitronates to imines that provided β-nitroamines **29**. To avoid retro-addition – a common complication in the synthesis of nitroamines - these intermediates were then reduced with SmI_2, and after PMB cleavage the vicinal diamines **31** could be obtained in high yields and with good diastereoselectivities).

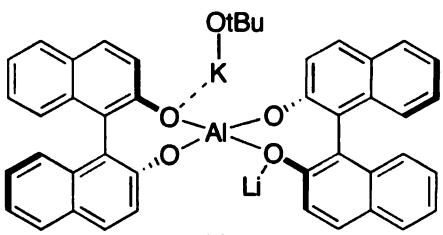
Scheme 9. Anderson's aza-Henry reaction



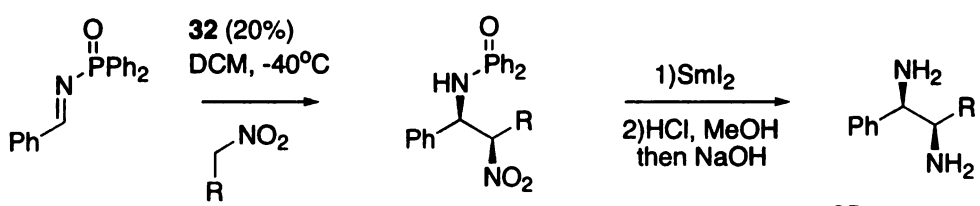
Anderson's group also reported preliminary studies in which imines and nitroalkanes were allowed to react in the presence of Bronsted acids and later the reaction was found to be catalyzed by Lewis acids like BF_3 and $Sc(OTf)_3$[21]. Thus, the stage was set for developing the catalytic, asymmetric variants of this transformation–goals addressed and achieved by the research groups led by Shibasaki and Jorgensen.

Shibasaki investigated the aza-Henry reaction conducted with the heterobimetallic catalyst **32** (Scheme 10)[22]. Since **32** shows concomitant Bronsted-basic and Lewis-acidic behavior, both the electrophile and the nucleophile can be activated. Under optimized conditions **34** could be obtained in 90% yield (syn:anti >6:1) with an enantiomeric excess of 80%. Among the disadvantages are the limitation to nitromethane, the restriction to N-phosphinoylimines **33**, and the large amount of catalyst required (20 mol%, which corresponds to 40 mol% chiral ligand).

Scheme 10. Shibasaki's protocol using the heterobimetallic complex **32**



32

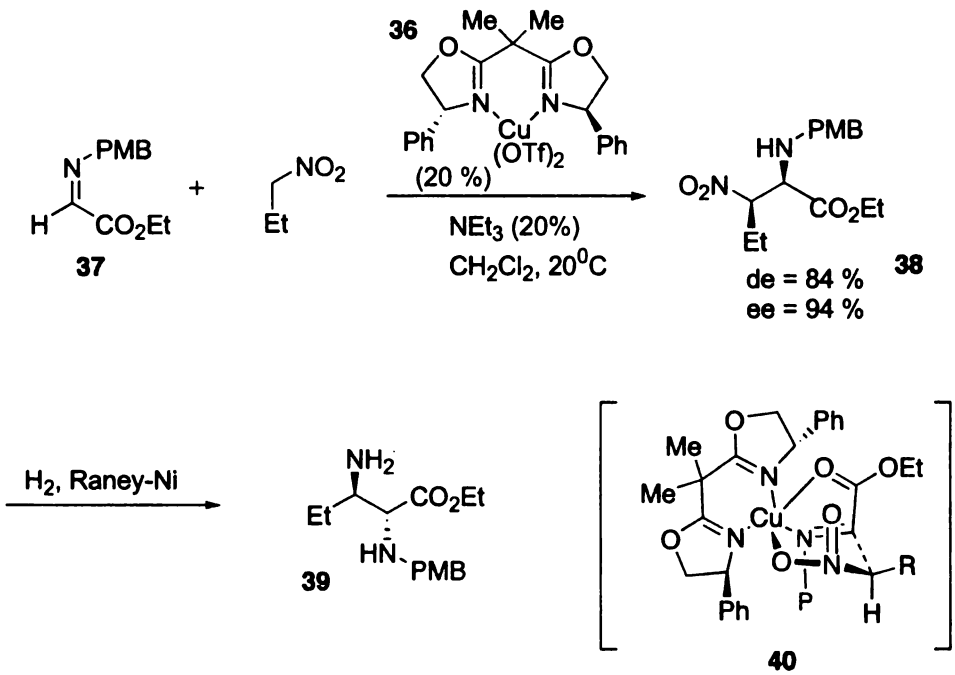


33 **34** **35**

One point in favor of this methodology is that vicinal diamines **35** can be obtained easily from **34** by reduction of the nitro group and cleavage of the phosphinoyl group.

The breakthrough in terms of handling and practicability was achieved by Jorgensen et al. (Scheme 11)[23]. They showed that application of the C_2 symmetrical chiral Lewis acid **36** (20 mol%) to the addition of nitroalkanes to α-iminoester **37** can afford aza-Henry products like **38** with high diastereo- and enantioselectivities.[23b] After reduction of the nitro moiety in **38** very valuable building blocks like α,β-diaminocarboxylic acids **39** can be obtained (Scheme 11).

Scheme 11. Jorgensen's aza-Henry reaction

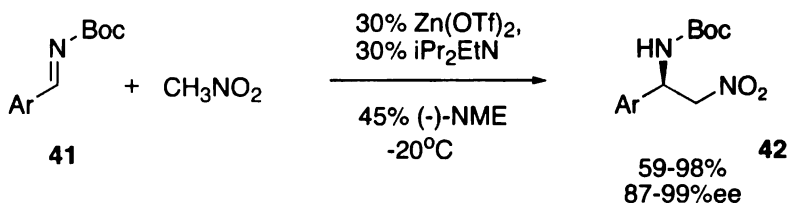


If silylated nitronates are employed, addition of base is not necessary for reaction with imine **37**.[23a] Owing to the high reactivity of the silylated nitronates, the reaction proceeds uncatalyzed even at -78°C. Reaction temperatures of -100°C were required to achieve high diastereoselectivities (erythro:threo >25:1) and high enantioselectivities (>95%ee for the erythro product) in this case. The high selectivity of the addition in both cases is attributed to the Zimmerman-Traxler transition state **40**, in which both reaction

partners are coordinated to the chiral Lewis acid. If one assumes a rapid equilibration of the E and the Z forms of the Copper nitronate, transition state **40** is formed exclusively, which explains the preferred formation of the erythro product.

Very recently, one more important metal catalyzed variant of the name reaction has been reported by Palomo's group featuring the addition of nitromethane to N-Boc protected imines **41**[24]. The breakthrough in this case is that good to excellent enantioselectivities of the desired products **42** can be obtained by exclusive use of commercially available, inexpensive materials such as $Zn(OTf)_2$ and N-methylephedrine.

Scheme 12. Palomo's aza-Henry reaction assisted by $Zn(OTf)_2$ and N-methylephedrine



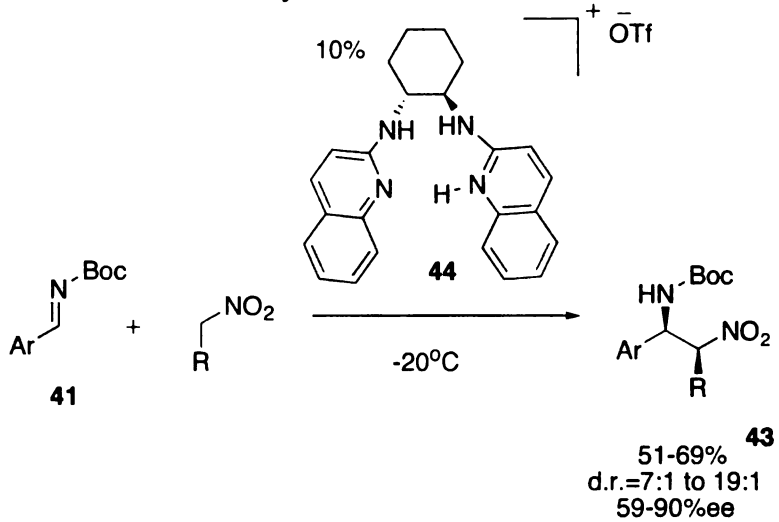
3.3 ORGANOCATALYTIC APPROACHES

The rapid development of organic catalysis[25] during the last few years has led to the appearance of several reports concerning the promotion of the aza-Henry reaction through the activation of the imine and/or the nitroalkanes through metal-free catalytic systems. The catalyst that have been used so far can be divided into three groups: (i) Chiral proton catalysts, (ii) Cinchona-alkaloid-based phase-transfer catalysts and (iii) chiral thiourea catalysts.

3.3.1 Chiral Proton Promoted Aza-Henry Reaction

In 2004 Johnston et al. developed a chiral bisamidine triflate salt that effects the diastereoselective addition of nitroethane to a range of electron-deficient N-Boc imines[26]. The catalyst **44** is a protonated chiral diamine based on diaminocyclohexane as the chiral schaffold. By using **44**, neither a Brønsted base additive nor preactivation of the nucleophile is necessary for the addition to occur.

Scheme 13. Johnston's aza-Henry reaction



The exact nature of the stereochemical determining catalyst-substrate complex was not clear, however, it was clear from the initial experiments that the proton on the quinoline moiety plays a key role in both substrate activation and orientation leading to asymmetric induction.

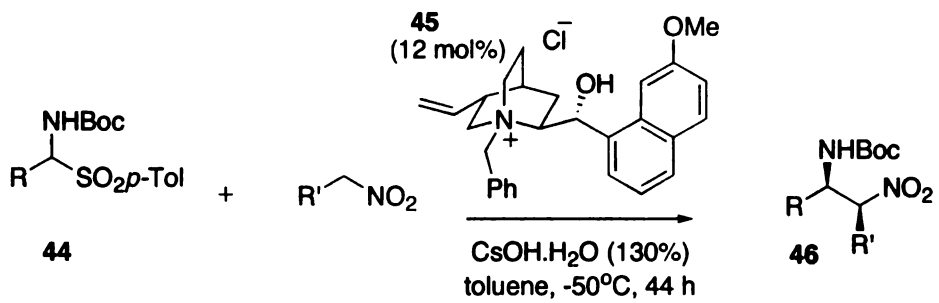
Johnston's method is unique in demonstrating the use of a chiral proton (a *polar ionic hydrogen bond*) alone as both the means of activation (function) and control (structure) of absolute and relative stereochemistry. It also constitutes the first example of a metal-free catalytic asymmetric aza-Henry reaction.

3.3.2 Cinchona alkaloid-based phase-transfer catalysts

Palomo's group found recently that R-amidosulfones are appropriate in situ precursors of enolizable aldehyde-derived azomethine compounds in the context of the asymmetric aza-Heny reaction. Thus, a new asymmetric aza-Henry technology was developed with broad substrate scope based on the use of R-amido sulfone substrates **44** and phase transfer catalysis (PTC)[27]. Given that in situ generation of imines from R-amido sulfones requires stoichiometric base[28], the base-promoted, nonselective background aza-Henry reaction constituted an initial obstacle[29]. It was postulated that phase transfer conditions using chiral quaternary ammonium salts in combination with a nonsoluble base would render the competitive undesired reaction marginal. Indeed, it was found that catalytic quantities of **45** in combination with $CsOH.H_2O$ (120-150 mol %) sufficed for the reaction of nitromethane with a variety of R-amido sulfones **44**. The enantiomeric excesses are generally high for in-situ generated aryl-substituted imines irrespective of the electronic nature of the aromatic ring: heteroaromatic imines being also tolerated. *Most remarkably, the aza-Henry reaction gave enantiomeric excesses regularly above 94% with*

an array of enolizable aldehyde-derived imines. Linear as well as branched chain alkyl amido sulfones **44** (R=alkyl) gave the corresponding adduct **46** in good yields and enantiomeric excesses in the 94-98% range indicating no significant sensitivity to the size of the alkyl group in **44**. Some representative examples are summarized in the following table.

Table 9. Palomo's approach using catalyst **45**



entry	R	R'	yield %	ee%(d.r.)
1	ethyl	H	80	96
2	iso-propyl	H	81	95
3	c-hexyl	H	77	98
4	Ph	H	79	91
5	2-furyl	H	72	84
6	Ph	Me	88	94(93:7)

Almost at the same time, Ricci's group reported on the same transformation using the same catalyst **45** but employing KOH instead of $CsOH.H_2O$[30]. His method concerns the addition of nitromethane to aliphatic and aromatic azomethine precursors **44** to afford products **46** (R'=H) with very good yields and ee's (73-99%).

3.3.3 Chiral thiourea catalysts

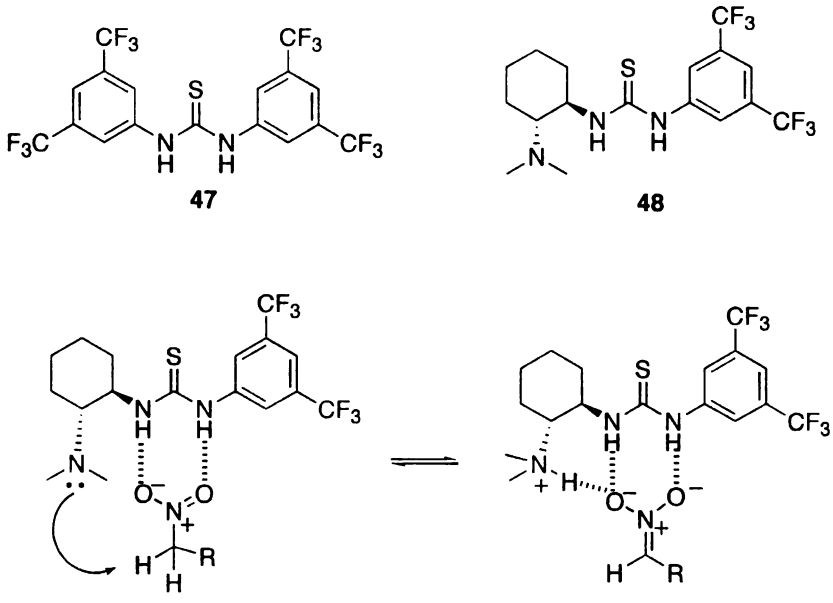
Electrophile activation by chiral small molecule H-bond donors has emerged as an important paradigm for enantioselective catalysis, with new applications and developments appearing at a rapidly increasing pace[31]. Particularly, the simultaneous action of two hydrogen bond donors has proven to be a highly successful strategy, both in enzymes and in synthetic catalyst systems. Several properties of the bifurcated hydrogen bond may contribute to its utility in catalysis. Such interactions benefit from increased strength and directionality relative to a single hydrogen bond. In an analogous manner, two-point binding is an extremely powerful strategy for asymmetric catalysis with metal-centered Lewis acids[32]. However, while the requirement for multidentate coordination to a chiral Lewis acid often imposes limitations upon substrate structure, in principle any Lewis base is capable of engaging in bifurcated hydrogen bonds. Electrophiles shown thus so far to be activated by double H-bond donors include aldehydes, ketones, esters, imines, N-acyliminium ions, and nitro compounds[31].

Concerning the catalysts used in double H-bond activation, the synthesis of chiral thioureas is facilitated from the ready availability of enantiopure chiral building blocks bearing primary aminofunctionalities. Therefore given the excellent general stability, high conformational rigidity[33] and Lewis base binding proclivities of thiourea derivatives, it is unsurprising that chiral analogues are rapidly emerging as versatile, functional group tolerant and easily prepared and modified catalyst templates for the promotion of a wide range of synthetically useful asymmetric carbon-carbon bond forming processes[34].

Along these lines, given the fact that the nitro group and the imine functionality are both capable of participating in H-bonding, it is not surprising that some protocols concerning thiourea-catalyzed aza-Henry reactions have already appeared in the literature.

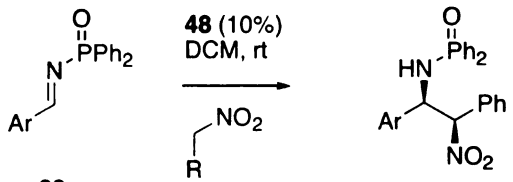
The first protocol for a thiourea catalyzed aza-Henry reaction was published in 2004 by Takemoto[35]. His design of the catalyst borrowed from Schreiner's thiourea **47**[36], which had been established a few years earlier for the promotion of Diels-Alder reactions. Takemoto's catalyst **48** was based on the electron withdrawing bis(trifluoromethyl substituted) aryl group which ensures the necessary acidity for the thiourea N-H bonds – and thus the capability in effective H-bond donation – and incorporates a dimethylamine group as a base for the activation of the nucleophile. Specifically, the corresponding nitronate could be produced from the nitroalkane with the bifunctional catalyst via the hydrogen-bonding activation with the thiourea moiety and subsequent deprotonation by the neighboring tertiary amino group

Figure 7. Design of Takemoto's catalyst for the activation of the nitro group in the aza-Henry reaction.



Using catalyst **48** at 10% catalyst loading Takemoto was able to promote the aza-Henry reaction between phosphinoyl imines and nitroalkanes with good yields and modest ee's. The results for various aromatic and heteroaromatic imines are shown in Table 10.

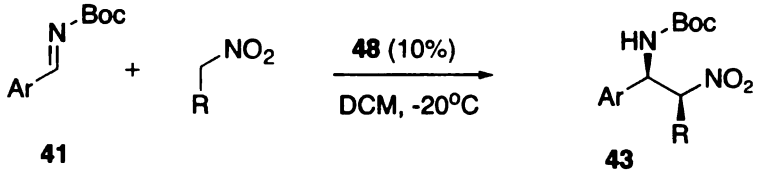
Table 10. Takemoto's Aza-Henry reaction of phosphinoyl imines



entry	Ar	R	yield %	%ee (dr)
1	Ph	H	87	67
2	4-Me-C_6H_4	H	72	63
3	4-Cl-C_6H_4	H	76	67
4	2-naph	H	78	70
5	2-furyl	H	85	76
6	2-pyridyl	H	91	68
7	2-thienyl	H	57	64
8	trans-styryl	H	68	65
9	Ph	Me	83	67 (73/27)

The same group reported a second protocol in 2006 for the name reaction using the same catalyst, but featuring N-Boc protected imines[37]. The reactions with N-Boc imines turned out to be much more efficient in terms of yields and enantioselectivities and a number of higher nitroalkanes could be successfully used affording syn products with high diastereoselectivities as well. Representative examples are given in the Table 11.

Table 11. Takemoto's aza-Henry reaction with N-Boc imines

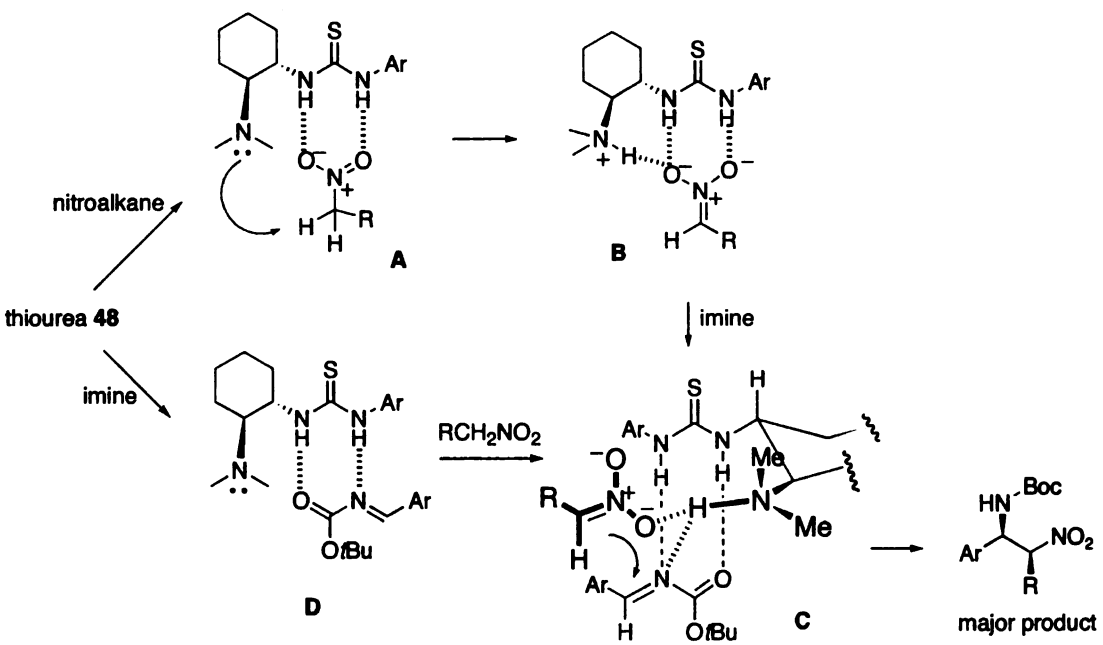


entry	Ar	R	yield%	% ee
1	Ph	H	90	94
2	4-$CF_3C_6H_4$	H	80	98
3	4-Me	H	82	93
4	4-$MeOC_6H_4$	H	71	95
5	1-naphthyl	H	85	95
6	3-pyridyl	H	89	98
7	Ph	Me	92	93(90/10)
8	Ph	CH_2Ph	84	97(83/17)
9	Ph	CH_2OBn	80	95(86/14)

Takemoto's protocol with N-Boc imines was the first report of a highly diastereo- and enantioselective aza-Henry reaction with *functionalized nitroalkanes* to give N-protected imines. To account for the highly stereoselectivity of the reaction, a ternary complex C of catalyst **48**, imine **41** and nitronate anion was proposed as a plausible transition state, in which the imine is hydrogen-bonded to the thiourea moiety and the amonium group of **48** is hydrogen bonded to the nitronate anion (Scheme 14). Ternary complex **C** can be considered to be generated through two different ways. On one hand, thiourea catalyst first activates the nitroalkane by hydrogen-bonding interaction which is followed by intra- or intermolecular deprotonation by the amino group of **48** to generate

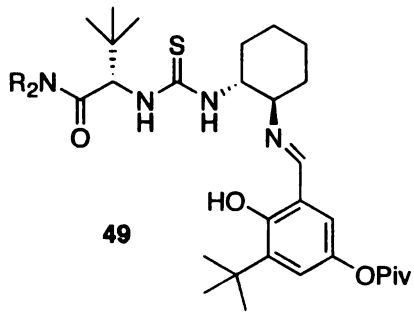
nitronate complex **B**. Subsequent binding of the imine to the thiourea moiety in place of the nitronate produces complex **C**. On the other hand, complex **C** might be formed by the successive interaction of the imine and the nitroalkane with thiourea catalyst **48** via binding and deprotonation (**D** to **C**). In any event, the thiourea moiety of **48** is believed to play a crucial role in activation of N-Boc imine in the nucleophilic addition step or nitroalkane in the deprotonation step. Complex C correctly predicts both the diastereomeric preference for the syn isomer as well as the absolute stereochemistry observed.

Scheme 14. Proposed reaction process for the Takemoto's thiourea-catalyzed aza-Henry reaction



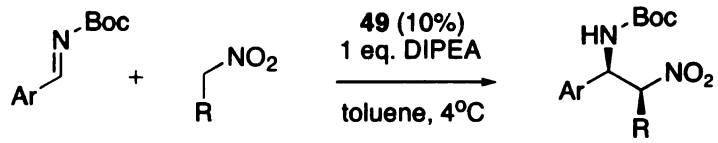
Another chiral thiourea catalyst successfully employed in the context of the aza-Henry transformation is Jacobsen's thiourea **49**[38]. Thiourea **49** can promote the addition of nitroethane to N-Boc imines with good dr ratios, while the yields and enantioselectivities for the resulting nitroamines are excellent.

Figure 8. Jacobsen's thiourea **49**



49

Table 12. Jacobsen's Aza-Henry reaction using **49**

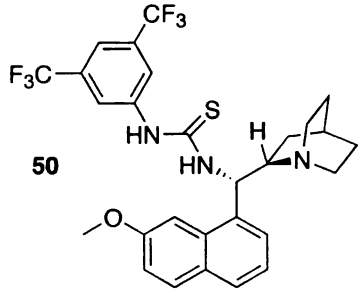


41 (2.5 eq.) **43**

entry	R	yield %	d.r.	% ee
1	Ph	96	15/1	92
2	4-Cl-C_6H_4	98	7/1	95
3	3-Cl-C_6H_4	85	7/1	96
4	2-Cl-C_6H_4	99	2/1	93
5	4-Me-C_6H_4	90	12/1	96
6	2-Me-C_6H_4	99	9/1	95
7	4-MeO-C_6H_4	95	16/1	96
8	3-pyridyl	79	7/1	97
9	2-furyl	95	6/1	93
10	2-naphthyl	91	5/1	97

Finally, Ricci's group has reported aza-Henry reactions of N-Boc imines with nitromethane using the cinchona alkaloid-derived thiourea **50**[39].

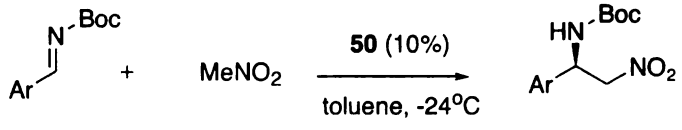
Figure 9. Ricci's thiourea **50**



50

Catalyst **50** can promote the reaction of nitromethanes – but not of other higher nitroalkanes – with N-Boc imines affording good yields and modest to excellent enantioselectivities.

Table 13. Ricci's aza-Henry reaction using catalyst **50**



41 (5 eq.) **42**

entry	Ar	yield %	% ee
1	1-naphthyl	87	88
2*	2-naphthyl	82	94
3	4-Cl-C_6H_4	77	94
4*	2-Br-C_6H_4	82	88
5	4-MeO-C_6H_4	65	82
6	2-thienyl	50	82
7*	2-furyl	58	63

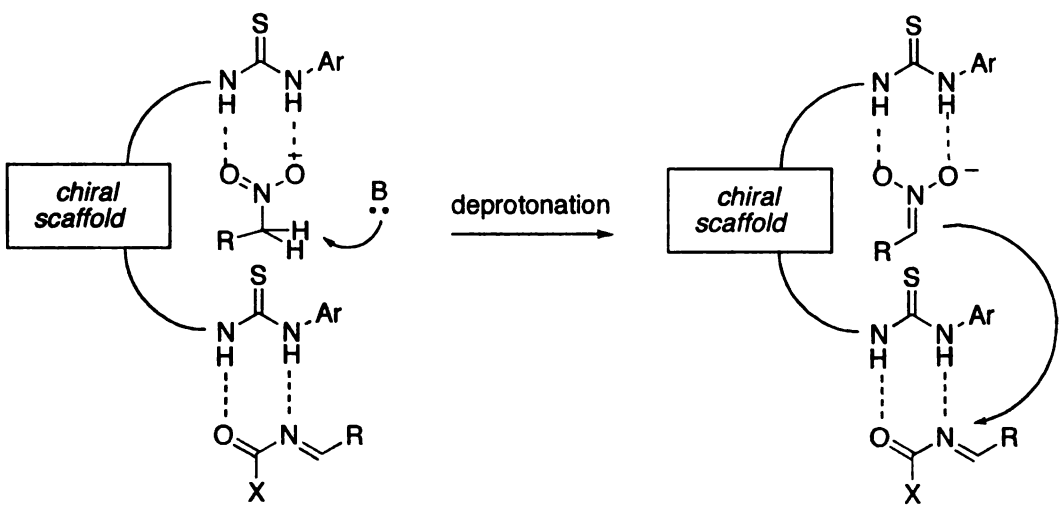
*Reaction at -40°C

3.3.4 Bis-Thiourea Catalysts for the aza-Henry reaction and related transformations

In the protocols discussed so far, concerning the mechanistic details of the transformations, it is clear that the imine and the nitroalkane are both capable of forming H-bonds with the thiourea catalysts. Jacobsen's thiourea **49** (Table 12) is not bifunctional and external base is added for the deprotonation of the nitroalkane, so it is not clear weather it is the imine or the nitroalkane that is interacting with the catalyst in the transition state of the reaction. Takemoto's and Ricci's thioureas are bifunctional and so they play a more definite role in the deprotonation step, but again the reaction features two components (imine and nitroalkane) both of which are potential H-bond acceptors, while the catalyst structures have only one thiourea moiety and thus it is not clear which substrate is bound to the catalyst.

Our interest in thiourea catalyzed aza-Henry reactions led us to consider the possibility of a catalyst that would incorporate two thiourea moieties within its structural framework, and thus provide the potential for the simultaneous activation of both reaction components, the imine and the nitroalkane.

Figure 10. The concept of bis-thiourea catalysis



A catalyst that would have two thiourea moieties should be able to interact with the imine and the nitroalkane at the same time, activating the two components while bringing them together in its chiral pocket. This could potentially result in well-defined orientations and transition states that would promote high enantioselectivities. Additionally, the concept of the bis-thiourea catalysis is interesting because it could be applied to many other transformations that involve activation through H-bonding.

The next chapter details on the development of a novel bis- thiourea organocatalyst for the asymmetric aza-Henry reaction.

CHAPTER 4

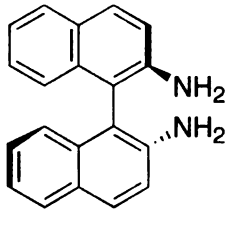
A NOVEL BIS-THIOUREA ORGANOCATALYST FOR THE ASYMMETRIC AZA-HENRY REACTION

4.1. IDENTIFICATION OF THE APPROPRIATE BIS-THIOUREA CATALYST AND IMINE SUBSTRATE

As was mentioned at the end of Chapter 3, the aim of the project presented in this chapter is the identification of an efficient aza-Henry catalyst that would bear two thiourea moieties in its structural framework, for the concurrent activation of the imine and the nitroalkane substrates.

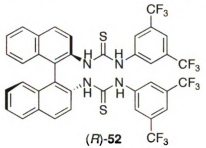
Concerning the chiral schaffold of the catalyst, we decided to focus our investigation on 1,1'-binaphthyl-2,2'-diamine **51** (BINAM, Figure 11), a chiral diamine that is rarely used in organic catalysis. A search for BINAM in Scifinder gives dozens of results for the use of the diamine as a ligand for metal catalysis, but its use in metal-free catalysis and particularly in the field of chiral thioureas, by comparison, has been very rare [40]. Intrigued by the fact that thioureas based on BINAM are largely unexplored, we designed and synthesized the new chiral thioureas **52** to **54**.

Figure 11. The chiral ligand BINAM

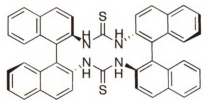


(*R*)-**51**

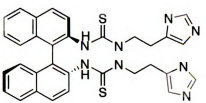
Figure 12. Structures of bis-thiourea catalysts



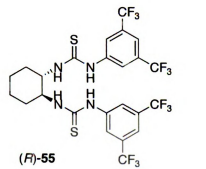
(*R*)-**52**



(*R*)-**53**



(*R*)-**54**



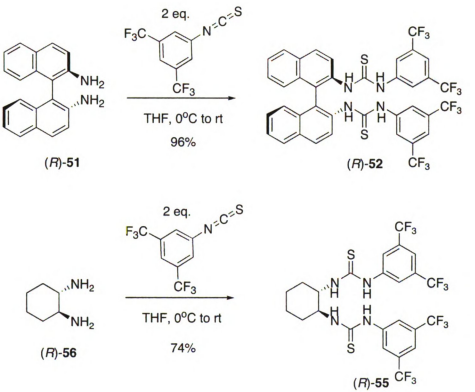
(*R*)-**55**

The design of catalyst **52** borrows from Schreiner's[36] and Takemoto's[35] thioureas featuring the electron withdrawing bis-trifluoromethyl phenyl substituent for enhancing the N-H acidity and thus H-bonding capability of the catalyst. Catalyst **53** was designed based on the speculation that two binaphthyl moieties around the reactive site may create a deeper and more efficient chiral pocket. Thiourea **54** has two thioureas and two histidines that could act as bases, so it was designed as a potentially bifunctional acid/base catalyst. The methylenes between the thioureas and the histidines in **54** would allow for the necessary degrees of freedom of rotation so that an ethyl histidine moiety could fold, approaching a nitroalkane molecule that would be bound to the thiourea and thus deprotonating it, promoting its reaction with an imine, bound to the second thiourea. Finally, the bis-thiourea catalyst **55**, which is based on cyclohexyl diamine, is a known catalyst that has been reported for an asymmetric Baylis-Hillman reaction[41]. Compound **55**

is the only known bis-thiourea catalyst in the literature, and we decided to evaluate its efficiency in the aza-Henry reaction in comparison with the BINAM-derived compounds.

The synthesis of compound **52** is straight-forward. Following the known procedure[41a] for the synthesis of **55** illustrated in Scheme 1, the new thiourea can be obtained from the reaction of BINAM with 3,5-bis(trifluoromethane)phenyl isothiocyanate in an almost quantitative yield after crystallization.

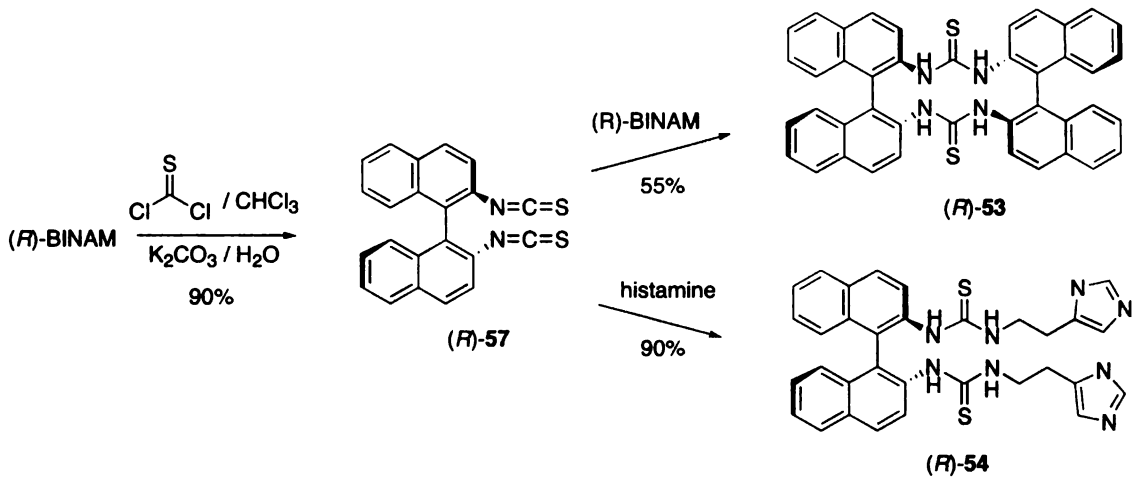
Scheme 15. Synthesis of bis-thiourea catalysts **52, 55**



The synthesis of catalysts **53** and **54** involves a simple two-step sequence through the intermediacy of the BINAM-bis isothiocyanate **57** (Scheme 16). Compound **57** can be obtained in a nearly quantitative yield from the reaction of (R)-BINAM with thiophosgene

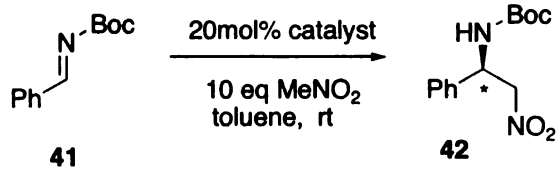
under basic conditions.[41b] Without any purification, **57** can be subjected to reaction with another (R)-BINAM moiety furnishing **53** (55%), or with histamine, affording **54** (90%).

Scheme 16. Synthesis of thioureas **53, 54**



The new bis-thioureas were evaluated in the aza-Henry reaction of nitromethane with N-Boc imine **41**. This particular imine was chosen as a model substrate since it has been established in the literature as an imine that is amendable to catalysis by urea and thiourea catalysts[34] (it is a bidentate imine since it features the N-carboxyl moiety that can potentially participate in double H-bonding). The results of the preliminary screening are shown in Table 14.

Table 14. Evaluation of the bis-thioureas in the aza-Henry reaction of N-Boc imine **41** (a)



41 **42**

entry	catalyst	Et_3N (eq.)	conversion % (b)	% ee (c)
1	(*R*)-**52**	-	0	-
2	-	0.2	20	-
3	(*R*)-**52**	0.4	100 (55) (d)	74
4	(*R*)-**53**	0.4	100	6
5 (e)	(*R*)-**54**	-	65	5
6 (f)	(*R*)-**54**	-	60	4
7	(*R*)-**55**	0.2	100 (50) (d)	8

(a) Reaction conducted with $MeNO_2$ (10 equiv), and several catalysts (20mol%) in toluene at room temperature overnight (except entry 1, which was run for 2 hours) with 0.25M in imine. (b) Determined by ^{1}H-NMR. (c) Enantiomeric excess was determined by HPLC analysis of **42** using a chiral column. (d) Isolated yield after column chromatography. (e) Reaction conducted in DMSO. (f) Reaction conducted in $MeNO_2$ (120 eq. with respect to the imine).

As can be seen from the data in Table 14, catalyst **52** can't promote the reaction without the presence of a base (entry 1). On the other hand, the base alone (without the presence of a catalyst) gives a very slow reaction (entry 2). On the contrary, when catalyst **52** is used (20 mol%) along with 40% Et_3N at room temperature, a quantitative conversion to the nitroamine **42** along with a very promising enantioselectivity (74%, entry 3) can be obtained. The reaction was very fast at rt, taking only ~2h for complete reaction of the imine. The selectivity of the catalyst **52** is superior to that of catalyst **55** (8% ee, entry 7), indicating that the BINAM schaffold is transfering stereochemical communication to the reaction center much more efficiently than its diamino cyclohexane analog. The isolated

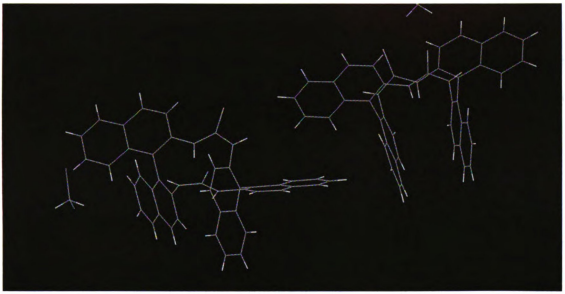
yields for these reactions were found to be in the range of 50-55%, and the inconsistency with the observed conversions can be attributed to possible decomposition of the sensitive imine during the course of the reaction, along with the tight separation from the catalyst and aromatic impurities presumably coming from decomposed catalyst in the SiO_2 column chromatography, in the case of entry 1 (**52** decomposes but **55** does not).

Catalysts **53** and **54** turned out to be inefficient in inducing any stereocontrol, affording very low ee's. In the case of **53**, the low asymmetric induction was in contrast to our initial anticipation from the assumption that two BINAM moieties would create an efficient chiral pocket for the reaction. The good conversion observed by ^{1}H-NMR for this reaction, though, indicates that the catalyst interacts with the substrates, but obviously in a way that lacks stereocontrol.

With a view towards understanding the structure of catalyst **53**, we determined the X-ray crystal structure of this compound (Figure 13). To our surprise the structure indicated that the preferred conformation of the bis-thiourea is C_2 symmetric only with respect to the relationship between the two binphthyls. The skeleton of the molecule folds in a way that the symmetry within each binaphthyl moiety "breaks" (which is in agreement with the NMR data for compound **53**, that indicates the presence of 12 aromatic protons and 20 carbons). The crystal structure also shows that the thiourea moieties adopt an *s-trans, cis* conformation instead of the expected *s-cis, cis*. The resulting structure is expected to leave a single N-H bond available for coordination to substrates. This N-H bond seems to be located outside the chiral cavity created by the binaphthyl moieties. The second N-H bond is between the two binaphthyls that seem to π-stack, and is probably less accessible. If the same conformation is favored in solution, that would explain the

inefficiency of catalyst **53** in exerting stereocontrol. On the other hand, the fact that conversion to the product occurred is interesting because it indicates that even a single thiourea N-H bond alone is enough for substrate activation and reaction promotion.

Figure 13. X-ray structure of compound **53**



On the other hand, catalyst **53** was found to be highly polar and insoluble in most common solvents, so polar solvents such as DMSO and nitromethane had to be used, leading to almost racemic products (enties 5 and 6).

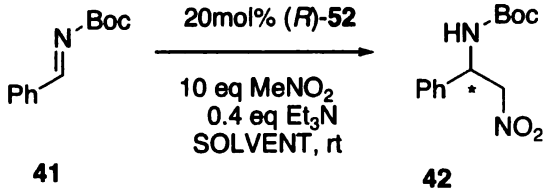
From the above study, catalyst **52** was chosen as the only bis-thiourea that was promising for its reaction outcome, and the investigation was then focused on the optimization of conditions.

4.2. OPTIMIZATION OF REACTION CONDITIONS

The search for the optimum conditions was based on four parameters: solvent, the effect of the base, temperature and catalyst loadings.

Concerning the optimum solvent, it was anticipated that non polar solvents that are not capable of participating in H-bonding with the substrates should promote the reaction more efficiently, given that a solvent that is an H-bond acceptor can interact with the N-H bonds of the thiourea and thereby "block" the reactive site. The results of the solvent search were in agreement with this notion: As can be seen in Table 15, there is a significant drop in the enantioselectivity when switching to THF (28% ee, entry 4), which presumably interacts with the catalyst, which in addition slows down the rate of the conversion. Benzene and dichloromethane gave satisfactory results, but the selectivity in toluene was the optimum.

Table 15. Solvent screening for the aza-Henry reaction with catalyst **52** (a)



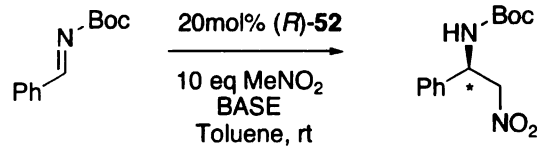
41 42

entry	solvent	conversion% (b)	%ee (c)
1	toluene	100 (55[d])	74
2	benzene	100	62
3	DCM	82	59
4	THF	52	28

(a) Reaction conducted with $MeNO_2$ (10 equiv), catalyst **52** (20%), Et_3N (0.4equiv) and 0.25M in imine using several solvents. Reactions run overnight. (b) Determined by ^{1}H-NMR. (c) Enantiomeric excess was determined by HPLC analysis of **42** using a chiral column. (c) Isolated yield after column chromatography.

With toluene as the optimum solvent, the effect of the base was examined in order to determine how the amount of base affects the yield and the selectivity. As can be seen in Table 16, the amount of the base surprisingly has a determining effect on the selectivity: the optimum induction (74% ee) is obtained when the level of Et_3N is 40-50%. Adding a whole equivalent of Et_3N causes a significant drop in the ee, and the same happens when only 20mol% Et_3N is used. Stronger or weaker bases (entries 5, 6) were found to give almost racemic products.

Table 16. Effect of the base on the reaction. (a)



41 **42**

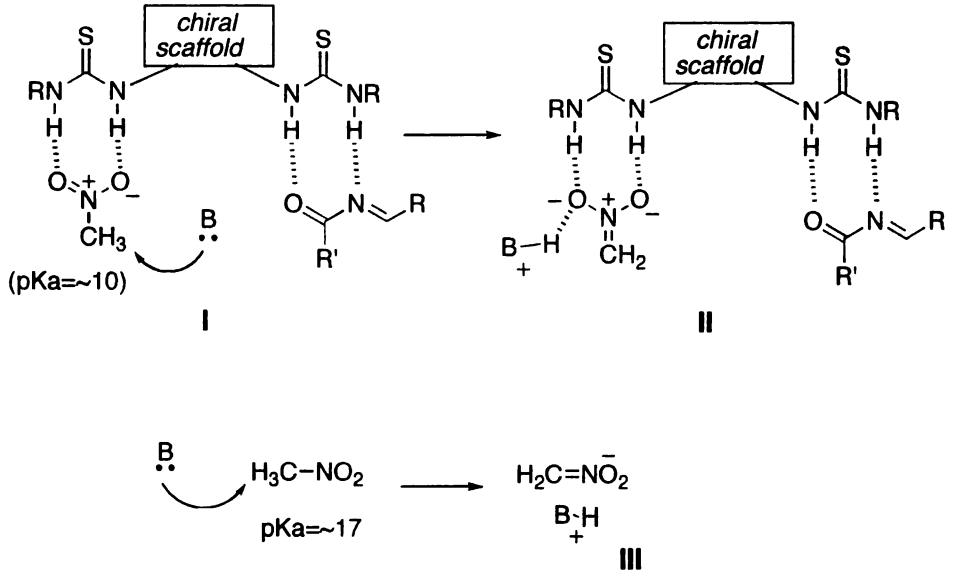
entry	base (equiv.)	pKa	yield % (b)	% ee (c)
1	Et_3N (0.2)	9.0(DMSO)	30	60
2	Et_3N (0.4)	>>	50	74
3	Et_3N (0.5)	>>	50	74
4	Et_3N (1.0)	>>	55	67
5	DBU (0.4)	12(H_2O)	100 (d)	2
6	N-Me-morpholine (0.4)	7.38	35	4

(a) Reaction conducted with $MeNO_2$ (10 equiv), catalyst **52** (20mol%) and 0.25M in imine in toluene at room temperature overnight. (b) Isolated yield after column chromatography. (c) Enantiomeric excess was determined by HPLC analysis of **42** using a chiral column. (d) Refers to conversion by ^{1}H-NMR.

One could rationalize these results if a few assumptions were made about the mechanism of the reaction. As shown in Scheme 17, it is reasonable to expect that

nitroalkane moieties bound to the thiourea will be much more acidic than the ones that do not interact. One would expect that the asymmetric induction in **42** will depend on the concentration of species **II**, if this is the reactive –and selective- species concerning the catalyzed pathway. The concentration of **II** will have an upper limit that will be determined not only by the amount of catalyst, but by the amount of the base as well. In other words, species **I** will have a concentration that will depend on the catalyst itself. For instance, 20% catalyst in a reaction of 0.25M substrate would afford a maximum concentration of 0.050M for **I** assuming saturation in the binding of the substrates to the catalyst. However, in order for **II** to reach the same level of concentration, the right amount of base, or a base with the proper pKb, will be needed.

Scheme 17. A tentative mechanistic hypothesis that could explain the effect of the base on the reaction



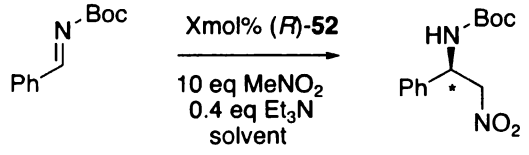
The pKa of bound $MeNO_2$ is expected to be around 10, similar to the pKa of the compound in water, where it is H-bonded by water molecules in a similar fashion. The pKa of unbound $MeNO_2$ is expected to be about 17, as it is in DMSO (where it isn't H-

bonded). Most of the nitroalkane in not bound, since there is only 20 mol% of the thiourea catalyst and a large excess of nitromethane (10 eq). Based on these considerations, a base with a pKa=~10 would be the right choice for promoting the conversion from **I** to **II**, avoiding the formation of species **III**. This is in accordance with Et_3N being the optimum base among the ones that were tried. It seems that DBU, which is a much stronger base compared to Et_3N, is able to promote the formation of **III** - and thus, the background reaction - to a degree enough for causing a significant drop-off in the selectivity. On the other hand, for the results in entries 1 to 4, it seems that 0.4-0.5 eq. triethylamine is the necessary amount for maximizing the concentration of complex **II**, and that a whole equivalent of the base will start promoting the background reaction, decreasing the stereoinduction in **42**. Concerning N-methylmorpholine, it seems that its lower basicity makes it inefficient in deprotonating nitromethane to the desired degree, and in this case the concentration of the "active catalyst" (or of **II**) is not very high (although one could argue that this particular base might H-bond to the catalyst through its oxygen atom and decrease the ee via catalyst deactivation).

Independent of the validity of the above assumptions and mechanism insights, one thing that is very clear from the above set of data is that triethylamine in the amounts of 40-50% is the optimum for the reaction, and thus we decided to proceed with further efforts to optimize the reaction by using 0.4 eq. triethylamine.

Next, the reaction was investigated at lower temperatures in an effort to enhance the asymmetric induction of **42**. The results are illustrated in Table 17.

Table 17. Optimization of temperature and catalyst loadings (a)



41 **42**

entry	cat.loading%	solvent	T°C	conversion% (b)	% ee (c)
1	20	toluene	rt	100 (55) (d)	74
2	20	toluene	-5	100	82
3	20	toluene	-35	83 (55) (d)	86
4	20	toluene	-55	50	84
5	20	mesitylene	-35	86	84
6	20	Cl-benzene	-35	93	84
7	10	toluene	-10	100 (50) (d)	80
8	10	mesitylene	-10	90	82
9	10	toluene	-35	53	78
10	5	toluene	-10	66 (30) (d)	71

(a) Reactions conducted with $MeNO_2$ (10 equiv), catalyst (*R*)-**52**, Et_3N (0.4equiv) and 0.25M imine in several solvents. Reaction time was ~36h except for entry 1 (2h). (b) Determined by ^{1}H-NMR. (c) Enantiomeric excess was determined by HPLC analysis of **42** using a chiral column. (d) Isolated yield after column chromatography.

The temperature was gradually reduced from rt to -55°C with maintaining the catalyst loading at 20mol%. As can be seen in entries 2 and 3 in Table 17, lowering the tempeature to –5°C and –35°C resulted in a significant enhancement of the enantioselectivity, to 82% and 86% respectively, without significantly affecting the

conversion of the imine. The reactivity of the catalyst was still satisfactory at –35°C, affording the same isolated yield for **42** as for rt. The rate of the reaction at -35°C was much slower than at rt (2h), but this could be overcome by using longer reaction times (36h). A further decrease in the temperature caused a drop-off in the reactivity, so –35°C was chosen as the optimum temperature. Other aromatic solvents such as mesitylene or chlorobenzene were almost as efficient at –35°C as toluene (entries 5 and 6). Reducing the catalyst loading to 10mol% still provided the chiral nitroamine with a high degree of enantioselection (80 and 82% ee in toluene and mesitylene respectively at –10°C).

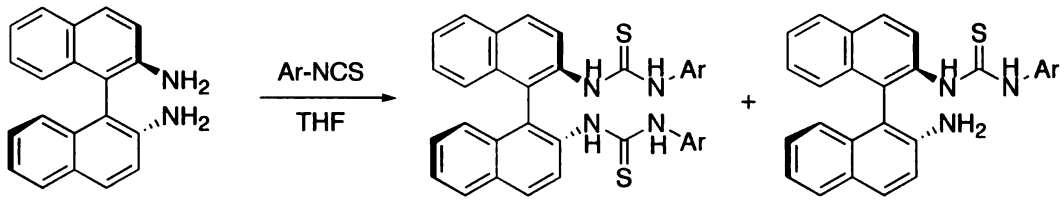
From the above data, the conditions in entry 3 (20 mol% catalyst and -35°C) were chosen as the optimum balance between yield and asymmetric induction. It should be noted here that the background reaction was tested at these conditions (using no catalyst and 40% triethylamine) and was found to give a 9% yield of racemic **42**.

4.3. SYNTHESIS AND EVALUATION OF DERIVATIVES OF CATALYST 52

Since catalyst **52** is readily obtained from the reaction of BINAM with 3,5-bis-(trifluoromethane) phenyl isothiocyanate, we reasoned that a derivatization of the catalyst with different functionalities on the aromatic substituents of the thiourea would be very interesting, because it would allow for a practical and convenient, based on the large amount of the commercially available isothiocyanates, comparison with the parent catalyst, and it might lead to the identification of other promising catalysts as well.

We synthesized a series of differently substituted bis-thiourea derivatives with variation of the electronic nature as well as on the steric bulkiness of the structures. The synthesis of the derivatives is shown in Table 18.

Table 18. Synthesis of thioureas **56a-61a** (a)



51 **56-61a** **56-61b**

entry	Ar	products	T°C	%yield (b) **a**	%yield (b) **b**
1	Ph	**56**	rt	50	50
2	p-NO_2-C_6H_4	**57**	rt	100	0
3	3,5-Cl_2-C_6H_4	**58**	rt	100	0
4	p-MeO-C_6H_4	**59**	rt	17	50
5	2,6-Me_2-C_6H_4	**60**	rt	0	0
6	2,6-Me_2-C_6H_4	**60**	70	0	50
7	1-naphthyl	**61**	rt	5	55
8	1-naphthyl	**61**	70	25	30

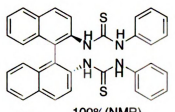
(a) Reactions run overnight except for entry 6, run for 2 days. (b) Isolated yield after column chromatography.

The reactions for the synthesis of compounds **57a** and **58a** were fast and quantitative, presumably because of the highly reactive electron-withdrawing isothiocyanates employed. Catalyst **58a** was obtained as a pure solid from the crude reaction product that needed no further purification. The reaction of the rest of the isothiocyanates turned out to be more complicated though, because the less reactive they were, the greater the amount of the undesired monosubstituted byproducts **56-61b** that was obtained. As a result, for compound **61** the ratio of di- to monosubstituted products was

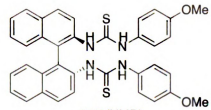
the least satisfactory, affording only a trace of **61a**. This could be partially overcome by increasing the temperature to 70°C which afforded a sufficient amount of the bis-thiourea for testing (25%, entry 8). The most demanding reaction was the one in entry 5, presumably because of the steric bulk at the 2,6-positions of the electrophile: compound **60a** couldn't be obtained even at elevated temperatures.

The new bis-thiourea derivatives were all tested in the aza-Henry reaction of N-Boc imine **41** with nitromethane at rt. The results are illustrated in Scheme 18.

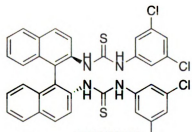
Scheme 18. Results for the screening of different thiourea derivatives in the aza-Henry reaction at rt



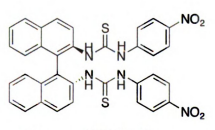
56a 100%(NMR) 5% ee



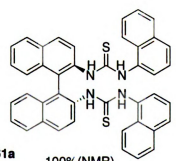
59a 36%(NMR) 0%ee



58a 73%(NMR) <5%ee



57a 100%(NMR) 16%ee



61a 100%(NMR) 4%ee

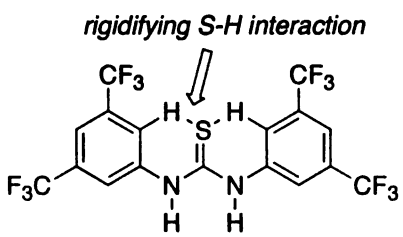
As can be seen from Scheme 18, the only thiourea that didn't afford a good conversion was **59a**. This is reasonable, since the N-H bonds of that thiourea are expected

to be the least acidic, and therefore the least efficient for H-bond interaction with the substrates.

All the rest of the thioureas afforded good conversions, but the asymmetric inductions of the product were disappointingly poor. One can expect that the H-bonding ability of thioureas **57a** and **58a** should be similar to that of **52**, but the inductions clearly demonstrate that even if there is H-bonding interaction, the communication of stereochemical information is ineffective. This difference might be associated with the bulkiness of the 3,5–bis trifluoromethyl groups and / or the arrangement in space of **52** compared to the rest of the thioureas. A better understanding of this issue will require further work – e.g. theoretical calculations or X-ray analysis of the catalysts.

In any case, the necessity of the 3,5–bis trifluoromethyl groups is not surprising on the basis of the literature associated with thiourea catalysis. Indeed, this particular substituent seems to dominate the structures of most of the thiourea catalysts that have been used. For example, Schreiner has studied the acceleration effects of various aromatic and aliphatic thioureas for a variety of non-asymmetric reactions and he has demonstrated

Figure 14. Schreiner's thiourea **47**



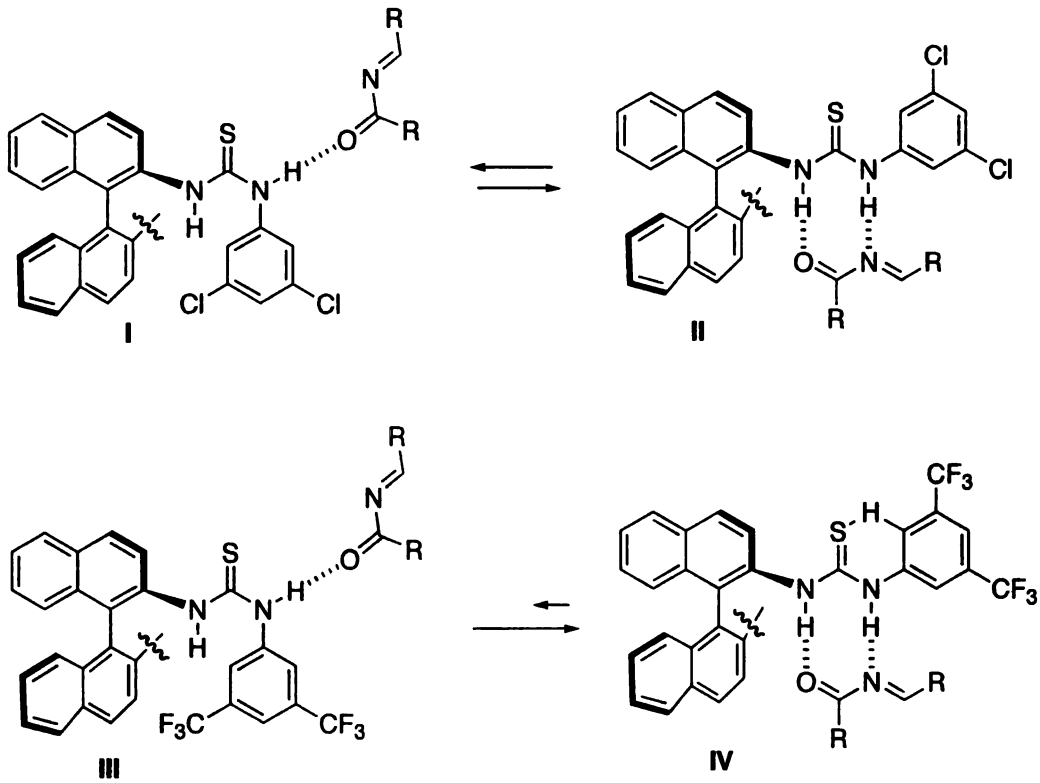
47

that catalyst **47** has been the most effective structure tested[36]. Schreiner has rationalized his results in terms of the importance of entropic effects; specifically it was proposed that

the (computationally determined) rotational barrier of catalyst **47** is relatively high due to an attractive interaction between the *ortho*-hydrogen atoms, which are polarized by the adjacent electron withdrawing substituent, and the Lewis basic sulfur heteroatom (Figure 14). This rigidifying interaction would minimize entropy loss upon binding of the substrate and thus facilitate catalysis[36].

In the context of the catalysts **56-61a**, the argument concerning the entropic effect of the S-H interaction discussed above could still apply (Scheme 19). In a comparison of catalyst **52** with **58a**, for instance,

Scheme 19. A possible mechanism to account for the high induction obtained with **52**



it could be argued that since the chloro- substituent is not as electronegative as the CF_3 group, this attractive S-H interaction shouldbe diminished, and the thiourea moiety would

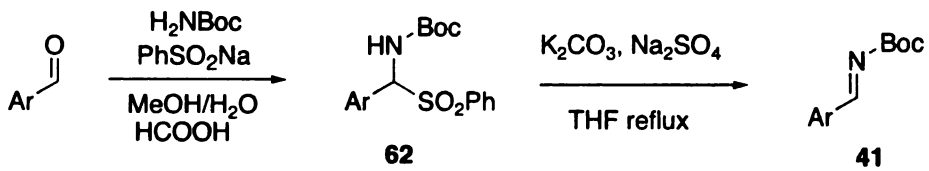
be more flexible in rotating and adopting different conformations, presumably less selective ones. On the other hand, for catalyst **52** the S-H interaction should make complex **IV** more abundant than **III**, resulting in bidentate binding and thus more well-defined orientations.

4.4. SUBSTRATE SCOPE

We next turned our attention to examining the scope of the asymmetric aza-Henry reaction for a series of differently substituted N-Boc imines and nitroalkanes.

For this purpose several imines were synthesized according to the standard procedure[38]. Table 19 shows the two-step sequence for obtaining a variety of electron withdrawing, donating or neutral aryl-substituted substrates **41**.

Table 19. Synthesis of aromatic N-Boc imines **41**

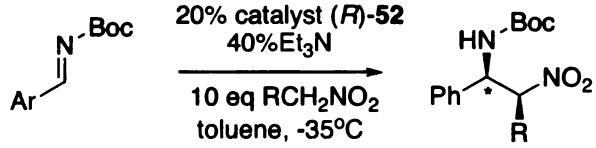


entry	Ar	series	%yield **62**	%yield **41**
1	Ph	**a**	100	98
2	p-Cl-C_6H_4	**b**	23	81
3	m-Cl-C_6H_4	**c**	77	99
4	o-Cl-C_6H_4	**d**	72	98
5	p-Br-C_6H_4	**e**	31	64
6	p-MeO-C_6H_4	**f**	84	77
7	o-MeO-C_6H_4	**g**	90	95
8	3-pyridyl	**h**	68	98
9	p-Me-C_6H_4	**i**	74	97
10	1-naphthyl	**j**	59	99

Most of the N-Boc imines were oils, and so they were used as crude products without any purification. It should be noted here that N-Boc imines are very sensitive to moisture and their synthesis and workup requires cautious handling. Additionally, it was found that the degree of their purity greatly influences the outcome of the aza-Henry reaction with catalyst **52**, especially regarding the enantioselectivities obtained. For example, when the reaction was performed with impure (partially hydrolyzed) imine **41a** that contained some benzaldehyde, product **42** was obtained in only 11% ee.

The results for the catalytic asymmetric aza-Henry reaction of the imines **41a-k** with nitromethane, nitroethane and nitropropane are summarized in Table 20.

Table 20. Reaction scope of the aza-Henry reaction of imines **41a-k** using catalyst **52** (a)



41 **42, 43a-k**

entry	Ar	R	time (h)	adduct	%yield (b)	%ee (c) (d.r.) (d)
1	Ph	H	36	**42**	55	86
2	p-Cl-C_6H_4	H	15	**43a**	62	85
3	m-Cl-C_6H_4	H	15	**43b**	55	91
4	o-Cl-C_6H_4	H	15	**43c**	61	74
5	p-Br-C_6H_4	H	24	**43d**	50	78
6	p-MeOC_6H_4	H	36	**43e**	50	89
7	o-MeO-C_6H_4	H	36	**43f**	40	65
8	3-pyridyl	H	22	**43g**	63	81
9	p-Me-C_6H_4	H	36	**43h**	48	86
10	1-naphthyl	H	36	**43i**	65	85
11	Ph	Me	36	**43j**	59	70 (e) (77/23)
12	Ph	Et	36	**43k**	63	80 (e) (80/20)

(a) Reaction conducted with RCH_2NO_2 (10 equiv), catalyst **1a** (20mol%), Et_3N (0.4equiv) and 0.25M imine in toluene at –35°C. (b) Isolated yield. (c) Enantiomeric excess was determined by HPLC analysis of **7a-l** using a chiral column. (d) Diastereomeric ratio was determined by HPLC. (e) Major (syn) diastereomer.

As can be seen from the data in Table 20, N-Boc imines with either electron donating or withdrawing groups can afford product **43** with moderate to good isolated yields and overall high selectivities. N-Boc imines with chloro substituents seem to be quite reactive, leading to quantitative conversions in short reaction times (15h) and to good isolated yields of the product along with high enantioselectivities, up to 91% ee (entries 2 to 4).

Electron donating groups slow down the reaction, but prolonged reaction times can afford satisfactory conversions and yields, along with good asymmetric inductions. The reason for the drop in the selectivity that is observed for the o-MeO substituted imine is not very clear at this point. On the other hand, electron neutral substituents don't have any effect on the selectivity of the reaction affording ee's always in the middle 80's (entries 9,10).

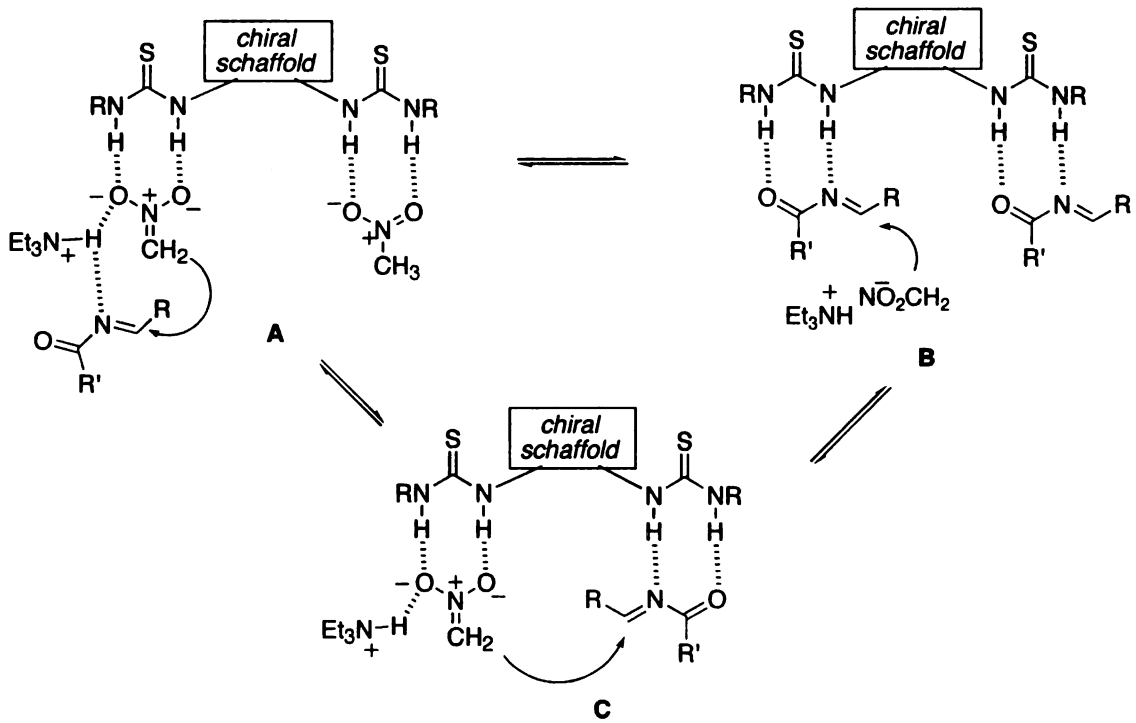
Finally, for the reaction of imine **41** with nitroethane a drop in the enantioselectivity is observed (70%ee, entry 11), while for the reaction with nitropropane, the enantio- and diastereoselectivity are still in a synthetically usefull range (entry 12), demonstrating that the asymmetric aza-henry reaction catalyzed by the bis-thiourea **52** is not limited only to nitromethane, but can be applied also to higher nitroalkanes.

A disadvantage of the above methodology is that the catalyst can not be recovered, since it partially decomposes during the course of the reaction and during column chromatography. The decomposition material usually has an R_f value similar to that of the product of the reaction, making the purification of some of the products tedious. Nevertheless, satisfactory yields in the range of 40-65% can be obtained for the resulting nitroamines.

4.5. AN INSIGHT INTO THE MECHANISM

A number of possible reaction intermediates can be envisioned for the reaction with catalyst **52**. It can be postulated that the two thiourea moieties can interact with two nitro groups (**A**), or with two imines (**B**), or with a nitroalkane and an imine at the same time (**C**), giving rise to three different species that interconvert with each other. These possible intermediates are shown in Scheme 20.

Scheme 20. Possible reaction intermediates



If the reaction occurred through intermediate **A**, the imine would have to be activated through the protonated triethylamine (if the imine interacting with the complex at all) in a "chiral nucleophile" mechanism.

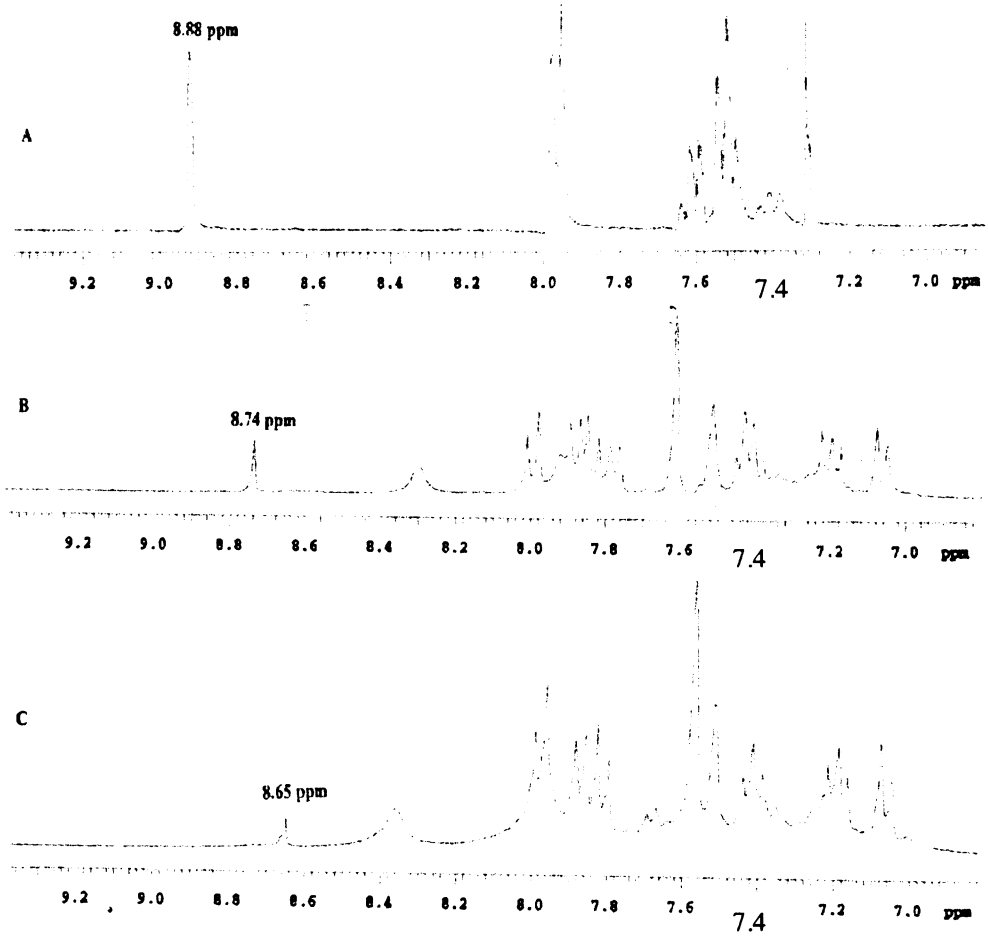
Complex **B** seems less possible, because the nitro group has been documented in the literature to be a very good thiourea coordinator[34]. It's also reasonable to suggest that $MeNO_2$ is interacting with the thiourea, since Et_3N is not basic enough to completely

deprotonate free $MeNO_2$ (pka=17 in DMSO vs 10 in H_2O). On the basis of that, mechanism **B** can be ruled out.

Finally, complex **C** describes our initial idea when designing the bis-thiourea catalysts, that is the dual activation of both reaction components.

To distinguish between mechanism **A** and **C**, we performed ^{1}H-NMR experiments in order to probe the interaction between the imine and the catalyst. Specifically, we prepared NMR samples of the imine alone and of imine / catalyst mixtures at different ratios. The results of this experiment are summarized in Figure 15.

Figure 15. ^{1}H-NMR Study as a probe for imine-catalyst interaction

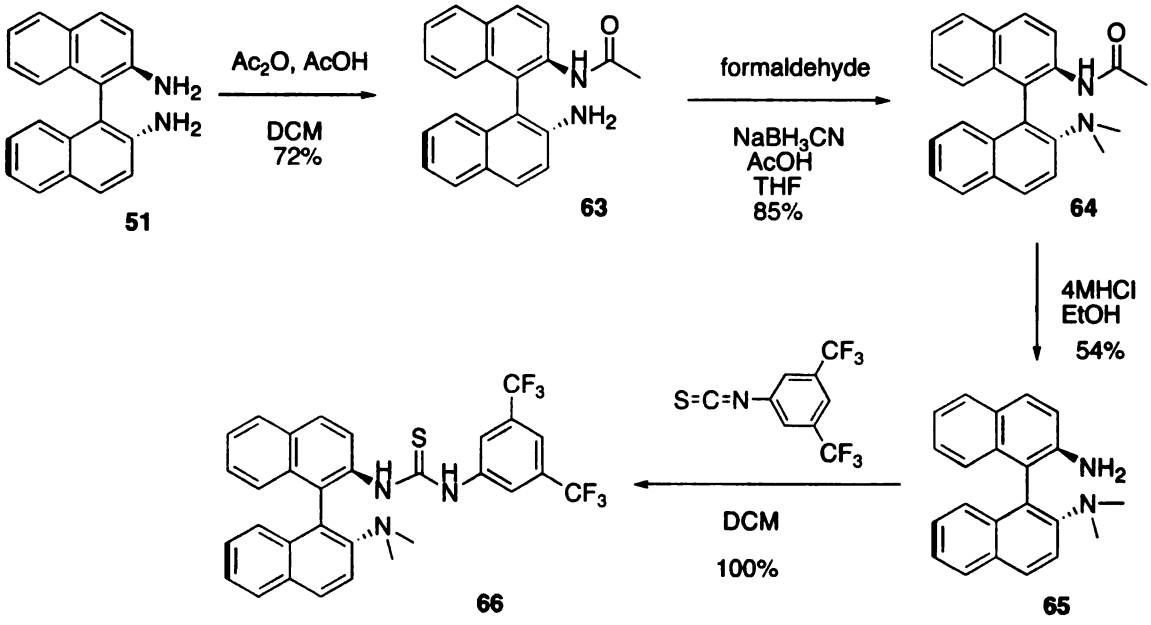


A: NMR of imine; B: 1eq. imine with 1 eq. catalyst **52**; C: 1eq. imine with 2 eq. catalyst **52**

As can be seen from the data in Figure 14, there is a significant change in the NMR of the imine while adding first one equivalent (B) and then two equivalents (C) of catalyst. The C(=N)H proton of the imine shifts from 8.88 ppm in the free imine to 8.65 ppm in the imine / 2 eq. catalyst mixture, strongly indicating that there is an interaction between the two species. On the basis of this experiment, mechanism **A** seems to be less possible than **C**. Subsequently, species **C** seems to be the actual intermediate of the reaction, or at least expected to contribute more than **A** or **B** to the reaction outcome.

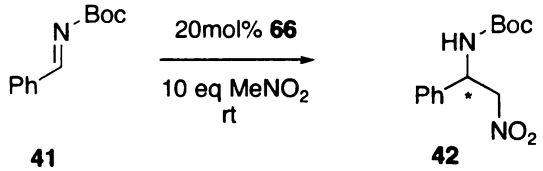
Additionally, the importance of both the thiourea moieties in the reaction mechanism was probed. Catalyst **66**, that bears only one thiourea in its structure, was synthesized and evaluated in the aza-Henry reaction. The catalyst was accessed in 4 steps from BINAM **51**, according to the procedure reported by Wang and coworkers[40b] (Scheme 21).

Scheme 21. Synthesis of thiourea **66**



Catalyst **66** was evaluated in the reaction of imine **41** with nitromethane in toluene and DCM and the data is shown in Table 21.

Table 21. Aza-Henry reaction of imine **41** using catalyst **66***



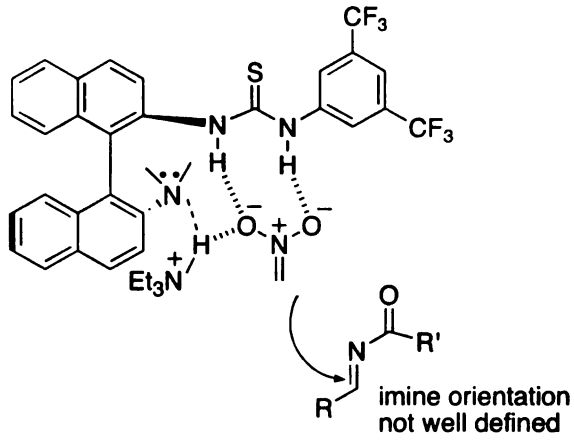
41 **42**

entry	solvent	Et_3N eq.	% yield	ee%
1	toluene	0	0	-
2	DCM	0	0	-
3	DCM	0.4	50	4

*Reactions run overnight, with 0.25M imine in DCM or toluene.

The reaction using catalyst **66** alone without an external base gave no product, presumably because the dimethylamine functionality of **66** is not basic enough to deprotonate nitromethane. When 0.4 eq. of triethylamine was added to the reaction mixture a 50% yield of the product was obtained, but with almost no asymmetric induction. This experiment shows that the presence of both thioureas is essential for the reaction outcome in terms of stereoinduction. One would expect that the intermediate for the reaction with **66** would feature nitromethane H-bonded to the thiourea, activated for deprotonation, but with the imine probably not interacting directly with the thiourea moiety (Figure 16). That would leave the imine without a well defined orientation, resulting in the very low induction that was observed. These observations with catalyst **66** are in accordance with mechanism **C** in Scheme 20 for the reactions with catalyst **52**.

Figure 16. Postulated mechanism for the reaction using **66** with triethylamine

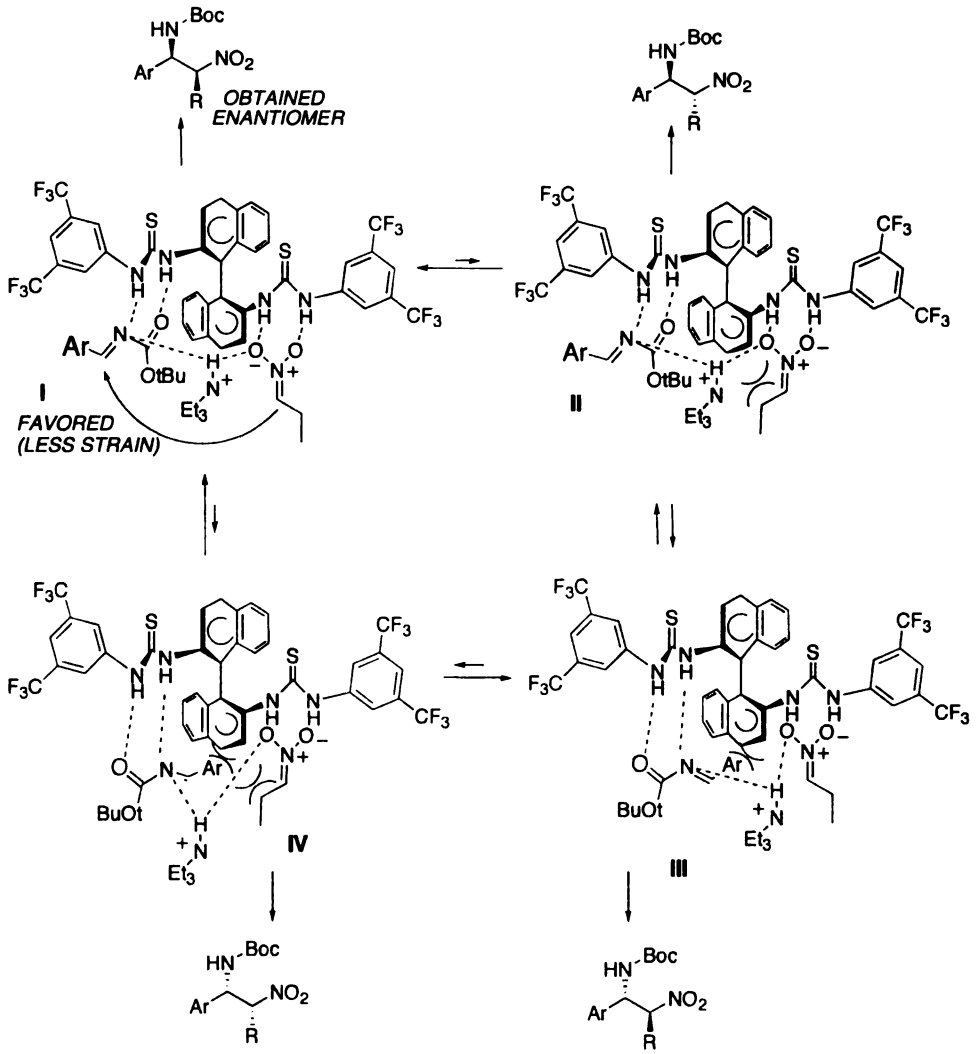


The absolute configuration of the products **42, 43** was determined by comparison of the HPLC data and the optical rotations of the products with the data reported in the literature. To account for the enantioselectivity and the diastereoselectivity of the transformation we propose the model shown in Scheme 22. The imine can interact with the thiourea adopting two different orienrations, one where the aryl group points to the catalyst (complexes **III** and **IV**) and one where it points away from it (**I** and **II**). It is proposed that the orientation of the imine with the aryl group away from the catalyst should be more energetically favored, because this way the strain associated with this interaction is minimized. This orientation exposes the *si* face of the imine towards nucleophilic attack from the activated nitronate, and this is in accordance with the absolute configuration of the stereogenic center bearing the N-Boc group.

Concerning the approach of the nitroalkane, it is clear that there are two different orientations as well. Again, the determining factor is probably the minimization of the steric strain of the alkyl chain of the RNO_2 resulting from close contacts with the catalyst structure. This hypothesis is in accordance with the data in Table 20, entries 11 and 12,

where a slightly higher selectivity is afforded when R=Et (product **43j**) compared with R=Me (product **43k**). The triethylammonium ion which results from the nitroalkane deprotonation might interact with the nitronate anion with hydrogen bonding, or with both the nitronate ion and the imine, as in Takemoto's model.[35]

Scheme 22. A plausible stereochemical model for catalyst **52**



Although the thiourea moieties in catalyst **52** presumably have some freedom of rotation and other structures and models could be also drawn, the model in Scheme 22 is a working hypothesis which can explain the observed selectivities.

4.5. CONCLUSION

In conclusion, a novel BINAM-based catalyst for the asymmetric aza-Henry reaction has been developed. The bis-thiourea catalyst probably functions according to a mechanism where both the components of the reaction are activated simultaneously by hydrogen bonding, indicating a mode of action different from that of the existing protocols and demonstrating the potential of bis-thioureas as an interesting class of unexplored catalysts. The catalyst is very easy to make and modify, and affords the aza-Henry products with modest to good yields, overall high enantioselectivities and synthetically useful diastereoselectivities.

CHAPTER 5

THE FIRST HIGHLY ENANTIOSELECTIVE ORGANOCATALYTIC DIRECT ADDITION OF NITROALKANES TO NITROOLEFINES

5.1. INTRODUCTION

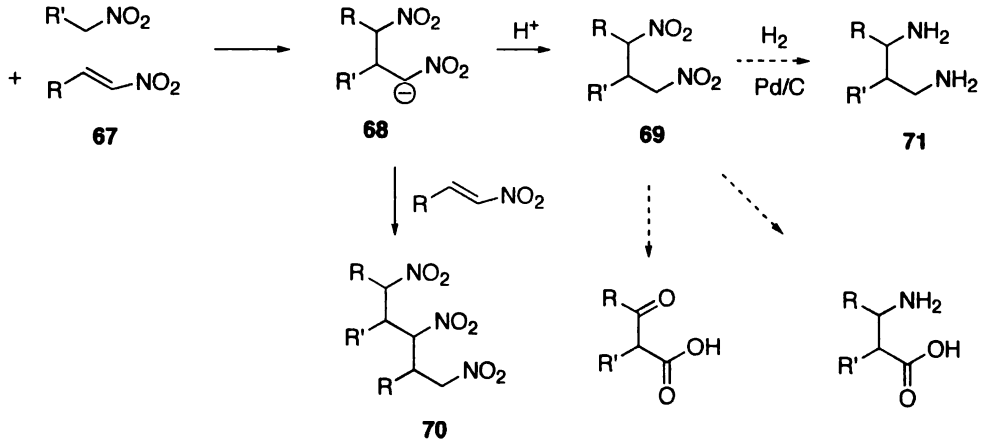
The use of nitroalkanes as reactive nucleophiles[42] and the use of nitroalkenes as Michael acceptors[43] have attracted significant interest in recent years in carbon-carbon bond formation reactions. Because of the activating effect of the nitro group, as well as its versatility as a masked functionality, nitro compounds have been quite useful in the synthetic arena[44a].

The Michael addition of nitroalkanes to nitroolefins is particularly interesting because the reaction products, 1,3-dinitro compounds (**69**), can be easily reduced by H_2 to 1,3-diamines **71**[45], a valuable functionality in the synthesis of complex molecules – given the number of natural products or pharmaceuticals that contain nitrogen - or other 1,3-difunctionalized compounds, heterocycles[46], and carbohydrate derivatives[47] (Scheme 23). Despite its synthetic value, this reaction is considerably overlooked and underdeveloped. This is partly because of the difficulty of controlling the addition of a nitronate to a nitroalkene. The initial product formed is the nitronate anion **68**, which is sufficiently reactive to also undergo conjugate addition to the nitroolefine **67**, thus resulting in a mixture of oligomerization products[48] including **70** and its higher congeners (Scheme 23), and in significantly reduced yields of the desired 1,3-dinitro products **69**.

Perhaps because of these difficulties, very few protocols for the above reaction have been published and are limited to one unasymmetric and two asymmetric methods

only. Thus, the addition of nitroalkanes to nitroolefins is one of the least developed and most intriguing types of Michael addition processes.

Scheme 23. The conjugate addition of nitroalkanes to nitroolefines as a useful route for the construction of valuable functionalities

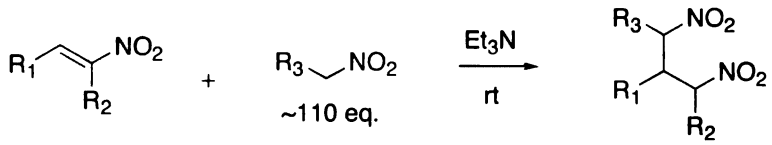


5.2 PROTOCOLS FOR THE CONJUGATE ADDITION OF NITROALKANES TO NITROOLEFINS

Protocols for the non-asymmetric conjugate addition of nitroalkanes to nitroolefins are extremely rare, although some early reports on the Michael addition of nitroalkanes – or their alkali metal salts – to nitroolefines (either isolated or generated in situ) had been described[49] in the late 40's to early 50's. The conditions for these reactions were harsh and the yields were variable and often low. According to the best of our knowledge, the only representative and relatively efficient method reported so far is reported by Alcantara's group in 1996[50]. According to that paper, reactions with the very reactive β-nitro esters as nucleophiles are fast in hexane or benzene, but less reactive aliphatic nitroalkanes are more sluggish, giving large amounts of polymers. Good yields of the desired 1,3-dinitroalkane products from these nitroalkanes can be obtained in reasonable reaction

times only if a large excess of nitroalkane (~110 eq) is used in a neat reaction (Table 22). The corresponding reactions in hexane or benzene are very slow, and in most cases the reactions are not diastereoselective, leading to mixtures of isomers.

Table 22. Alcantara's method for the synthesis of 1,3-dinitroalkanes

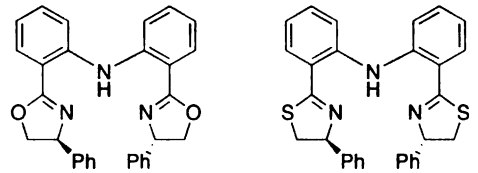


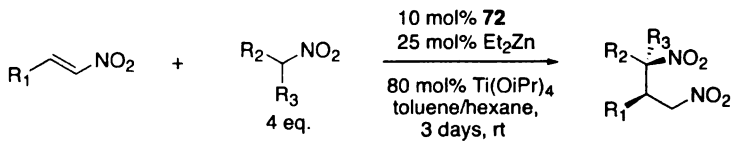
entry	R_1	R_2	R_3	time(h)	solvent	yield%
1	Gal	H	H	20	none	72
2	Gal	H	Me	24	none	68
3	Ph	H	H	1.5	none	51
4	Ph	H	Me	7	none	95
5	Ph	H	COOMe	2	hexane	66
6	Ph	Me	H	26	none	98
7	4-MeO-C_6H_4	Me	Me	24	none	80
8	furyl	Me	Me	120	none	72
9	isopropyl	H	COOMe	3	hexane	79

The breakthrough came in 2006 when Du's group reported a highly enantioselective version of the reaction using C_2-symmetric tridentate bis(oxazoline) and bis(thiazoline) zinc complexes[45]. This group had used these catalysts before in the context of Lewis acid catalyzed Henry reactions of nitromethane with α-keto esters[51]. The ability of these zinc species to activate nitroalkanes was applied successfully in the conjugate addition of the latter species to a series of substituted nitrostyrenes, affording the first

enantioselective protocol for the reaction with up to 95% ee for the resulting 1,3-dinitro compounds (Table 23).

Table 23. The first asymmetric addition of nitroalkanes to nitroolefines



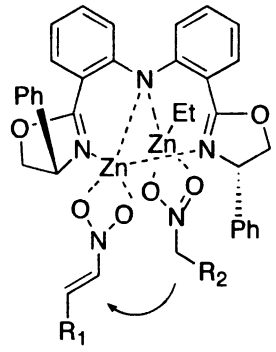


entry	R_1	R_2	R_3	yield%	d.r.	%ee
1*	Ph	Me	H	87	11.7/1	95
2	4-MeC_6H_4	Me	H	83	6.1/1	91
3	4-$MeOC_6H_4$	Me	H	83	6.5/1	89
4	2-$MeOC_6H_4$	Me	H	90	5.8/1	91
5	3,4-$(MeO)_2C_6H_4$	Me	H	67	9.6/1	86
6*	4-FC_6H_4	Me	H	79	9.3/1	92
7	2-FC_6H_4	Me	H	87	6.2	90
8	2-ClC_6H_4	Me	H	83	3.8/1	91
9	2-naphthyl	Me	H	83	3.8/1	88
10	2-furyl	Me	H	67	6.7/1	88
11	$PhCH_2CH_2$	Me	H	80	3.4/1	72
12	Ph	Et	H	88	4.1/1	88
13	Ph	Me	Me	0	-	-

*Ligand **73** was used.

As can be seen from the data in Table 23, Du's method is highly efficient for the synthesis of enantioenriched *syn*-1,3-dinitro products. The reaction is broad in scope since either electron rich or electron deficient nitrostyrenes can be used, and additionally, heteroaromatics (entry 10) and aliphatics (entry 11) can be also tolerated. Branched nitroalkanes though turned out to be sluggish nucleophiles (entry 13).

Figure 17. Proposed mechanism for Du's asymmetric addition

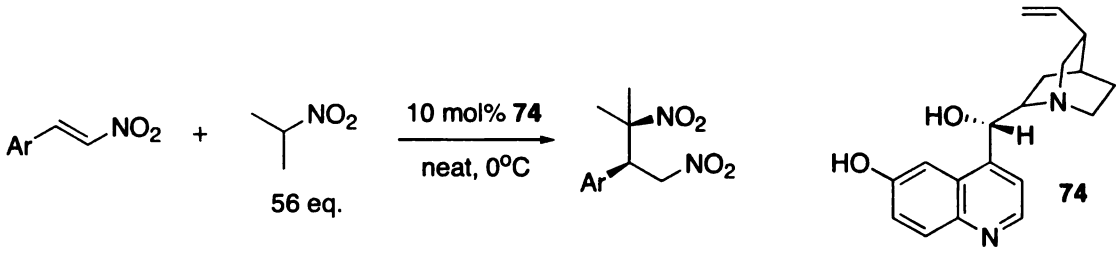


The conjugate addition of nitroalkanes to nitroolefines is proposed to work through the model depicted in Figure 17 (although the authors ignored the role of Ti), with the Zn activating nitroethane for deprotonation and at the same time forming a complex with the nitroolefin, which is oriented in the chiral pocket so that its *Re* face is exposed for nucleophilic attack[45].

The second protocol for the direct conjugate addition of nitroalkanes to nitroolefines was reported by Wang's group in the same year[52]. It described the addition of branched nitroalkanes – mainly 2-nitropropane – to nitrostyrenes under neat conditions using the modified *Cinchona* alkaloid **74** to obtain 1,3-dinitro products in good yields and modest to good enantioselectivities (67-85%ee, Table 24). This particular method has a major drawback: the catalyst is not reactive enough to provide reasonable reaction times even without the use of a solvent and under a large excess of the nitroalkane. Several days

are required for the reactions to go to completion (presumably the branched nitroalkane is too hindered to be a reactive nucleophile).

Table 24. Wang's protocol using catalyst **74**



Ar	t(days)	%yield	ee%	Ar	t(days)	%yield	ee%
Ph	6	79	78	2,6-$Cl_2C_6H_3$	7	75	80
4-FC_6H_4	7	76	73	4-$MeOC_6H_4$	12	78	67
4-ClC_6H_4	8	70	83	2-$MeOC_6H_4$	8	73	84
2-$CF_3C_6H_4$	9	78	83	2-$BnOC_6H_4$	7	80	77
2-ClC_6H_4	10	73	81	2-thiophene	10	78	70

Finally, Maruoka's group has published the enantioselective addition of *preformed silyl nitronates* to nitrostyrenes, a surrogate to the reaction of interest that requires the separate preparation of the highly reactive silylated nitroalkanes for use as nucleophiles[48]. Using catalyst **75**, *syn* products can be obtained in excellent yields and good to excellent enantioselectivities. As may be expected for the reactions of these highly reactive species, very low temperatures (-78°C) have to be used in order to achive the maximum inductions.

Figure 18. Maruoka's catalyst for the formal addition to nitroalkenes

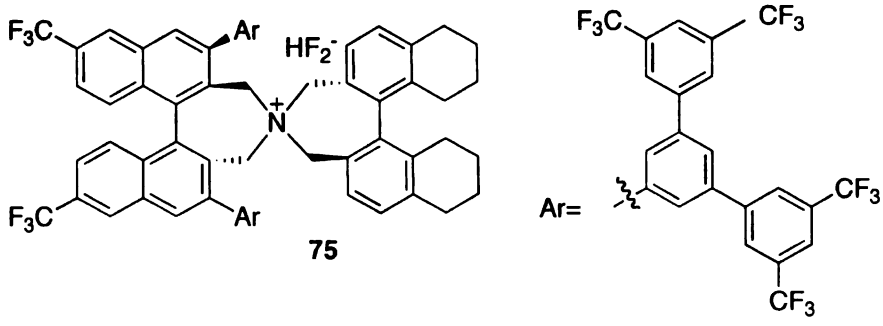
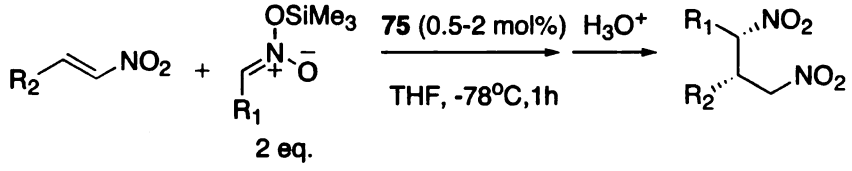


Table 25. Maruoka's formal addition using catalyst **75**



entry	R_1	R_2	mol.% **75**	yield%	d.r.	%ee
1	Et	4-$MeOC_6H_4$	1	99	>95/5	91
2	>>	2-$MeOC_6H_4$	0.5	99	>>	87
3	>>	2-ClC_6H_4	0.5	98	>>	80
4	>>	2-naphthyl	0.5	95	>>	89
5	>>	furyl	2	92	>>	93
6	>>	thiophenyl	2	85	>>	91
7	>>	cyclohexyl	1	99	>>	92
8	>>	*n*-hexyl	1	93	>>	76
9	Pr	Ph	1	99	>>	91
10	$MeOCH_2$	Ph	1	99	82/18	83

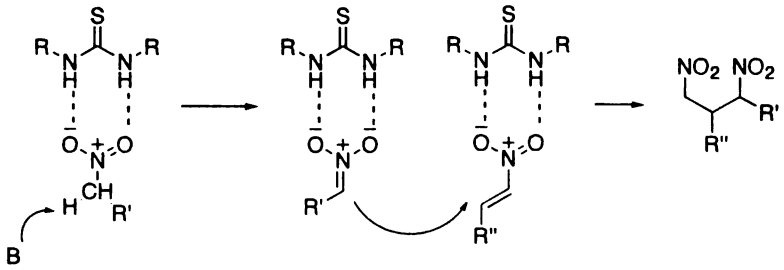
5.3. THE CONJUGATE ADDITION OF NOTROALKANES TO NITROOLEFINES BY MEANS OF THIOUREA CATALYSIS

It is clear from discussion in the previous section that the addition of nitroalkanes to nitroalkenes is a reaction that is just starting to be developed, and that there is plenty of room for improvement. There are a lot of aspects to address and improve, namely the problem of oligomerization, the diastereoselectivity in the non-asymmetric reaction, and the enantioselectivities, that are modest in the case of Wang's organocatalyzed protocol[52]. The development of an efficient protocol for a diastereoselective non-asymmetric synthesis of 1,3-dinitro compounds, as well as the identification of catalyst structures – either metal based or metal free – that can induce high asymmetric inductions in these products would be highly desired.

Our interest in the addition of nitroalkanes to nitroalkenes – as well as in the field of thiourea catalysis – focused our approach towards the development of an efficient protocol for this reaction in an investigation of the use of thioureas as catalysts. It is known that thioureas can activate nitrostyrene (and other nitroolefins) for the addition of a vatiety of nucleophiles[34]. On the other hand, the activation of nitroalkanes and the enhancement of their acidity through their interaction with thioureas is also known, in several reports where the successful employment of nitroalkanes as reactive nucleophiles is described[34]. Despite all these reports, a thiourea promoted addition of nitroalkanes to nitroolefines has never been reported in the literature, although it would be expected that the application of thioureas could facilitate the above transformation and possibly control the selectivity of the addition (Scheme 24). A careful review of the field of thiourea catalysis reveals that, concerning the employment of thioureas as catalysts, this particular

transformation is probably one of the few reactions involving nitro compounds that has not been addressed so far[31,34].

Scheme 24. The conjugate addition of nitroalkanes to nitroolefines promoted by thioureas



Our approach is depicted in Scheme 24. It is expected that the use of thioureas for the above reaction will activate the nitroalkane, enhancing its acidity, and activate the nitroolefine, enhancing its reactivity of the C-C double bond. The presence of a catalytic amount of a thiourea - for substrate activation - and the presence of a base - for nitroalkane deprotonation – should be sufficient for reaction acceleration, and might lead to a chemoselective and diastereoselective reaction outcome. The chemoselectivity is an important issue since polymerization can cause a decrease in yield of the Michael adduct or require large amounts of nitroalkane to maintain good yields.

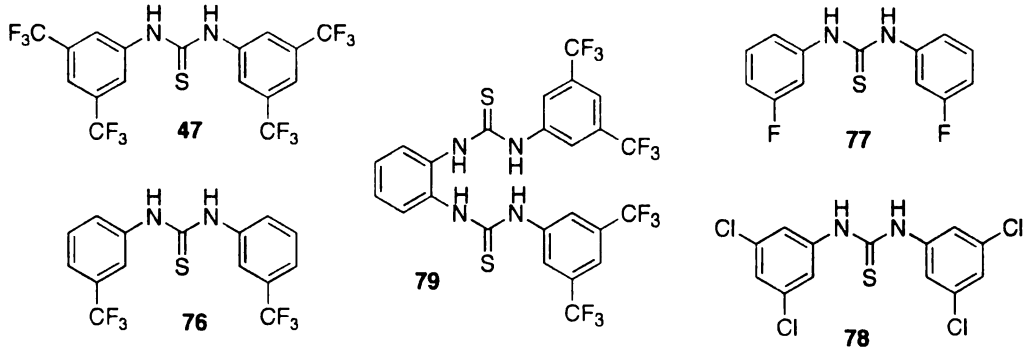
The rest of the chapter describes the use of thioureas in the context of the conjugate addition, in an investigation that was focused on i) the employment of simple aromatic thioureas for the promotion of the unasymmetric reaction and ii) the development of a novel chiral thiourea catalyst for a highly enantioselective conjugate addition methodology.

5.3.1. Development of the thiourea catalyzed non-asymmetric addition

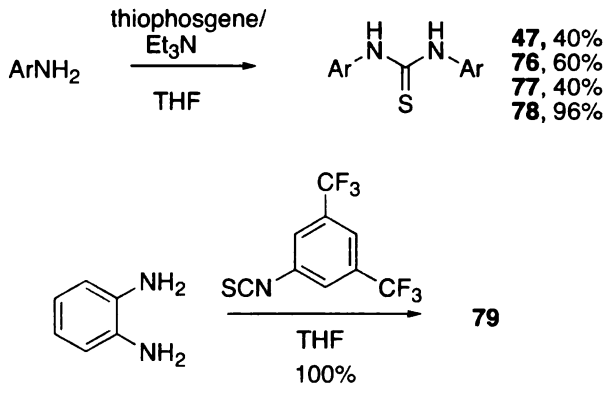
It was realized that an investigation of the thiourea promoted addition of nitroalkanes to nitroolefines should be first focused on the non-asymmetric reaction, and on the effects that simple achiral thioureas would have on the transformation, since as it was mentioned, the employment of thioureas in this particular type of reaction has never been described before in the literature.

The small symmetrically substituted aromatic thioureas **76-78** shown in Figure 19 have been reported before in the literature in various studies conducted by Schreiner's group and other research groups, for the acceleration of several transformations including Diels-Alder, Bayllis-Hillman, or Claisen rearrangements[34]. Schreiner has established that diaryl thioureas of this type with electron withdrawing substituents on the meta and/or para positions are the most effective candidates for rate acceleration in a diverse set of reactions[34,36]. Thus, it was judged that this type of thioureas should be the focus of our study. Additionally, we decided to also make and evaluate the bis-thiourea **79**, based on the idea that two thioureas incorporated in the same structure might result in activation of both reactants.

Figure 19. The substituted aromatic thioureas used in this work



Scheme 25. Synthesis of aromatic thioureas **47, 76-79**

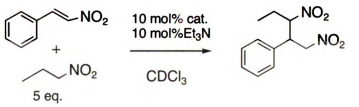


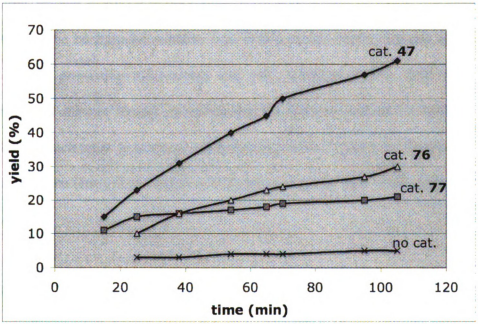
The synthesis of thioureas **47** and **76** to **79** was accomplished using standard literature procedures.[41c] As shown in Scheme 25, thioureas **47, 76-78** can be accessed from the reaction of commercially available substituted anilines with thiophosgene and triethylamine in THF. On the other hand, thiourea **79** can be made from 1,2-diaminobenzene with 3,5-bis-trifluoromethylphenyl isothiocyanate.

We started our investigation by looking at the effect that the thioureas **47** and **76-79** have on the rate acceleration of the conjugate addition. The reaction between trans-β-nitrostyrene and 1-nitropropane was used as a model reaction in $CDCl_3$, employing only 5 equivalents of nitropropane, a very small excess compared to Alcantara's protocol, and using 10 mol% thiourea and 10 mol% triethylamine. The rate of the reactions was followed by ^{1}H-NMR using the catalyst as an internal standard. Thiourea **78** was not soluble in $CDCl_3$ and therefore was not evaluated. The results for reaction with thioureas **47, 76** and **77** are shown in Scheme 26. As can be seen in Scheme 26, the reaction without thiourea (using 10 mol% Et_3N) is very slow, affording only a 5% yield of the desired 1,3-dinitroalkane after 3h. On the other hand, the rate acceleration that thioureas **47, 76,** and

77 can cause is very significant: Thioureas **76** and **77** can increase the relative rate of the reaction by approximately 5 and 6 times, respectively. It is obvious that thiourea **47**, bearing the 3,5-bis-(trifluoromethyl) moiety is the most efficient catalyst, leading to almost quantitative conversion of the starting nitrostyrene in 2 hours, and affording ~60% yield of the desired 1,3-dinitroalkane.

Scheme 26. Rate accelaration of the conjugate addition using thioureas **47, 76, 77**



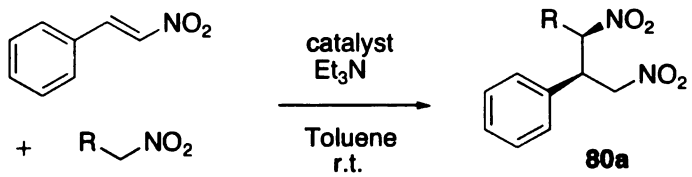


The results shown in Scheme 26 were very promising at that point, because it showed the potency of thioureas in promoting the coupling between the two nitro-components. The diastereoselectivity of the reaction was not determined – the yields in Scheme 26 refer to that for the combined syn and anti products. Since good yields can be

obtained in only two hours these results prompted further investigation of these thioureas, especially **47**.

Next, the efficiency of thioureas **47** and **76-79** was investigated in regard to the yield and the diastereoselectivity of the addition of various nitroalkanes. The results for the reactions of nitroethane, 1-nitropropane and 1-nitrobutane with nitrostyrene are shown in Table 26. Nitroethane affords a mixture of diastereomers (entry 1), however it was delightful to observe that the control of the selectivity for the rest nitroalkanes is much better. All thioureas can control the selectivity of the reaction in favor of the *syn* isomer, furnishing the desired product in good yields (up to 83%) and affording d.r. ratios between 77/23 and 87/13. The background reaction without thiourea (10 mol% Et_3N, entry 7) is very slow, leading to a trace of the product after an overnight period. It was interesting to observe that the background reaction even with a stoichiometric amount of base is still inefficient in promoting the reaction and only furnishes a 39% yield with a slight preference for the *anti* isomer, revealing that the catalytic and the background reaction complement each other in terms of stereocontrol (Table 26, entry 8). Finally, the reaction with nitrobutane (entry 9) is consistent with the rest, giving 82% yield of the *syn*-enriched product.

Table 26. The conjugate addition of nitroalkanes to nitrostyrene catalyzed by thioureas (a)



80a

entry	R	catalyst (mol%)	mol% Et_3N	yield% (b)	d.r. (syn/anti) (c)
1	Me	**47** (10)	10	85	55/45
2	Et	**47** (10)	10	83	77/23
3	Et	**76** (10)	10	66	78/22
4	Et	**77** (10)	10	58	87/13
5	Et	**78** (10)	10	75	80/20
6	Et	**79** (10)	10	67	84/16
7	Et	-	10	7	n.d.
8	Et	-	100	39	40/60
9	*n*-Pr	**47** (10)	10	82	77/23

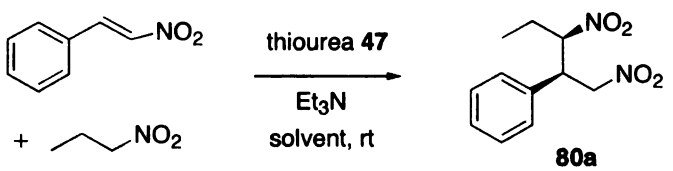
(a) Reaction conducted with 0.22M with respect to nitrostyrene in toluene for 12h using 10 equivalents of nitroalkane. (b) Isolated yield of the mixture of diastereomers. (c) Determined by HPLC analysis.

It was interesting to observe that in all of the reactions in Table 26 all of the thioureas can promote the formation of the desired product and at the same time suppress the production of polymeric material. The excess of nitroalkane used in the above reactions was only 10 equivalents, much lower than in Alcantara's protocol (~110 eq.).[50] Nonetheless, the rate acceleration that thioureas afford in favor of the desired product is

apparently high enough to provide quite clean reactions (in terms of the amount of polymer formed). The reaction catalyzed only by Et_3N (entry 8) gave a higher amount of polymeric material, as judged by the messy crude ^{1}H-NMR spectrum obtained.

Since catalyst **47** turned out to be the optimum for the reaction, the addition of 1-nitropropane to nitrostyrene catalyzed by thiourea **47** was next examined in different solvents and using various catalyst loadings in order to optimize the conditions and the results are summarized in Table 27. The yields of the products were determined by the ^{1}H-NMR spectrum of the crude reaction mixture with triphenylmethane as internal standard. The catalyst loadings for the reactions in toluene were gradually reduced as indicated in entries 1 to 4. The diastereoselectivity of the reaction remains intact when the catalyst is reduced from 10 to to 2 mol%, while a small drop-off is observed in the rate of the reaction (entry 3, 58%). This can be suppressed by adding more nitropropane and increasing the reaction time. For example, by using 20 equivalents of nitroalkane and keeping the catalyst loading at 2 mol%, a very good yield of the product can be obtained (85%, entry 4) in 2 days reaction time and no decrease is observed in the *syn* to *anti* ratio. The reaction in other solvents also afforded good yields and d.r.'s, with THF being the only exeption, which is as expected for a solvent that can function as an H-bond acceptor and decelerate the reaction (entry 8, 45%).

Table 27. Optimization of conditions for the reaction using thiourea **47** (a)



80a

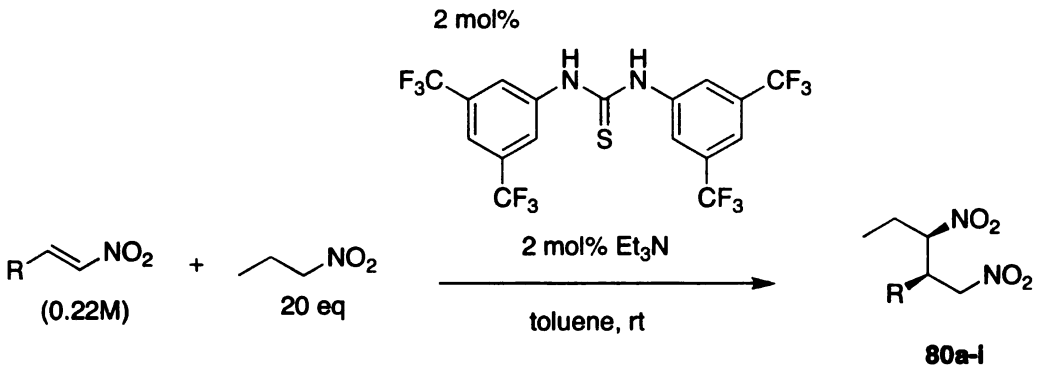
entry	solvent	mol% **47**	mol% Et_3N	eq. *n*-prNO_2	yield% (b)	d.r. (c)
1	toluene	10	10	10	83	77/23
2	toluene	4	4	10	63	80/20
3	toluene	2	2	10	58 (d)	79/21
4	toluene	2	2	20	85	77/23
5	-	2	2	20	82	73/27
6	benzene	10	10	10	89	68/32
7	DCM	10	10	10	78	75/25
8	THF	10	10	10	45	77/23

(a) Reactions conducted in the corresponding solvent, for 12-15h, except entries 2-5 which were run for 2 days. Entries 1-5 were run with 0.22M with respect to nitrostyrene, entries 6-8 were run with 0.1M with respect to nitrostyrene. (b) Determined by ^{1}H-NMR of the crude mixture. (c) Determined by HPLC analysis. (d) Incomplete conversion.

After optimization of the solvent and catalyst loading, the conditions on Table 27, entry 4 were chosen as the optimum and the scope of the reaction was examined for a series of differently substituted nitrostyrenes. As can be seen from the data in

Table 28, a number of differently substituted nitrostyrenes can undergo the thiourea catalyzed addition to give the *syn* 1,3-dinitroadducts **80a-i** in good yields. Electron rich nitrostyrenes (entries 2 to 4) were less reactive and needed longer reaction times (40h) to go to completion, while electron deficient substrates (entries 5 to 9) afforded complete conversions in only 16 hours. In every case, the starting material underwent complete conversion (90-100%) with only small amounts of polymer formed, and the reactions were in general very clean compared to the background reaction (Table 26, entry 8). It seems that the thiourea catalyst is accelerating the formation of the desired adducts suppressing the overaddition process and affording very good turnovers. Additionally, the reactions favor the formation of the *syn* diastereomer in good selectivities that range from 3/1 to 9/1.

Table 28. Reaction scope for the thiourea catalyzed addition of 1-nitropropane to β-nitrostyrene (a)



80a-i

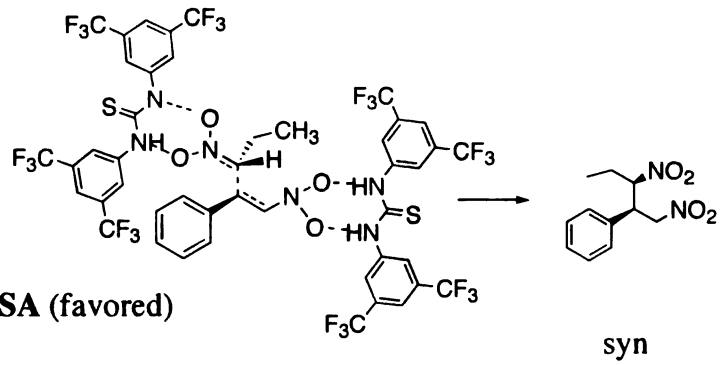
entry	R	adduct	overall yield%	yield% syn (b)	d.r. (c)
1	Ph	**80a**	87	75	77/23
2	4-MeO-C_6H_4	**80b**	82	73	75/25
3	2-MeO-C_6H_4	**80c**	83	66	80/20
4	4-Me-C_6H_4	**80d**	72	56	77/23
5	2-Cl-C_6H_4	**80e**	80	68	85/15
6	4-Cl-C_6H_4	**80f**	73	58	80/20
7	4-Br-C_6H_4	**80g**	66	57	86/14
8	3-Br-C_6H_4	**80h**	75	69	92/8
9	2-Br-C_6H_4	**80i**	66	60	90/10

(a) Reactions run overnight except entries 2-4 which were run for 40h. (b) Isolated yield after column chromatography. (c) Determined from the ratio of isolated products except entries 1 and 2, which were determined by the ^{1}H-NMR of the crude reaction mixture.

An explanation for the preferential formation of the *syn* isomer can be obtained from the examination of the corresponding transition states for the two diastereomeric dinitroalkanes (Scheme 27). It seems that the lowest energy transition states for both the *syn* and the *anti* product formation would be the ones where the groups with the largest A

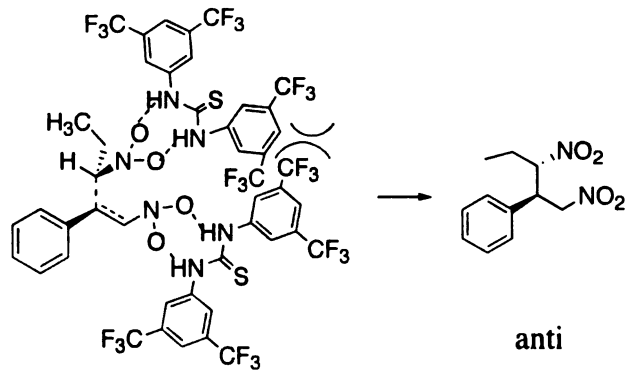
values would be *anti* to each other. That means that the phenyl group of the nitrostyrene (A=3.1 kcal/mol) and the ethyl group of the nitropropane (A=1.9 kcal/mol) have to adopt an *anti* relationship (the A value of the NO_2 group is 1.1 kcal/mol). In the TS A, which gives the *syn* product, this requirement also results in the nitro groups being opposite to each other. On the contrary, considering the TS B that gives the *anti* product, the *anti* relationship of the phenyl and the ethyl group results in the nitro groups coming close to each other and pointing to the same direction, creating a steric hindrance between the two thioureas. The steric congestion of the TS B seems to be a plausible explanation for the observed stereoselectivity, although more experiments should be done to verify this hypothesis (e.g. rate studies to prove that the reaction is second order in catalyst).

Scheme 27. A possible explanation for the preference of the syn diastereomer formation in the reaction catalyzed by thiourea **47**



TSA (favored)

syn



anti

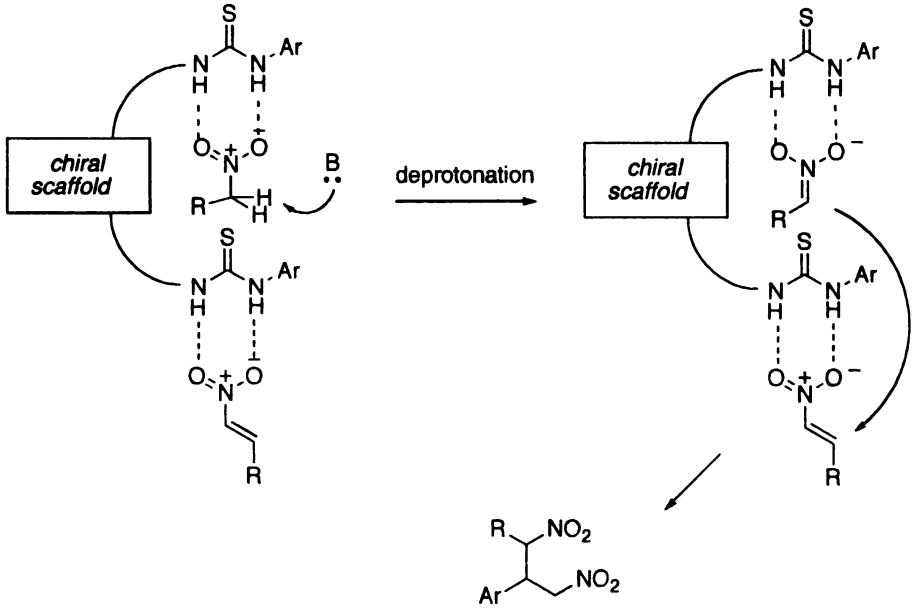
TS B (unfavored)

5.3.2 Development of the asymmetric conjugate addition of nitroalkanes to nitroolefines

The success of thiourea catalyst **47** in promoting the *syn*-selective non-asymmetric addition of 1-nitropropane to β-nitrostyrene prompted the investigation of an enantioselective variant using chiral thiourea catalysts. The reaction design for the asymmetric variant is shown in Schemes 28 and 29 and includes two different approaches.

a) *Bis-thiourea catalysts that can mutually activate both reaction components* (Scheme 28). In this approach, one thiourea moiety is used for H-bond activation of nitrostyrene and the second thiourea moiety is activating the nitroalkane for deprotonation. In this case an external base will have to be used for the deprotonation, leading to the formation of a nitronate, in a complex that will feature the two components in close proximity for reaction. This concept was the one that was used for the development of the asymmetric aza-Henry reaction in Chapter 4.

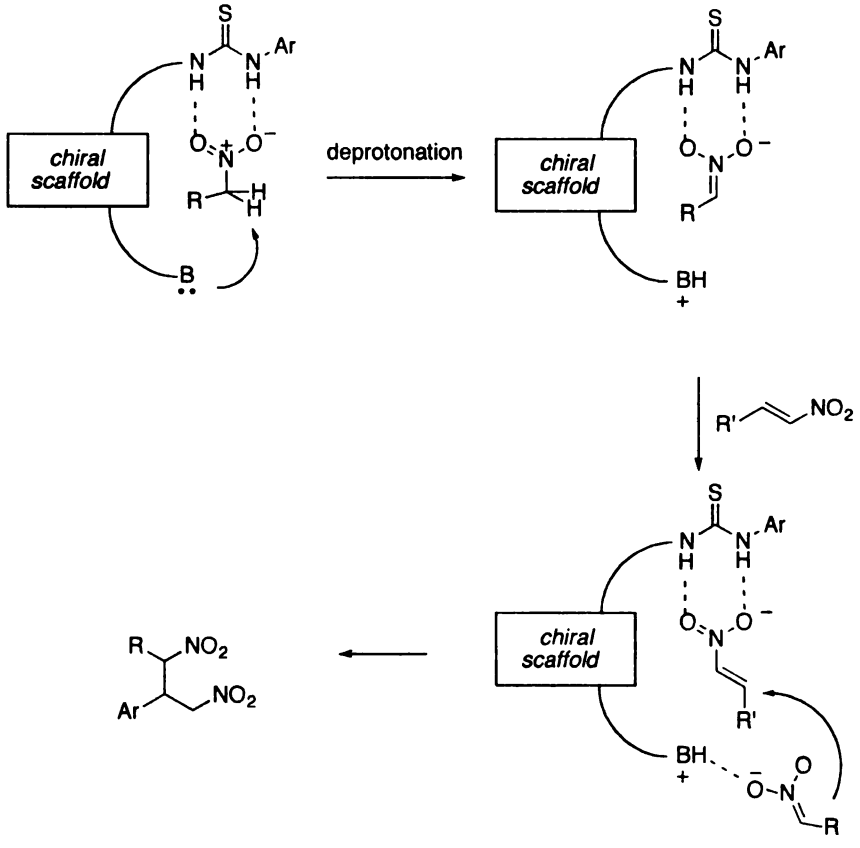
Scheme 28. Bis-thiourea approach for the conjugate addition



b) *A bifunctional thiourea catalyst that will incorporate the base in its structural framework* (Scheme 29). In this approach, that has been used by Takemoto and other groups for other transformations[37], the nitroalkane will be deprotonated by the basic moiety of the catalyst probably through H-bonding activation from the thiourea. The nitroolefin could then displace the nitronate and interact with the thiourea, while the nitronate anion should be held by the positively charged basic moiety through H-bonding, in a complex that would again feature the two reaction components in close proximity for reaction.

The investigation to be described in this chapter was thus focused on identifying efficient catalysts for both approaches.

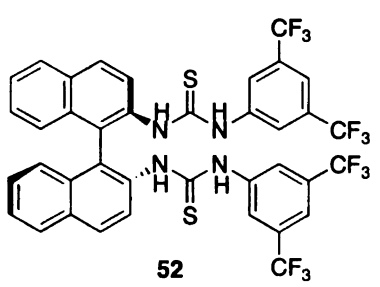
Scheme 29. Bifunctional thiourea approach for the conjugate addition



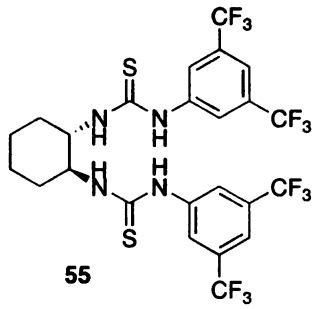
5.3.2.1 Identification of the optimum chiral thiourea catalyst

Concerning the first approach, involving bis-thiourea catalysts, the bis-thioureas **52** and **55** were evaluated for the reaction of β-nitrostyrene with 1-nitropropane and 1-nitroethane. These reactions were studied in various conditions and the results are shown in Table 29.

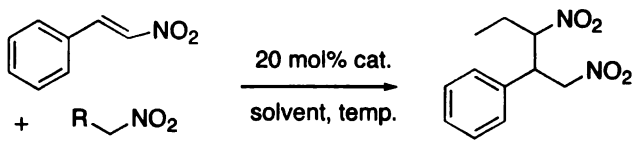
Table 29. Reactions of nitroalkanes with β-nitrostyrene using catalysts **52** and **55**



52



55



entry	R	catalyst (%)	Et_3N (%)	solvent	T(°C)	yield%	d.r. (syn/anti)	%ee
1	Et	**52** (20%)	20	DCM	25	80	70/30	23
2	Et	**52** (20%)	20	DCM	-20	80	85/15	22
3	Et	**52** (20%)	20	toluene	-80	25	81/19	34
4	Et	-	40	toluene	25	35	56/44	-
5	Et	**52** (20%)	5	toluene	25	80	90/10	19
6	Et	**55** (20%)	5	toluene	25	100	80/20	17
7	Et	**52** (20%)	0	toluene	25	0	-	-
8	Me	**52** (20%)	20	DCM	-20	100	63/37	0

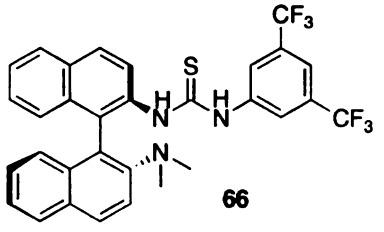
As can be seen in from the data in Table 29, the reaction with catalyst **52** at rt afforded a promising yield for the syn isomer but the enantioselectivity was disappointing (23%, enatry 1). An effort was made to increase the induction by lowering the temperature to -80°C (entries 2, 3) but with no result other than a dramatic drop-off in the rate of the reaction. The background reaction was then measured to determine whether it is responsible for the low inductions, and it was found that 40 mol% Et_3N can afford ~35% product at rt. The background reaction was slower than the catalyzed reaction, but nevertheless it was significant. In order to diminish its effect, lower amounts of Et_3N were tried (5 mol% with catalysts **52** and **55**) but these efforts did not improve the selectivity. In the absence of Et_3N no reaction was observed, which means that the catalyst itself is not able to promote the deprotonation of the nitroalkane to the nitronate. Finally, the reaction with nitroethane was unsuccessful as well, affording racemic product.

From the above results it became evident that the first approach that was to utilize bis-thioureas as catalysts was not successful, since neither **52** nor **55** was able to afford satisfactory inductions for the Michael addition product.

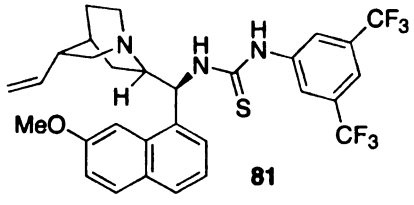
The investigation then switched gears to the second approach, that is to the identification of efficient bifunctional catalysts.

A careful look into Wang's development of an organocatalytic protocol for the Michael addition of nitroalkanes to nitroolefins[52] revealed that bifunctional thioureas could actually be promising candidates for the promotion of the enantioselective conjugate addition. A part of his screening of catalysts included the bifunctional catalysts **66** and **81** in a neat reaction without solvent. As can be seen in Table 30, catalyst **66** (which is a catalyst Wang's group has developed for other asymmetric reactions) affords a modest but promising enantioselectivity but the reactivity of the catalyst is not sufficient. On the other hand, catalyst **81** is obviously more reactive,but the increased reactivity does not translate to increased selectivity.

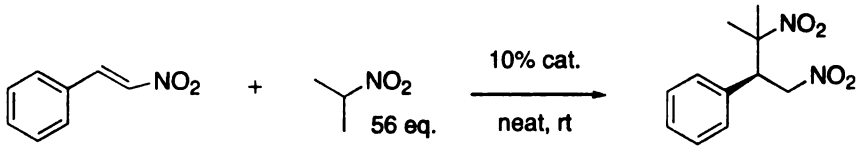
Table 30. Wang's catalyst screening



66



81



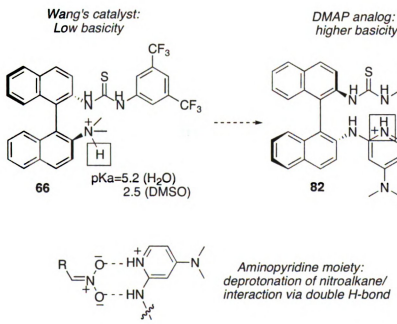
catalyst	yield%	%ee
66	29	48
81	73	30

The above results that Wang's group reported are interesting because they reveal that a thiourea catalyst could be efficient for the addition of nitroalkanes to nitroolefines, if it incorporated a base that would be strong enough to promote the nitroalkane

deprotonation. It is obvious that **81** is reactive enough and this may be attributed to the strong basicity of its nitrogen. Wang's catalyst, on the other hand, suffers from the low basicity of the nitrogen that is in conjugation with the binaphthyl ring.

The above considerations inspired an interesting idea: it was envisioned that the reactivity problem associated with the low basicity in Wang's catalyst (**66**) could be solved if the catalyst was derivatized with a more reactive base. Along these lines, catalyst **82** was designed, that features a dimethylaminopyridine (DMAP) moiety in its structure. Catalyst **82** should be more reactive than **66** simply on the basis of the higher basicity of the DMAP moiety compared to that of the dimethylaniline in **66** (Figure 20).

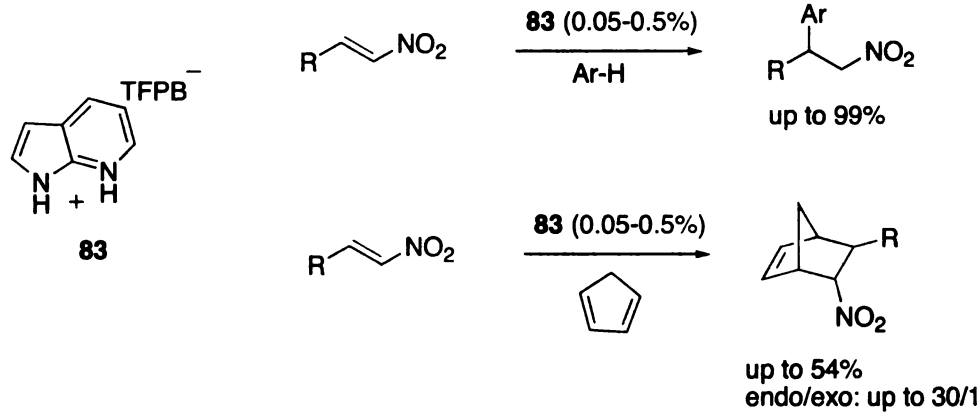
Figure 20. Design of a novel bifunctional catalyst based on BINAM



In addition to the greater basicity of catalyst **82**, another unique feature of this catalyst is that after deprotonation of nitroalkane the 2-aminopyridinium moiety would be

expected to interact with the resulting nitronate through double H-bonding, possibly resulting in a well-defined orientation in the chiral pocket. The ability of 2-aminopyridinium ions to interact with nitro groups is documented in recent literature reports. For example, Takenaka's group found in 2007 that 2-aminopyridinium ion **83** can activate nitroalkenes through double H-bonding toward the addition of N-methylindole and the Diels-Alder reaction with cyclopentadiene[53].

Scheme 30. 2-Aminopyridinium catalyst for nitroalkene activation

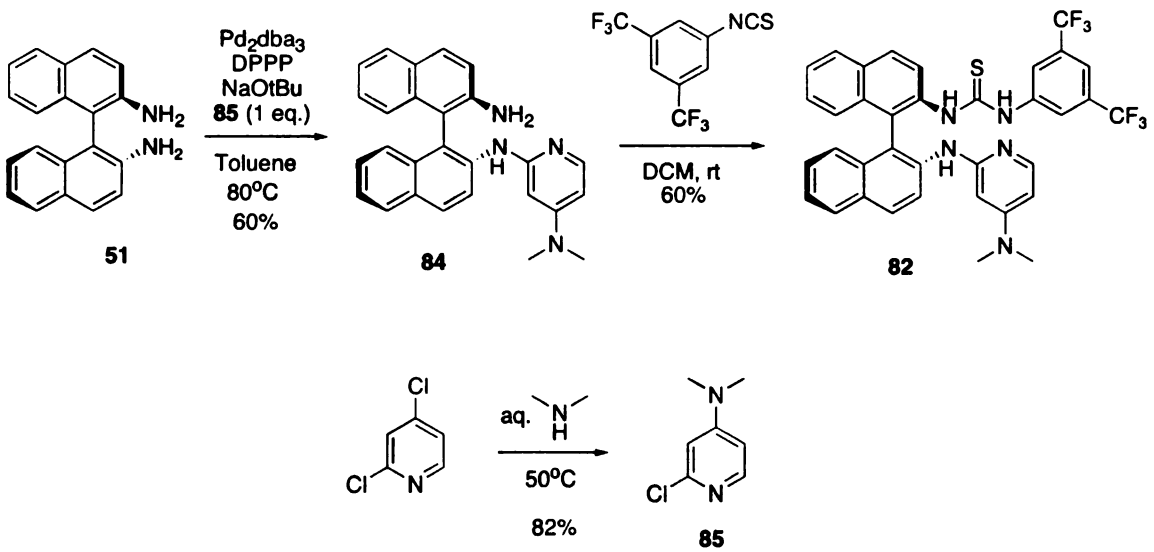


In the case of catalyst **82**, the aminopyridinium ion of the catalyst could interact via H-bonding either with the nitroolefin or the nitronate ion, but it is anticipated that it will most likely form an ion pair with the latter, which is negatively charged and thus more electron rich.

Catalyst **82** can be synthesized trough a simple two-step sequence starting from the commercially available (*R*)-BINAM **51**. The first step involves a Buchwald amination of 2-chloro-4-dimethylaminopyridine using Pd catalysis. The reaction using a 1:1 stoichiometry between (*R*)-BINAM and 2-chloro-DMAP **85** gives 60% isolated yield of the desired monosubstituted product **84**, along with a small amount of disubstituted adduct

that can be easily separated with column chromatography. 2-Chloro DMAP can be obtained from 2,4-dichloropyridine through an a nucleophilic aromatic substitution using dimethylamine.

Scheme 31. Synthesis of catalyst **82**

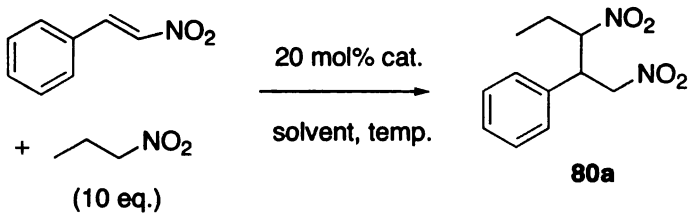


The second step involves the formation of the thiourea moiety from the reaction of **84** with 3,5-bis(trifluoromethyl)phenyl isothoocyanate. The product **82** can be obtained in 60% isolated yield after chromatography purification.

The preliminary results from the evaluation of the new catalyst were very promising. In terms of reactivity, the data in Table 31 present a comparison with catalyst **66**: catalyst **66** showed no reactivity for the given set of conditions (10 equivalents nitroalkane in dichloromethane at r.t.) while **82** provided the dinitro adduct **80a** in an excellent 90% yield as determined by NMR spectroscopy. Note that in the absence of solvent catalyst **66** can promote the addition of a nitroalkane to a nitroalkene to a small degree. A preference for formation of the syn diastereomer was observed along with 78% ee, which at this point

was very satisfactory. Reactions in other solvents revealed that benzene is actually the optimum in terms of the stereoinduction (80%ee, entry 4).

Table 31. Evaluation of the new catalyst **82** in the conjugate addition (a)



entry	catalyst	solvent	yield% (b) **80a**	d.r. (c) (syn/anti)	% ee (c)
1	**66**	DCM	0	-	-
2	**82**	DCM	90	59/41	78
3	**82**	toluene	90	63/37	78
4	**82**	benzene	88	64/36	80

(a) Reactions run with 0.1M with respect to nitrostyrene for 12h. (b) Determined from the crude ^{1}H-NMR spectrum using triphenylmethane as internal standard. (c) Determined by chiral HPLC.

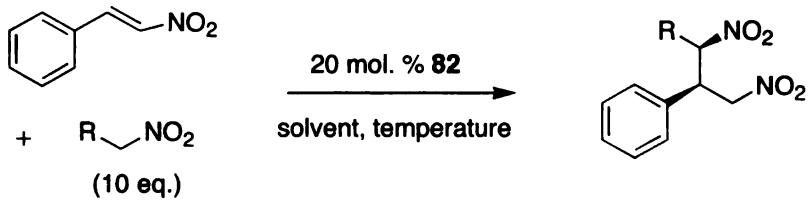
After this study, catalyst **82** was chosen as the optimum catalyst for the reaction and an effort to improve the result through an investigation of various conditions was conducted.

5.3.2.2 Preliminary efforts for optimization

The effort towards optimizing the conditions for the reaction of β-nitrostyrene with nitroalkanes using catalyst **82** begun with variations in the temperature of the reaction with 1-nitropropane. Specifically, lowering the temperature to -25°C was attempted in order to achieve higher selectivities. Unfortunately this had a dramatic effect on the rate of the reaction which decreased significantly and resulted in only 31% yield (Table 32, entry 2). The opposite would be expected when warming up the reaction, however, in the case of

this particular transformation there is one complicating factor, the formation of the polynitrostyrene (discussed previously). It turnes out that increasing the temperature to 50°C causes an increase in the rate of the polymer formation which is apparently higher than the increase in the rate of the formation of the desired product. This seems to be the explanation for the result in entry 3. The reaction at 50°C actually gave complete conversion of the starting material, but with a much lower yield of the desired product that at room temperature. The decrease in the mass balance is assumed to be due to the formation of polymer and this is consistent with the complicated NMR spectrum that was observed for the crude reaction mixture. Unfortunately, temperature seemed to be a limiting factor and it was obvious that any further optimization had to be conducted only at room temperature.

Table 32. Preliminary optimization of conditions using catalyst **82** (a)



entry	R	solvent	T(°C)	yield%*	d.r.	%ee syn	% ee anti
1	Et	benzene	rt	80	60/40	82	70
2	Et	toluene	-25	31	n.d.	n.d.	n.d.
3	Et	benzene	50	54	50/50	80	70
4	Et	neat	rt	100	50/50	78	72
5	Et	benzene, 4A M.S.	rt	62	45/55	40	44
6	Me	benzene	rt	100	57/43	62	60
7	Pr	benzene	rt	96	55/45	81	79
8	**Et**	**benzene**	**rt**	**75**	**66/33**	**82**	**n.d.**

(a) Reactions run with 0.1M with respect to nitrostyrene for 12h. *Entries 1-7: ^{1}H-NMR yield using triphenylmethane as internal standard. Entry 8: Isolated product after silica gel chromatography.

Two more experiments were conducted with 1-nitropropane: a neat reaction without any solvent (entry 4), in order to increase the rate and the yield, and a reaction using molecular sieves, in an effort to ensure dry conditions and removal of any traces of moisture that would interact with the catalyst and/or the nitrocompounds (entry 5). Unfortunately, neither change was helpful, since the neat reaction was too fast and unselective in terms of the d.r. ratio (entry 4), and the molecular sieves had a diminishing

effect on the selectivities (entry 5). The latter was not expected, and the effect of the sieves on the reaction outcome is not clear.

Finally, a few more nitroalkanes were tried in the reaction at r.t. Nitroethane (entry 6) gave a lower but still respectable enantioselectivity (62% for the syn product) along with excellent yield, while 1-nitrobutane (entry 7) afforded results similar to those with 1-nitropropane, showing that the reaction is not very substrate sensitive (at least concerning the nitroalkane) and can be applied to different nitroalkane nucleophiles. Among the last two substrates, 1-nitropropane was chosen for further study because of the easier separation of the enantiomers in the chiral HPLC.

It should be noted here that for all the experiments in Table 32 the yield that is reported is determined from the crude ^{1}H-NMR spectrum using triphenylmethane as a standard. Specifically, a known amount of triphenylmethane was added to the reaction mixture at the end of every reaction and the yield was calculated by integration of aliphatic protons of the product and the methine proton of the standard that has a characteristic absorption at ~ 5.5 ppm. This accuracy of this method was checked by performing a couple runs where the product was isolated by chromatography. The data in entry 8 refers to isolated product and is the average of two runs. The consistency with the data in entry 1 allowed for the reliable use of triphenylmethane as a standard in further experimentation and optimization. In addition, the high polarity of the catalyst allowed for a convenient determination of the ee's and d.r. ratios without the need of column purification: All that was needed in order to obtain this data was to simply filter the crude reaction mixture through a short Pasteur pippete containing a small amount of silica gel. The polymer and the catalyst stayed on the top of the silica, and product of very good

purity was eluted, which allowed for very clean HPLC spectra. This method proved to be very useful in rapidly optimizing the reaction without the need to perform column chromatography for each and every entry, thus saving a lot of time. The method described here was applied to all the experiments that are discussed in the following sections, except of course the section that deals with the substrate scope, where isolation and purification of products was required.

A second point of importance is the reactivity and the chemoselectivity of the catalyst **82**. For the reactions conducted at r.t. the conversion is always nearly quantitative, with only small amounts of polymer formed (<20%). The chiral thiourea seems to activate the starting materials in favor of the formation of the desired adduct suppressing the production of oligomers or polymers, just as the achiral thiourea **47** did for the non-asymmetric addition (Table 28).

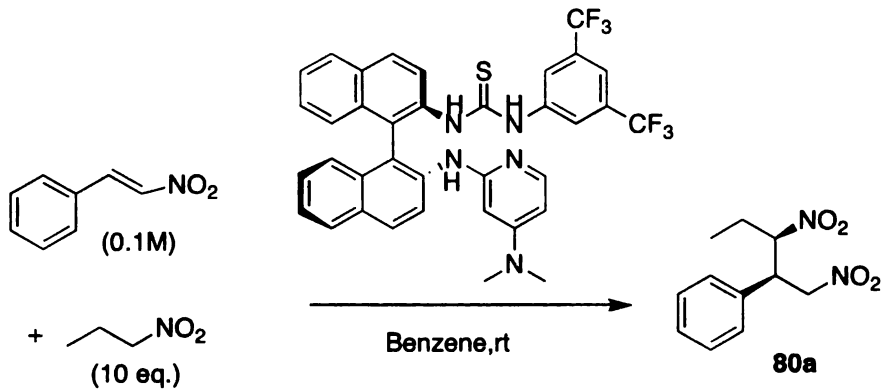
5.3.2.3 Effect of catalyst loading: discovery and investigation of a highly unusual selectivity trend

The experiments discussed in the previous section led to the conclusion that the optimum conditions for the maximum yield and selectivity of the reaction are met when the reaction is conducted at room temperature in benzene. Up to this point the experiments have been performed using 20 mol.% catalyst, along with 10 equivalents of 1-nitripropane. The next objective thus was to try to reduce the catalyst loading in order to achieve a satisfactory balance between the amount of catalyst spent and the yields and selectivities obtained.

The investigation was first focused on the effect of catalyst loading. A series of experiments were conducted using 10 equivalents of 1-nitropropane in benzene at room

temperature. All conditions were kept consistent and a number of different catalyst loadings from 0.5% to 100% were screened. Analysis of the data led to a completely unexpected result from the above study: It was intriguing to observe that a reduction of the catalyst loading not only didn't cause a drop in the selectivities, but on the contrary, it lead to an unexpected enhancement of the selectivities! As can be seen from the data in Table 33 a stoichiometric amount of catalyst affords a preference for the anti isomer, with ee's in the 60's and 70's, while catalyst loadings from 20% and lower favor the syn isomer, with the asymmetric induction increasing very significantly. The enantioselectivity of the syn adduct spans a range from 70% (entry 1) to 95% where the catalyst is used in only 0.5 mol.% with respect to the nitroolefin. A significant increase in the diastereomeric ratio was also observed for reduced loadings, with an increase to 86/14 for the lowest loading (entry 7). This selectivity trend is obviously extremely unusual. Additionaly, the fact that catalyst loadings as low as 0.5% can induce selectivities as high as 95% demonstrates that thiourea **82** is a remarkably selective catalyst.

Table 33. An unusual selectivity trend observed for the catalyst loading study for **82** (a)



entry	cat.load.%	NMR yield% (b)	d.r. (syn/anti)	% ee (syn)	% ee (anti)
1	100	60	39/61	70	63
2	20	80	60/40	82	70
3	10	40*	71/29	84	60
4	5	70*	76/24	90	70
5	2	43*	82/18	94	n.d.
6	1	<30*	87/13	94	n.d.
7	0.5	18*	86/14	95	n.d.

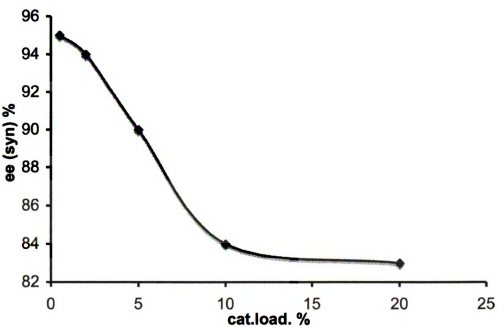
(a) Reactions were run for 15h except entry 7 which was run for 40h. (b) Determined using triphenylmethane as internal standard. *Incomplete conversion

It should be noted here that the rate of the reaction slowed down significantly when the catalyst was used in a loading of 10 mol% or less. For entries 3 to 7, the conversion was incomplete and a significant amount of starting material was unreacted. Nevertheless, it is worth mentioning that for those reactions with reduced loadings the crude ^{1}H-NMR spectrum was generally cleaner with respect to polymer formation. In

general, the lower the catalyst loading that was used, the less polymer was formed and the cleaner the reaction mixture that was obtained.

The trend that the enantioselectivity for the syn product followed with respect to the catalyst loading was very smooth, and this is apparent when plotting the induction for the product and the catalyst loading, as illustrated in Figure 21.

Figure 21. Plot of the asymmetric induction for syn – **80a** versus the catalyst loading

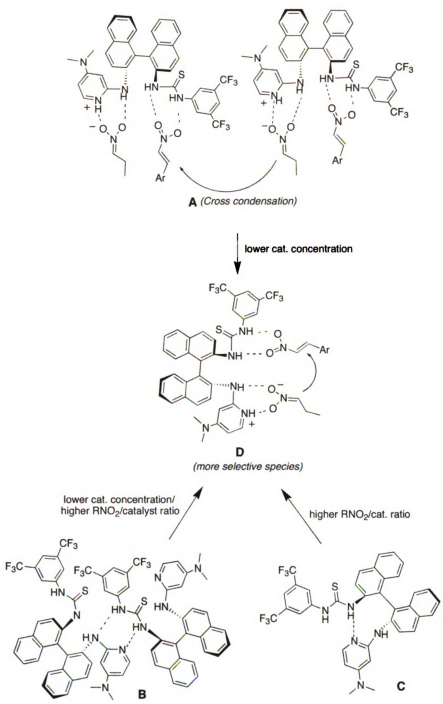


It is obvious that 0.5-2 mol% seems to be the optimum catalyst loading with respect to the selectivities, but unfortunately these amounts of catalyst are not practical because the yields of the product are not acceptable. The solution to this problem came with further optimization and will be described later on in the next section.

The investigation was then focused on rationalizing the above set of data in order to shed light on the mechanism of this transformation. A careful look into the selectivity trend shows that there are two factors that could possibly operate in the higher inductions observed upon decrease of the catalyst loading: (a) the decrease of the catalyst concentrations and / or (b) the increase of the nitropropane/catalyst ratios (since the catalyst amount is reduced across the table but the substrate amount is kept constant).

Three different scenarions were envisioned in order to account for the unusual effects that these two factors could have on the selectivities: A) stereochemichal "scrambling" could happen if a nucleophile bound to one catalyst moiety reacts with an electrophile bound to another catalyst when the catalyst concentration (or loading) is high enough and catalyst moieties have a higher probability of coming close to each other in solution. This hypothesis is illustrated in Figure 22 as pathway **A**. If it is presumed that pathway **D**, which represents the design in the original model, is the more selective, then the scrambling of stereochemistry at high catalyst concentrations (pathway **A**) would occur because the nitroalkane would attack nitrostyrene in a stereochemically less defined way, or even attack the opposite side of the C-C double bond rather than the one that is exposed in **D**. According to this scenario, reducing the catalyst loading should disfavor pathway **A** and result in higher enantioselectivity.

Figure 22. Possible scenarios to account for the catalyst loading effects

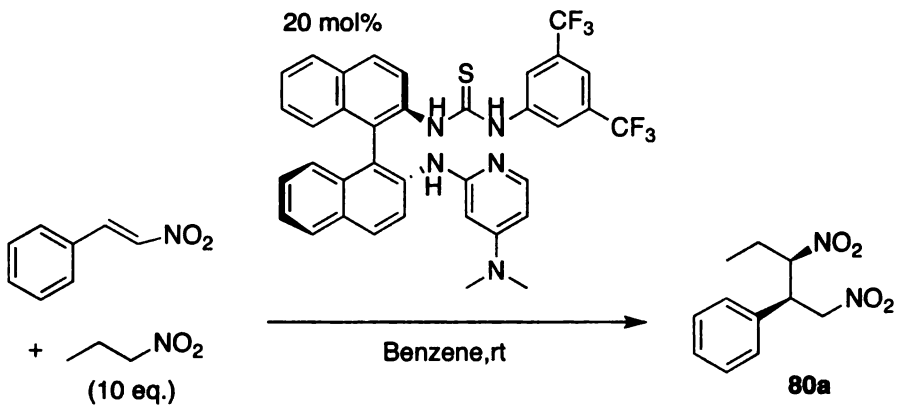


B) Intermolecular H-bond between different catalyst moieties that would lead to catalyst self-aggregation (species **B** in Figure 22) when the catalyst loading is high and the nitroalkane / catalyst ratio is small. This scenario seems reasonable on the basis of the potential of the electron-rich sp^2 nitrogen of the DMAP moiety of the catalyst to accept an H-bond. As the nitroalkane/catalyst ratio increases (low cat. loadings) it is expected that the interaction of the catalyst with the substrates will be more favorable, and this interaction can break-up the aggregates and lead to species **D**. The magnitude of the nitroalkane/catalyst ratio indeed ecomes very large when switching from 100 mol% catalyst loading (ratio=10/1) to 20 mol% catalyst (ratio=50/1), to 5 mol% catalyst (200/1) and then to 0.5 mol% catalyst (2000/1), and so at these very high ratios it is expected that the catalyst would increasingly be more likely to associate with the substrates than with itself. The observed trend on the selectivities then can be explained if the aggregated species **B** can also catalyze the reaction but in a less enantioselective fashion than **D**.

C) Intramolecular H-bonding of the catalyst as indicated in species **C** would leave only one thiourea N-H bond available for substrate activation, and this should presumably lead to less defined substrate orientations and thus to lower asymmetric inductions. Species **C** involves an intramolecular interaction and thus does not depend on the concentration of the catalyst itself, but its formation should be clearly dependent on the nitroalkane/catalyst ratio. Again, low catalyst loadings would translate to high nitroalkane/catalyst ratios, which should promote the break-up of the intramolecular H-bond (just as in the case of **B**) and the formation of the more selective species **D**. As with species **B**, the explanation of the observed trend would require that species **C** be able to catalyze the reaction with lower inductions than species **D**.

We next embarked on a series of studies in order to distinguish between scenarios **A**, **B** and **C**, and to probe the mechanism of this highly enantioselective addition. First, it is obvious that pathway **A** should be clearly concentration-dependent and that dilution of the reaction mixture should disfavor the formation of **A** and lead to higher inductions. A series of reactions were conducted where the same set of teagents and catalyst was dissolved in different amounts of benzene so that the catalyst loading and the nitroalkane/catalyst ratio were kept the same while the concentration of all the species including the catalyst were varied. The results of these experiments are depicted in Table 34.

Table 34. Concentration study of the reaction (a)



entry	[catalyst], M	yield%(NMR) (b)	d.r.	%ee (syn)	%ee (anti)
1	0.040	77	58/42	84	70
2	0.010	71	64/36	85	70
3	0.005	55	52/48	78	64
4	0.003	45	55/45	67	48
5	0.002	31	55/45	70	42

(a) Reactions run for 48h. (b) Determined from the ^{1}H-NMR of the crude reaction mixture using triphenylmethane as internal standard. All entries gave incomplete conversion of nitrostyrene.

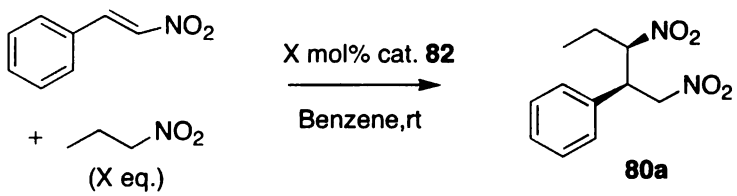
The concentration study turned out to be very informative since the results were the exact opposite of what would be expected if pathway **A** was operating. When the reaction was performed at more diluted concentrations a very significant drop in the ee's of both the syn and the anti products was observed. This clearly rules out pathway **A**. The dependence of pathway **B** on the concentration in not very clear at this point. An increase of the concentration may promote the formation of the aggregated species **B**, but on the other hand the increase in the concentration may allow for a more efficient interaction of the catalyst with nitropropane, thus disfavoring the aggregation. Thus, these two effects would offset each other.

The concentration study also led to an important observation: An increase of the catalyst concentration is accompanied by higher inductions. This was not the case in the catalyst loading study (Table 33) where increased loadings – and thus, catalyst concentrations - gave lower inductions. This observation was the key in realizing that for the catalyst loading study, the factor operating in the catalyst loading trend is probably not the catalyst concentration itself, but rather, the nitroalkane/catalyst ratio. In other words, the nitroalkane/catalyst ratio was responsible for the unusual selectivity trend in the data in Table 33, and not the catalyst concentration itself.

Support for this idea was provided by a simple control experiment: two different catalyst loadings from Table 33 were tested again, this time with the amount of 1-nitropropane adjusted so that the nitropropane/catalyst ratio would remain the same. These reactions gave the same enantioselectivity for the major (syn) product. These two catalyst loadings had afforded a significant difference in the enantioselectivities under the conditions in Table 33 (82% and 90% ee), and so the results here demonstrate clearly that

the nitropropane/catalyst ratio is the determining factor for the highly unusual selectivity trend associated with **82**.

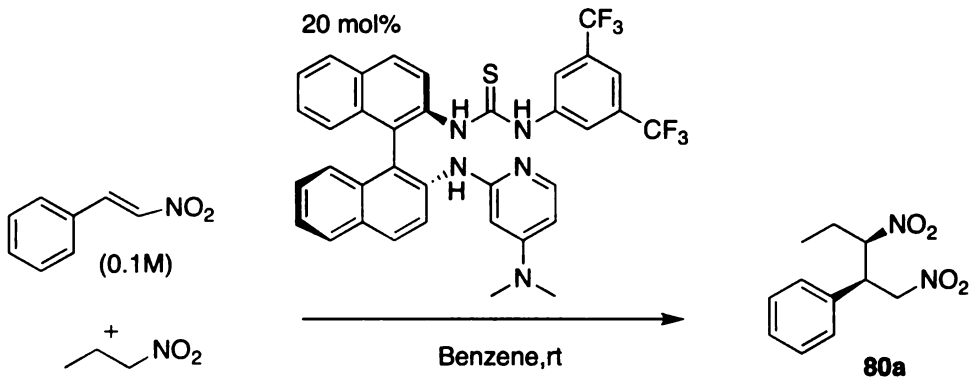
Table 35. Cat. loading study with stable nitroalkane/catalyst ratio



X	n-prNO_2/catalyst ratio	%ee (syn)
20	100	92
5	100	92

The idea that the nitroalkane/catalyst ratio is determining the selectivities was further probed with a survey of the effects that the amount of 1-nitropropane has on the reaction outcome. It would be expected that increasing the amounts of nitroalkane for a given catalyst loading should lead to increased inductions. Along these lines, a set of reactions was undertaken where catalyst loading and concentration were kept constant and the number of equivalents of nitroalkane was varied, from 2 to 30-fold excess with respect to the nitroolefin. This study served in two purposes: it was not only a control experiment for probing the importance of the nitroalkane/catalyst ratio, but also a survey for the determination of the optimum amount of 1-nitropropane that should be used in the reaction. The results are presented in Table 36.

Table 36. Effect of nitroalkane equivalents (a)



entry	equivalents n-$PrNO_2$	time(h)	NMR yield% (b)	d.r. (syn/anti)	%ee syn	%ee anti
1	2	60	36	46/54	82	70
2	5	60	43	46/54	83	74
3	10	15	85	60/40	82	70
4	15	15	100	63/37	83	71
5	20	15	85	65/35	85	72
6	30	15	100	66/33	87	76

(a) Entries 1-3 were run for 60h. Entries 4-6 were run for 15h. All reactions gave complete conversions except entries 1,2. (b) Determined from the ^{1}H-NMR of the crude reaction mixture using triphenylmethane as internal standard.

The results from the study on the variation of the equivalents of nitroalkane were interesting both in terms of the effect on the diastereoselectivity and the enantioselectivity of the syn adduct. Concerning the diastereomeric ratio, there is a slight preference for the anti isomer at small excesses of the reagent (enties 1 and 2) that inverts to a 2/1 selectivity for the syn product when the reagent is used in more than 15 fold excess (entries 4 to 6). Concerning the enantioselectivity of the syn adduct, the induction stays at 82-83% ee for 2-15 equivalents of nitropropane, but for larger excesses of 20 and 30 equivalents an

increase at 87% ee was seen. The ee of the anti product also went up from 70 to 76%, with only the result in entry 2 showing a deviation from an otherwise smooth trend. The trends in the selectivities in general agree with the notion about the nitroalkane/catalyst ratio is directly proportional to the asymmetric induction.

As a bonus from the optimization of the reaction through the above experiments, it was delighting to observe that the ee of the product can be increased by just adding more nitropropane to the reaction mixture. On the other hand, considering about the rate and the yield of the transformation, it became apparent that at least 10 equivalents of the nucleophile should be used in order to obtain good yields in a reasonable amount of time.

The question of whether the catalyst concentration or the RNO_2/catalyst ratio is responsible for the selectivity trend has been answered, however the question of whether species **B** or **C** is operating is still pending, because the results of all these experiments to this point are in accordance with the involvment of either species. In other words, the RNO_2/catalyst ratio should be expected to influence both species in the same direction, as illustrated in Figure 22. To distinguish more clearly between species **B** and **C** and to determine whether the suspected self-association of the catalyst is intramolecular or intermolecular, non-linear studies were conducted. In non-linear studies the relationship between the enantiomerical purity of the product and that of the catalyst is surveyed. Usually a non-linear relationship indicates the existence of catalyst aggregates, while a linear one indicates that the catalyst functions as a monomer. For the purpose of this study, three different samples of scalemic catalyst were prepared by mixing (R) and (S) -**82** to make catalyst samples that were 20%, 50% and 80% ee. The study was undertaken in reactions using both 2% and 20% catalyst, such that the possibility of aggregation at

different concentrations of the catalyst can be tested. In the beginning of the discussion it was mentioned that species **B** in Figure 22 should be favored at low RNO_2/catalyst ratios. The equivalents of nitropropane used in these experiments for 2% and 20% catalyst were 30 and 15 respectively, such that the conditions wouldn't disfavor the formation of the suspected polymer in the second case. In other words, in case the high catalyst loading (20%) created a catalyst aggregate, the RNO_2/catalyst ratio used here was much smaller than in the reaction with 2% (75/1 versus 1500/1) so that it wouldn't break up the aggregate and give a misleading linear plot. The results of the study are illustrated in Figure 23.

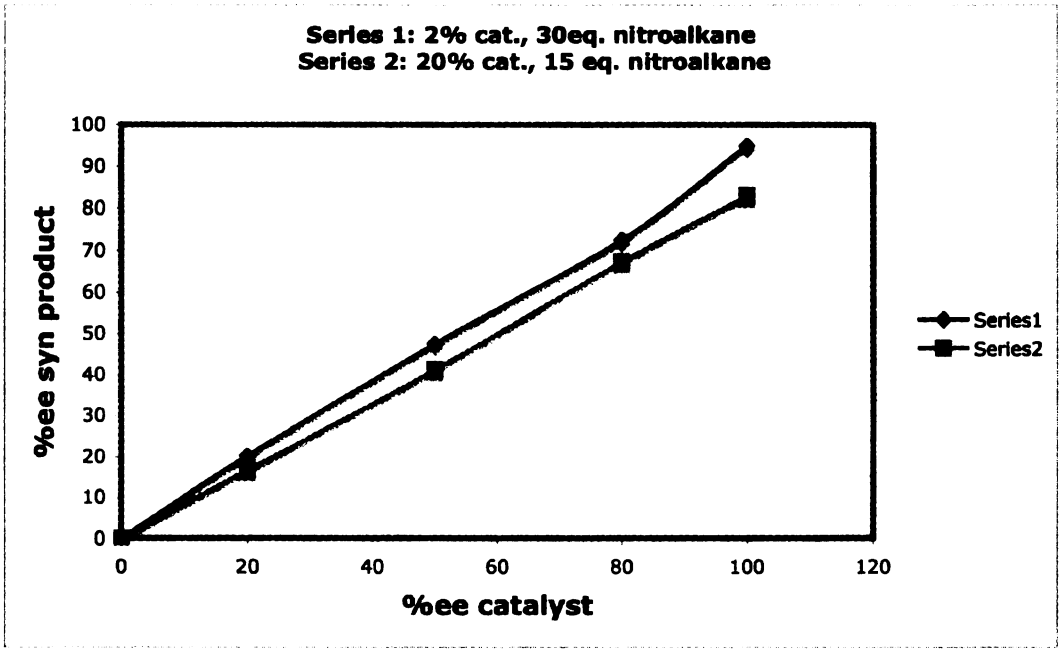


Figure 23. Plot of optical purity of **82** versus optical purity of syn-**80a**

The non-linear studies in Figure 23 show that there is a linear relationship between the ee of the catalyst and the ee of the major diastereomer of the product **80a**, both at 2%

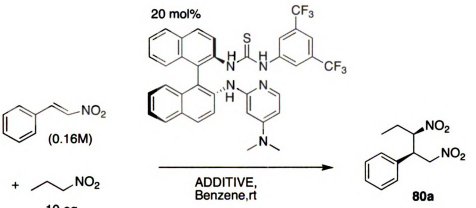
and 20% catalyst loading. This indicates that even when the catalyst is used at high concentrations or loadings, it still functions as a monomeric species, even if the RNO_2/catalyst ratio is much smaller. This study may not disprove the existence of aggregated catalyst, but it is a strong indication that the active species is a monomeric form of the catalyst **82**. ***Consequently, the intramolecular H-bonded shown in Figure 22 as species C is the only scenario that fits all the data obtained so far.*** In case species **C** is operating than the data obtained from the concentration study in Table 34 make sense if the increase in the concentration leads to more efficient interaction between the catalyst and the substrates, and helps to break-up the itramolecular H-bond in the catalyst.

Given the fact that excess 1-nitropropropane can lead to increased asymmetric induction that presumably results from altering the catalyst structure through disruption of H-bonding leading to the conversion of species **C** to **D** (Figure 22), one could argue that other compounds that could mimic the H-bonging ability of 1-nitropropane should in principle do the same. In other words, it would be expected that additives that could H-bond with the catalyst and break-up the self-association should promote the formation of species **D** just as nitropropane does, if our hypothesis is correct. This idea was intriguing not only because it would give us one more probe to test our hypothesis, but also because some additives might work even more efficiently than 1-nitropropane affording even higher inductions and the identification of such additives would furthermore contribute to the optimization of the reaction.

Along these lines, a series of additives were tested in the reaction of nitrostyrene and 1-nitropropane using 20 mol% catalyst. The additives were chosen on the basis of mimicking the ability of 1-nitropropane in forming H-bonds with the catalyst, and thus

small molecules that can function as H-bond acceptors were chosen. The results of this study are presented in Table 37.

Table 37. Survey of additives in the reaction with catalyst **82** (a)



entry	additive (eq.)	yield% (b)	d.r.	ee% syn
1	-	100	66/34	88
2	$PhNO_2$ (5)	83	58/42	92
3	THF (5)	62	63/37	89
4	MeCN (5)	83	64/36	92
5	DMSO (5)	trace	nd	nd
6	EtOAc (5)	67	57/43	89

(a) Reactions run for 12 h. (b) Determined from the ^{1}H-NMR of the crude reaction mixture using triphenylmethane as internal standard.

First of all, it was observed that all the additives slowed down the reaction, some to a small extent ($PhNO_2$, MeCN) and others more significantly (THF, EtOAc) while only a trace of the product was obtained when DMSO was used. This is consistent with the presumtion that all the additives interact with the catalyst. In particular DMSO, as maybe

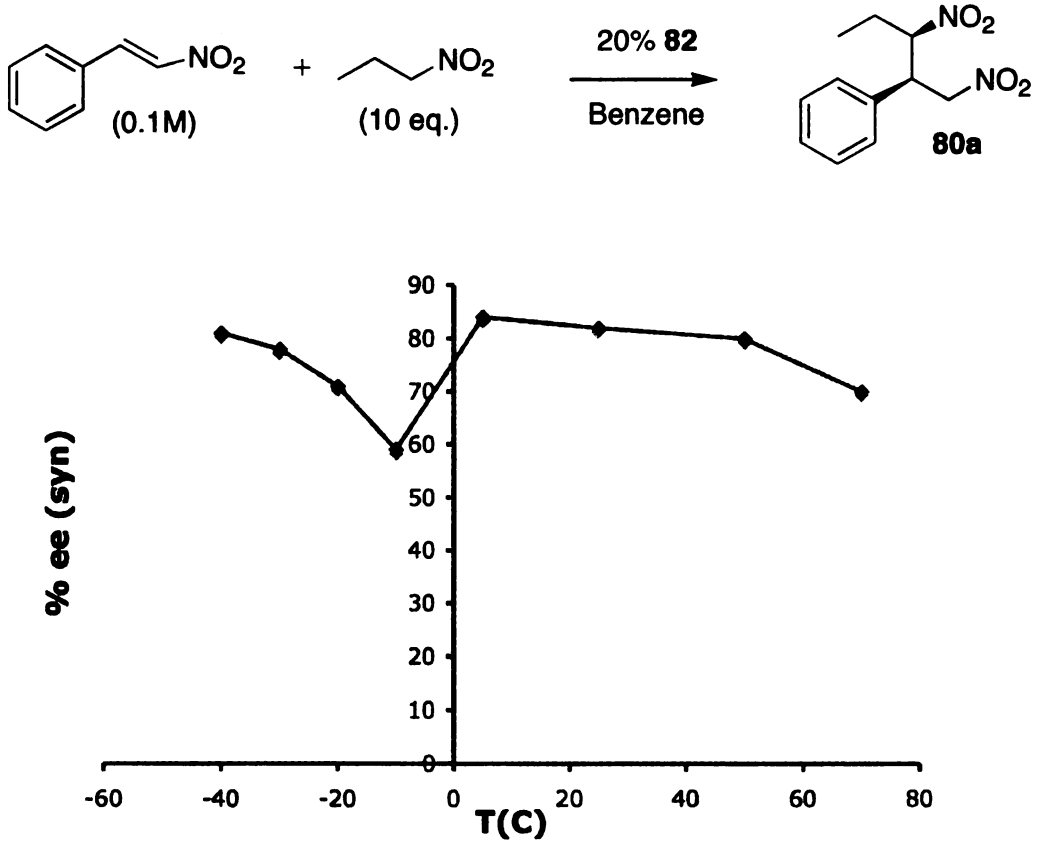
expected, seems to completely block the catalyst preventing its interaction with the substrates. Out of the five additives that were tested, both $PhNO_2$ and MeCN afforded an increase in the ee from 88% to 92%. This small but real change suggests that these two additives interact with the thiourea of the catalyst shifting the equilibrium from the self associated catalyst **C** to the more selective complex **D**, in accordance with the proposed mechanism. It was also very interesting to observe that when acetonitrile is used as a solvent the yield and the selectivities drop significantly (51%, 62% ee), as is typically the case in thiourea catalysis when polar H-bonding acceptor solvents are employed. However when acetonitrile is used as an additive in small amounts it contributes to the enhancement of the ee.

Finally, the hypothesis of catalyst self-inhibition through species **C** was further probed with temperature experiments. If, as proposed, catalyst self-inhibition is operating as a factor in regulating the reaction selectivities, it would be expected that this inhibition should be favored at low temperatures, where the energy provided to the system is lower. As the temperature rises one would expect that the increased energy of the system should give to the molecules the necessary energy to overcome the entropic barrier of breaking an intramolecular H-bond in the catalyst which can lead to intermolecular H-bonds between the catalyst and the substrates. This scenario would lead to a counter inturtive outcome, lowering the temperature would lead to decreased asymmetric inductions.

As a test of this hypothesis, the ee of the syn product was studied as a function of temperature in a range between -40 and 70°C. Unfortunately, at high temperatures the catalyst underwent decomposition according to the crude ^{1}H-NMR spectrum. Experiments at low temperatures provided quite interesting results. Lowering the temperature from 5 to

-10° C led to a sharp decrease in the induction from 84% to 59% ee. This is in accordance with internally H-bonded catalyst, because lowering the temperature, and thereby the energy provided to the system, should otherwise lead to increased inductions. The trend that was observed actually was not a gradual enantioselectivity decrease. As shown in Figure 24, the ee starts rising again when going to -20 and -30°C and at -40°C the induction is back to the initial levels. It seems that the internally H-bonded catalyst is maximized at -5 to -10°C, and

Figure 24. Temperature study of the asymmetric addition



at lower temperatures the increased selectivities from the reaction either through species **D** or **C** takes over and almost recovers the induction.

In any case, the sharp drop in the selectivity when lowering the temperature is not usually encountered in asymmetric catalysis when monomeric catalytic species is involved in the reaction, and the result that was observed here is an indication for some sort of intramolecular interaction, in agreement with the intramolecularly H-bonded species **C**.

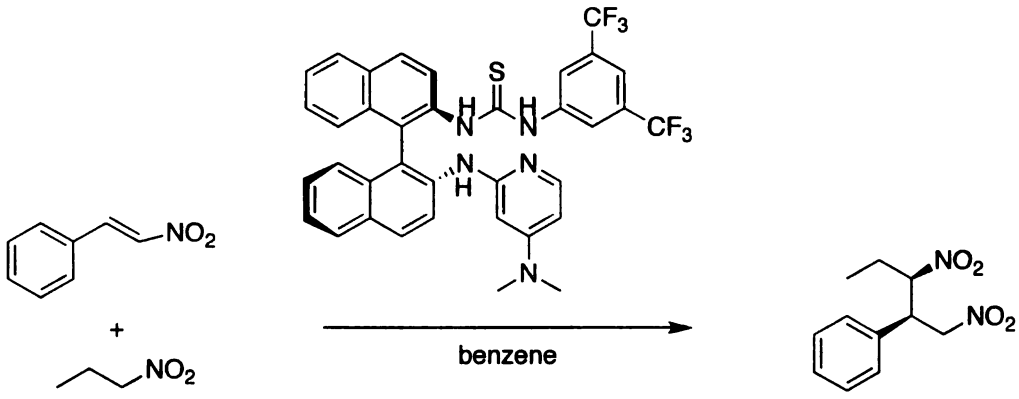
5.3.2.4 Optimization of conditions and substrate scope

From the studies described in the previous section, the effect of most of the reaction parameters has already been defined for catalyst **82** in the reaction of nitrostyrene with 1-nitropropane. The next objective is then to achieve the best combination of these parameters so that the optimum balance between yields and selectivities can be identified.

In the case of the asymmetric addition with catalyst **82**, it was fortunate to observe that the unusual selectivity patterns described in the previous section were such that an increase in both the concentration and the amount of 1-nitropropane favor an increase not only in the yields, but also in the diastereoselectivities and the enantioselectivities as well.

Thinking about catalyst loading, tha data in Table 33 suggests that in order to make the reaction more selective small catalyst loadings have to be used. According to the the data however, loadings smaller than 20% afford incomplete conversions and low yields. Catalyst loading is apparently the only factor that has opposing effects on the yields and selectivities. On the other hand, since an increase in equivalents of nitropropane and higher concentrations favor the selectivities, it would be expected that using a large excess of nitropropane and high concentrations would help to overcome this issue of sluggish reactivity at 2 mol%, 1 mol% or even 0.5 mol% catalyst loadings. Therefore, further optimization was focused on the objective of "pushing" these reactions to give higher conversions and yields. The results are presented in Table 38.

Table 38. Optimization of reaction variables (a)



entry	cat.load.%	[C] nitrostyrene	$prNO_2$ equiv.	time (h)	yield% (b)	d.r. (c)	ee% (c) (syn)
1	2	0.2M	20	16	23	84/16	94
2	2	0.2M	30	40	90	84/16	94
3	2	0.3M	30	40	100	80/20	93
4	1	0.2M	30	40	66	87/13	95
5	0.5	0.2M	30	40	40	88/12	96
6	0.5	0.4M (neat)	30	40	40	80/20	94

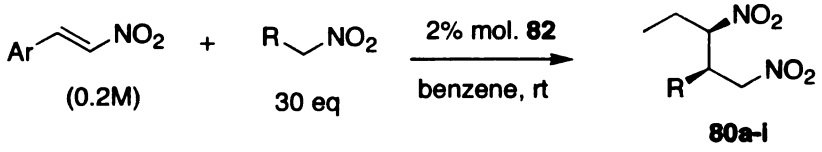
(a) Reactions were run for 12h. (b) Determined from the ^{1}H-NMR of the crude reaction mixture using triphenylmethane as internal standard. (c) Determined by chiral HPLC.

As can be seen from the data in Table 38, using 2 mol% catalyst affords only 23% yield of **80a** and a lot of unreacted nitrostyrene was observed under the conditions in entry 1. However, this was solved by using more forcing conditions. Apparently increasing the amount of nitropropane, the reaction time and the concentration leads to an excellent NMR yield with the selectivities in the same high levels (entries 2 and 3). The same strategy was attempted for the reactions with 1 mol% and 0.5 mol% catalyst loadings, but

in these cases it was not possible to push the yields to a satisfactory level, even when neat conditions were employed (entries 4 to 6).

From the above study summarized in table 38, the conditions in entry 2 were chosen as the optimum and then the scope of the asymmetric addition of 1-nitropropane to nitroolefins was studied using these parameters. Various differently substituted nitrostyrenes were tested and the results are shown in Table 39.

Table 39. Substrate scope of the asymmetric addition of nitroalkanes to nitrostyrenes using catalyst **82** (a)



entry	Ar	R	adduct	overall yield% (b)	yield% syn (b)	d.r. (c)	%ee (syn)
1	Ph	Et	**80a**	80	60	84/16	95
2	4-MeO-C_6H_4	Et	**80b**	60	47	85/15	94
3	2-MeO-C_6H_4	Et	**80c**	55	45	80/20	94
4	2-MeO-C_6H_4	Et	**80c**	94	72	80/20	94
5	4-Me-C_6H_4	Et	**80d**	72	58	80/20	94
6	2-Cl-C_6H_4	Et	**80e**	84	62	74/26	92
7	4-Cl-C_6H_4	Et	**80f**	75	62	83/17	92
8	4-Br-C_6H_4	Et	**80g**	75	65	87/13	93
9	3-Br-C_6H_4	Et	**80h**	69	62	90/10	94
10	2-Br-C_6H_4	Et	**80i**	78	58	75/25	92
11	Ph	*n*-Pr	**80j**	78	70	90/10	91

(a) Reactions run for 40h except entries 7 and 8 which were 17h and entry 4 which was 60h. All reactions were 0.2M in nitroolefin except enrty 4 which was 0.33M. (b) Isolated yields after column chromatographic purifiction. (c) Determined by the weight of the separated diastereomers except entries 1-4 which were determined by ^{1}H-NMR.

As can be seen from the data in the Table 39, the reaction is highly efficient for a range of substituted nitrostyrenes. Good isolated yields in the range of 69-94% of the adducts **80a-i** can be obtained with only 2 mol% catalyst, demonstrating a catalyst with very efficient turnover ability. In the case of the electron rich methoxy-substituted styrenes

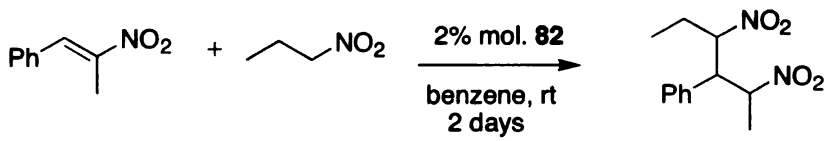
the rates of the reactions were slow when the optimum conditions were employed, and isolated yields of 47% and 45% were obatained for the syn adducts for the 4-MeO and the 2-MeO substrates respectively. This problem could be suppressed in the case of the 2-MeO adduct **80c** (entry 4) by performing the reaction at a higher concentration (0.3M) for a prolonged time (60h). In this way an excellent overall yield could be obtained (94% overall) without any loss in the selectivities. The same didn't work for the 4-MeO substrate, though, since its conversion remained the same (~70%) despite the efforts to push the reaction. Electron deficient chloro and bromo substituted nitrostyrenes reacted faster and gave mostly complete conversions of the starting material, some of them in short reaction times (17h for 4-Cl and 4-Br).

On the other hand, electron neutral, withdrawing or donating groups do not seem to affect the selectivities. The diastereoselectivities are in the range of 74/26 tp 90/10 in favor of the syn adduct, while the asymmetric inductions are all between 92-95%, demonstrating a highly efficient enantiodiscrimination with excellent consistency.

On the other hand, the reaction with 1-nitrobutane (entry 11) is consistently efficient, giving a slightly higher diastereomeric ratio along with 91% ee for the *syn* isomer, indicating that the reaction is not restricted to 1-nitropropane, but could be potentially applied to higher nitroalkanes.

Switching from trans-β-nitrostyrene to the more demanding trans-α-methyl-β-nitrostyrene proved disappointing. A reaction using 2 mol% catalyst was run for 2 days and afforded no product but only unreacted starting material (Scheme 32).

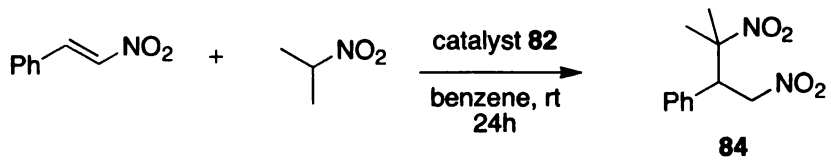
Scheme 32. Reaction with trans-α-methyl-β-nitrostyrene



0%, no reaction

An effort to extend the scope to branched nitroalkanes turned out to be more promising. 2-Nitropropane features a secondary nitro group and thus is much less reactive than 1-nitropropane. Addition of 2-nitropropane to nitrostyrenes have only been reported by Wang's group[52] and according to their protocol many (6-12) days are required for the completion of these transformations. When the reaction of 2-nitropropane with nitrostyrene was attempted using 10 mol% catalyst **82**, a 55% yield of the adduct **83** was obtained with 68% ee (Table 40). Lowering the catalyst loading to 5% afforded a better induction (76%) which is in accordance with what has been seen for 1-nitropropane, however, the increased induction is at the expense of the yield, although in this case the reaction was somewhat dilute (0.13M) and that might be a reason for the sluggishness.

Table 40. Reaction with 2-nitropropane using catalyst **82**



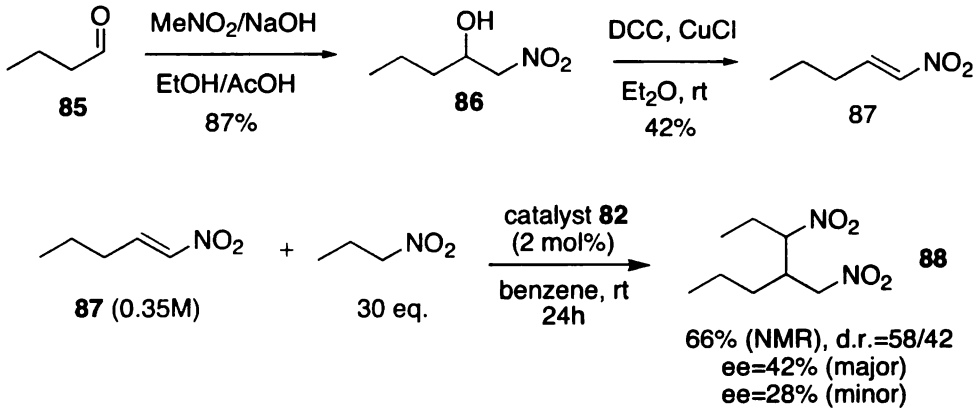
84

entry	%catalyst	equiv. 2-nitropropane	NMR yield%	%ee
1 (a)	10	27	55	68
2 (b)	5	55	27	76

(a) Reaction was run with 0.2M with respect to nitrostyrene. (b) Reaction was run with 0.13M with respect to nitrostyrene.

Finally, an effort was made to extend the scope of the reaction to aliphatic nitroolefins. Nitroalkene **87** was synthesized according to a common procedure[44b] from butyraldehyde **85** through an addition of nitromethane to make **86** followed by an elimination of water using CuCl and DCC (Scheme 33). Reaction of **87** with 1-nitropropane using 2 mol% catalyst **82** afforded a 66% conversion to the dinitro compound **88** in a clean reaction, according to the crude ^{1}H-NMR spectrum, as a 58:42 mixture of diastereomers with 42% and 28% ee's for the major and the minor diastereomer respectively. The pruduct was not isolated though because most of it was lost during purification because of its volatility.

Scheme 33. Synthesis and reaction of the aliphatic nitroolefine **88**

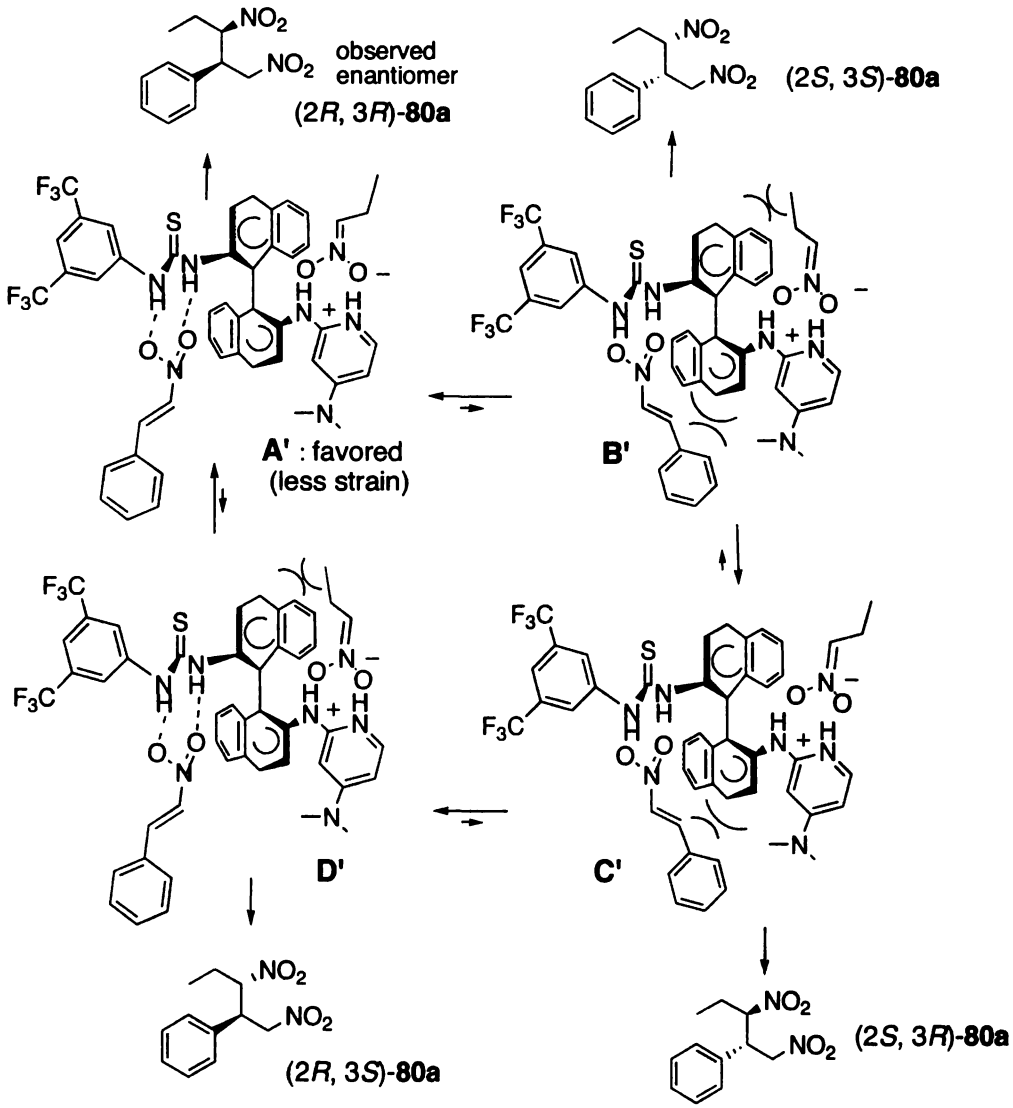


Although the result is not up to the level of the reactions with nitrostyrene, the good conversion and the enantioselectivity of the major diastereomer suggest that a further optimization and effort to extend the reaction to other aliphatic nitroalkenes would be worthy.

5.3.2.5 Proposed Stereochemichal Model for the asymmetric addition using thiourea 82

According to the generalized mechanism for the role of bifunctional catalysts in the conjugate addition of nitroalkanes to nitroolefins that was illustrated earlier in the chapter (Scheme 29) the key reactive intermediate is believed to involve the DMAP moiety of the catalyst interacting with the deprotonated 1-nitropropane as a cation/anion pair, along with the nitrostyrene which is held through H-bonding interaction from the thiourea group. A postulated mechanism that accounts for the observed stereochemical outcome with thiourea **82** is depicted in Figure 25.

Figure 25. Postulated stereochemical model



The absolute stereochemistry of the major enantiomer was determined by a comparison with the HPLC data and the optical rotation values of the corresponding compounds from the literature (for the known compounds **80a-c**, **80e**). The proposed stereochemical model is similar to the one for the BINAM derived bis-thiourea catalyst **52** that was developed for the asymmetric aza-Henry reaction and described in chapter 4. The major enantiomer (2*R*, 3*R*)-**80a** is believed to be derived via the intermediate **A'**, where

both components of the reaction orient themselves in the chiral pocket in such a way as to minimize the steric interaction with the (*R*)-BINAM moiety of the catalyst. The opposite enantiomer is obtained through **B'**, which is very unfavored due to the fact that both of the substrates experience unfavorable contacts with the binaphthyl core. The expected energy difference should be high, and it seems like a reasonable explanation for the excellent ee and the very efficient enantiodiscrimination for the syn adduct. The same factors make intermediates **C'** and **D'**, which afford the anti isomers, energertically unfavored and explain the diastereoselectivity in favor of the syn isomer, as well. In other words, the anti adduct is disfavored because both intermediates **C'** and **D'** involve steric interactions that are absent in **A'**. This model is in accordance with the higher diastereoselectivity that was observed for 1-nitropropane and 1-nitrobutane in comparison with nitroethane, since it would be expected that bulkier nitroalkanes would impose a higher energy cost for intermediate **D'**. Considering the ee of the minor diastereomer, which is determined by the energy difference between **C'** and **D'**, it is smaller than the ee of the syn product and thus makes sense since **C'** and **D'** each has one negative steric interaction, and thus the dicrimination between these two diastereomeric transition states shouldn't be as high as that for **A'** versus **B'**.

Again, as in the case of the aza-Henry bis-thiourea catalyst **52** (chapter 4), the above model is a working hypothesis that explains the stereochemical outcome. Given the conformational freedom that both the thiourea moiety and the DMAP group can experience other slightly different models could be proposed. The above model just represents a straight-forward representation of the reaction according to the assumptions described earlier.

5.4 SUMMARY AND CONCLUSION

In conclusion, the thiourea catalyzed conjugate addition of nitroalkanes to nitroolefines has been studied both in its non-asymmetric and enantioselective version.

Concerning the non-asymmetric Michael reaction, it was found that using 2 mol% of Schreiner's thiourea **47** along with 2 mol% triethylamine can lead to the *syn*-selective synthesis of 1,3-dinitroalkanes in good yields.

The successful employment of thiourea **47** to the addition of nitroalkanes to nitroolefins prompted the investigation of an asymmetric variant. As a result, the first highly efficient protocol for an organocatalytic direct addition of nitroalkanes to nitroolefines has been developed. The reaction is promoted by a novel bifunctional DMAP/thiourea catalyst and affords enantiopure *syn*-1,3-dinitro compounds with only 2% cat. loading. The asymmetric inductions in the products are remarkably consistent (92-95% ee for the addition of 1-nitropropane to nitrostyrene) and no drop-off is observed even when *ortho*-substituted styrenes are used.

A unique selectivity trend was discovered for this reaction according to which, the less catalyst used, the higher the enantioselectivity of the reaction, this effect was correlated with the nitroalkane/catalyst ratio. It was demonstrated that an increase in this ratio leads to increasd inductions, presumably because the interaction of the catalyst with nitroalkane changes its structure in solution to a more selective species. This idea can be formulated as a self-deactivated catalyst, and a series of experiments were done to probe this.

As a result of this unusual selectivity trend, ee's up to 96% could be obtained with only 0.5% catalyst loading, demonstrating a catalyst that is remarkably selective.

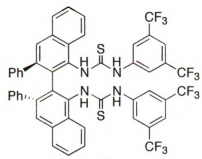
CHAPTER 6

TOWARDS VAULTED BIARYL-DERIEVED THIOUREAS AND THE SYNTHESIS OF VANAM

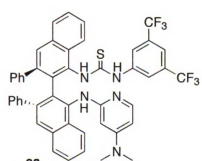
It was demonstrated in chapters 4 and 5 that 1,1'-binaphthyl-2,2'-diamine is an efficient chiral schaffold for thiourea mediated catalysis. The success of BINAM in inducing high enantioselectivities in the asymmetric addition of nitroalkanes to imines using catalyst **52** and to nitroolefines using catalyst **82** showed the potential of biaryl-based thiourea catalysts in a field dominated by cyclohexane diamine and Cinchona alkaloid-based organocatalysts.

These results along with the work that has been done in our laboratory with the ligands VANOL and VAPOL (see chapter 1) prompted the consideration of catalysts **89-90** that are based on the vaulted binaphthyl structural unit.

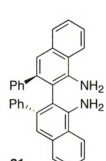
Figure 26. Vaulted biaryl thioureas and diamines



89



90



91

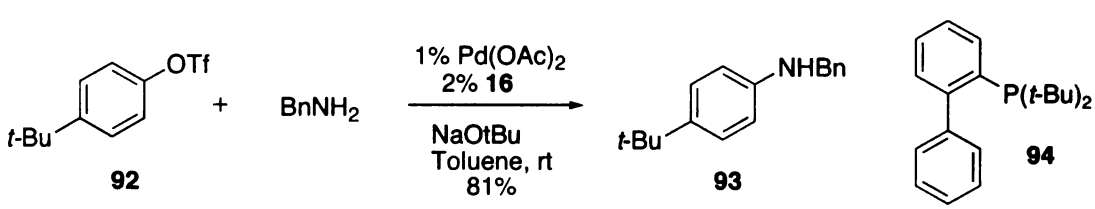
Catalysts **89** and **90** feature a vaulted biaryl unit that would be expected to communicate stereochemical information closer to the reaction center, that is the thiourea

and/or DMAP moieties, and so their synthesis and application in these reactions – or other related transformations – would be highly desirable. The chiral diamine **91**, which would be the starting material for the above catalysts, is not known in the literature. Therefore, the key issue in the synthesis of these novel catalysts is the synthesis of the diamine-analog of VANOL. Some preliminary efforts towards the synthesis of diamine **91** have been undertaken, and this chapter details the results of thess studies.

6.1 Examination of Buchwald amination as a key step in the synthesis of 91

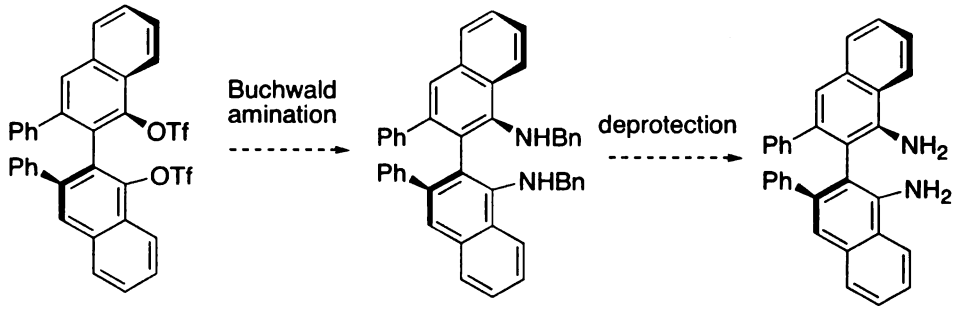
Concerning the synthesis of arylamines, one of the most powerful protocols reported in the literature involve the reactions of aryl triflates (or bromides and chlorides) with primary or secondary amines under Pd catalysis, described by Buchwald and coworkers[54]. For example, the reaction of triflate **92** with benzylamine using a catalyst formed in situ from $Pd(OAc)_2$ and ligand **94** affords the secondary arylamine **93** in 81% yield (Scheme 34)[55].

Scheme 34. Buchwald amination of triflate **95**



It was reasoned that this kind of amination reaction could be used as a key step in the synthesis of **91** according to the sequence illustrated in Scheme 35.

Scheme 35. Proposed synthesis of **91** using Buchwald amination as a key step

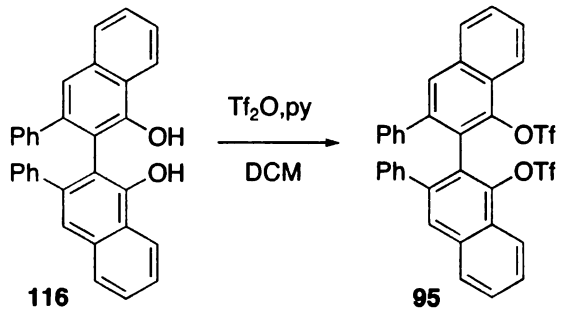


95 **96** **91**

A number of different amines could be coupled with VANOL triflate **95** – which should be easily obtained from VANOL – with benzyl amine being a good example of an amine that could be subsequently deprotected easily to give **91**.

The investigation of this stratgy started with the synthesis of triflate **95**. The reaction of racemic VANOL with triflic anhydride in the presence of pyridine afforded a very good yield of the biaryl triflate **95**, both on a small scale as well as on a 1g scale reaction (Scheme 36).

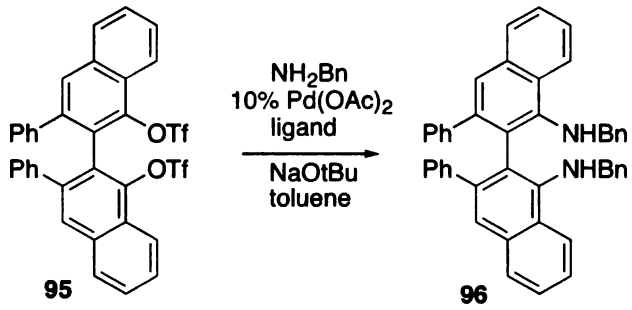
Scheme 36. Synthesis of VANOL triflate



116 **95**

150 mg scale: 91%
1g scale: 80%

Table 41. Initial efforts for the synthesis of **96**



ligand	conditions	result
94	rt, triflate added all at once	0% **96**, triflate hydrolyzed
BINAP	80°C, triflate added over 1h	0% **96**, triflate hydrolyzed

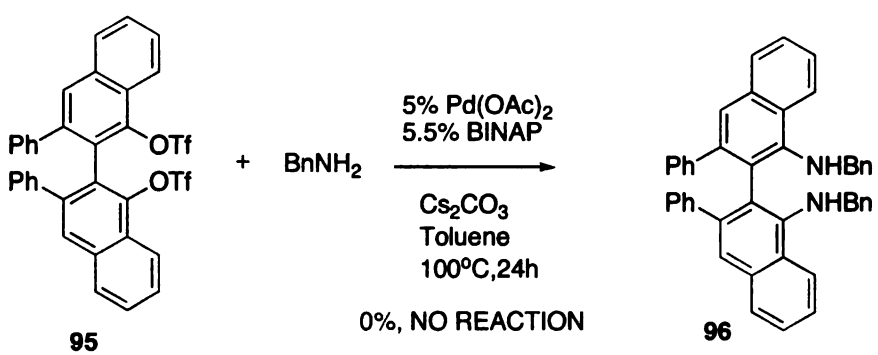
The first attempts to couple **95** with benzylamine using the conditions illustrated in Table 41 were disappointing. The reaction using ligand **94** at rt and adding the triflate all at once led to the hydrolysis of a big portion of **95** and the formation of free VANOL (Table 41).

The hydrolysis of triflates during Pd catalyzed amination reactions is a common problem according to the reports of Buchwald and Hartwig[54]. This hydrolysis is attributed to the rapid cleavage of the triflate by attack of NaOtBu (or other strong bases) on sulfur leading to the corresponding phenoxide. It is usually associated either with the electronic nature of the triflate (electron deficient triflates are prone to hydrolysis) or the strength of the base that is used. In the case of compound **95** there is no issue with the electronic nature of the substrate, but still it seems that the substrate is not stable under the given conditions. Hartwig has reported that slow addition of the triflate to the reaction mixture

can prevent the undesired hydrolysis[56]. Along these lines, an experiment was performed where **95** was added over a 1h period, but with no success (Table 41).

A second way to avoid triflate hydrolysis is using a relatively weak base for the amine deprotonation step. Buchwald has reported an improved method using weaker bases such as Cs_2CO_3 for the amination of halides and triflates that affords higher yields and improved functional group compatibility[57]. The use of Cs_2CO_3 was tested in the reaction of benzylamine with **95**. The hydrolysis of **95** was completely prevented this time and no free VANOL was obtained, but the reaction didn't afford any product either. All the starting material remained unreacted under the conditions shown in Scheme 37.

Scheme 37. An attempt for Buchwald amination of **95** using Cs_2CO_3

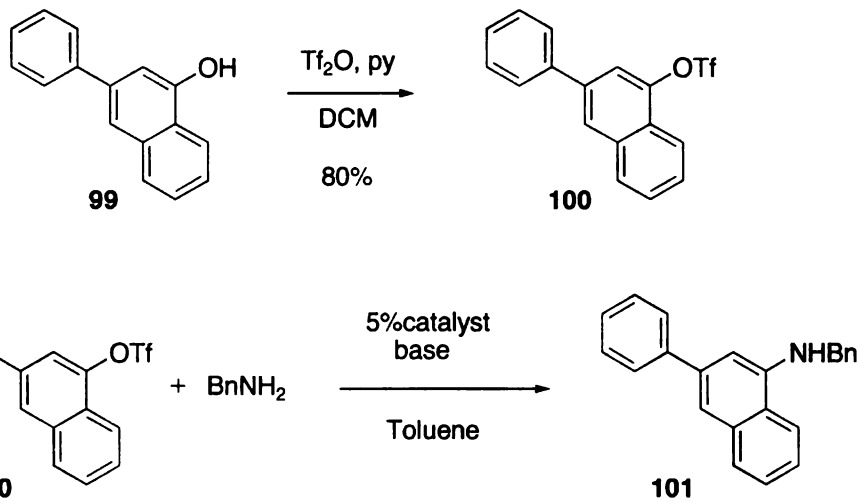


At this point, it was suspected that the bulkiness of the VANOL triflate might be responsible for the failure of these attempts. Since **95** remains unreacted under forcing conditions even when hydrolysis is prevented, this probably means that the triflate is probably too bulky for the oxidative addition step, particularly when the ligand that is used for Pd also is considerably bulky.

To test this hypothesis it was reasoned that the coupling should be tried with the triflate **100** obtained from the mononer precursor of VANOL, **99**. The result from the coupling of **100** should give information about weather the bulkiness of VANOL triflate is the reason for the failure of its coupling.

To test whether the bulkiness of VANOL is responsible for its unreactivity in the Pd catalyzed coupling, triflate **100** was made in 80% yield from **99** and it was subjected in coupling reactions with benzylamine using different bases. The results are shown in Scheme 38.

Scheme 38. Synthesis and amination of triflate **100**



entrty	catalyst	base	T(°C)	%yield **101**
1	$Pd(OAc)_2$/BINAP	NaOtBu	80	0%
2	$Pd(OAc)_2$/**94**	K_3PO_4	80	0%
3	$Pd(OAc)_2$/BINAP	Cs_2CO_3	100	87%
4	$Pd(OAc)_2$/**94**	Cs_2CO_3	100	28%

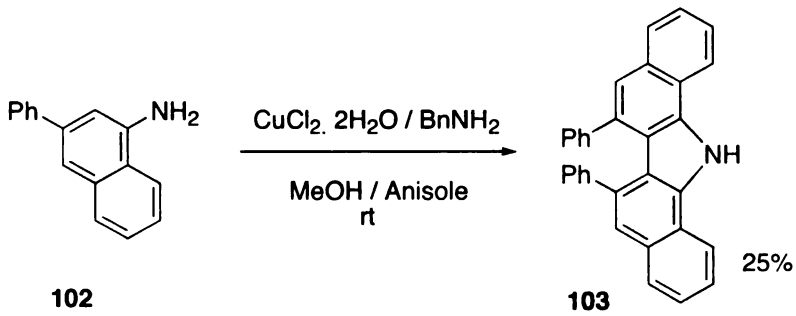
The use of NaOtBu afforded the same result as for the attempted coupling of **95**. A big amount of **100** was hydrolyzed and **99** was obtained as a major product from the reaction in entry 1. The use of K_3PO_4 afforded no reaction and recovery of unreacted **100**. The use of Cs_2CO_3 though afforded the desired product **101** in excellent yield when BINAP was used as a ligand (entry 3) and with a lower yield when **94** was employed (Scheme 34). These two last results in entries 3 and 4 confirm that the triflate **95** is presumably too bulky for the Pd catalyzed coupling under the above conditions. The fact that the monomer **100** can afford an excellent yield whereas the VANOL triflate gives no reaction implies that the formation of the intermediate of the oxidative addition that features Pd coordinated both by BINAP and VANOL triflate is probably disfavored due to steric congestion.

6.2. Examination of a synthesis of 91 through oxidative coupling of arylamines

A second pathway that was examined for the synthesis of **91** involves the use of oxidative coupling between substituted anilines.

The synthesis of **91** through oxidative diaryl coupling in fact has been attempted before in the literature by Kocovsky's group, but without success[58]. When Kocovsky employed the free aniline **102** in an oxidative coupling using $CuCl_2$ he obtained carbazole **103** as the only product in 25% yield. The driving force for the formation of compound **103** is the loss of ammonia. Kocovsky proposed that the loss of ammonia is not occurring through the formation of **91** as an intermediate, but instead, via a competing pathway that involves N-N coupling of **102** and a subsequent 3,3-rearrangement.

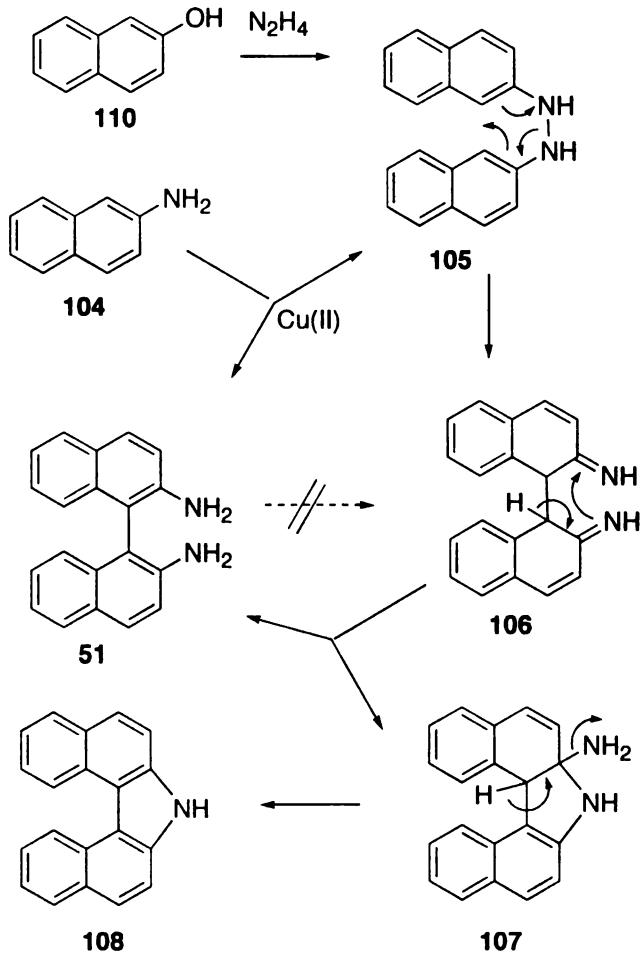
Scheme 39. Oxidative coupling of **102** using $CuCl_2$



102 **103**

Specifically, through the oxidative coupling of a number of substituted aniline derivatives and control experiments, he postulated the mechanism shown in Scheme 40 to account for the formation of the resulting diamines and carbazoles.

Scheme 40. Postulated mechanism for the $CuCl_2$ mediated oxidative coupling of substituted anilines



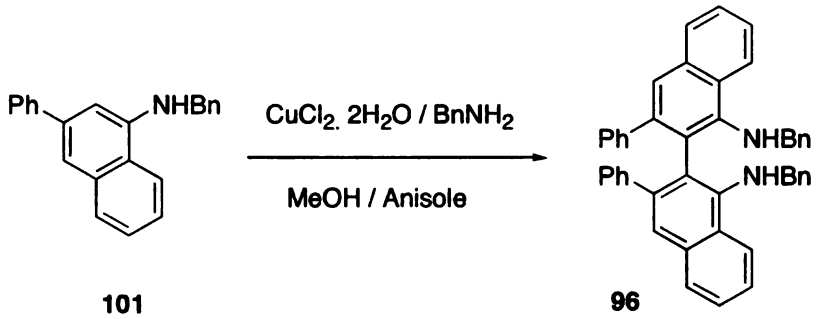
110 **105** **104** **106** **51** **108** **107**

According to this mechanism, naphthylamines like **104** can undergo a Cu(II) mediated oxidative coupling either affording directly **51** (C-C coupling) or **105** through coupling at nitrogen. Intermediate **105** can undergo a 3,3-sigmatropic rearrangement to give **106**, which subsequently can tautomerize to **51** or alternatively lead to the carbazole precursor **107**, that can release ammonia to afford **108**. For 2-naphthylamine **104** the major product was the diamine **51** while only a trace of carbazole was detected (~1%). For the coupling of other aniline derivatives though the percentage of carbazole formation was much higher and in the case of the coupling of **102**, as mentioned before, only carbazole was obtained. This mechanism was supported by the fact that the Bucherer-type reaction of 2-naphthol with hydrazine that is expected to proceed through intermediate **105**, was found to readily afford **51**[59]. Additionally, when the isolated diamines like **51** were subjected to the condition of the oxidative coupling no carbazole was obtained, which implies that the carbazole byproducts are not produced by loss of ammonia from the diamine, but instead, via the alternative N-N coupling pathway. The same control experiment was not performed with VANAM since no diamine was produced or isolated from the coupling of **102**, but the authors presume that its behavior should be similar to that of **104**[58].

Concerning the synthesis of VANAM, it was reasoned that if compound **102** was substituted at nitrogen then the formation of the carbazole byproduct should be disfavored since the ammonia loss would not be an issue anymore. This way, even in the case of N-N coupling the 3,3-rearrangement would hopefully result in the preferential formation of the desired diamine. This synthetic route using the oxidative coupling as a key step would add one more key step to the sequence, which is the resolution of the racemic diamine **96**.

Along these lines, substrate **101** was tested in the oxidative coupling using $CuCl_2$ and following the conditions reported by Kocovsky for the corresponding reaction with **102**. The results, shown in Scheme 41, were rather disappointing. Koockovsky's conditions (r.t.) afforded no reaction and complete recovery of the starting material. An attempt to push the reaction by heating at 100°C also did not produce a reaction.

Scheme 41. Attempted oxidative coupling of **101** using $CuCl_2$

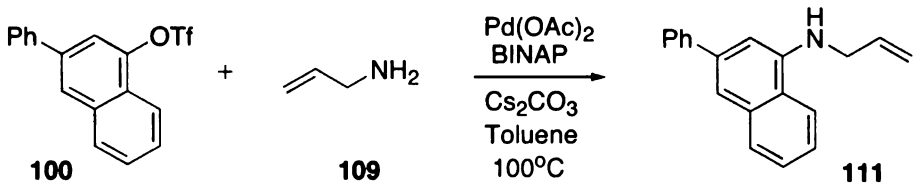


101 **96**

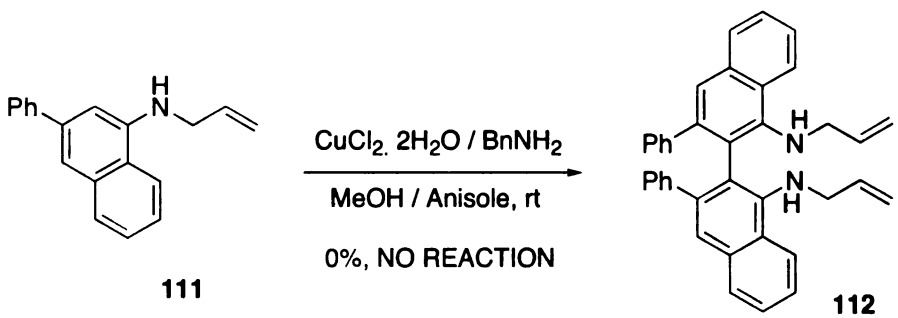
temperature (°C)	result
25	no reaction
100	no reaction

It was suspected that the failure of the above reaction might be a result of the bulkiness of the substrate **101**. The position of coupling is ortho, ortho- disubstituted by a phenyl group and a benzyl group, and that might impose a considerable energy barrier for the coupling of the two units. In this case, it was envisioned that the solution may be the employment of substrates that bear smaller N-substituents.

Scheme 42. Synthesis and attempted oxidative coupling of **111**



entry	scale	time	% catalyst	equiv. **109**	% yield
1	300 mg	12h	5	1.2	14
2	300 mg	2d	10	2.4	60
3	1g	2d	10	2.4	57

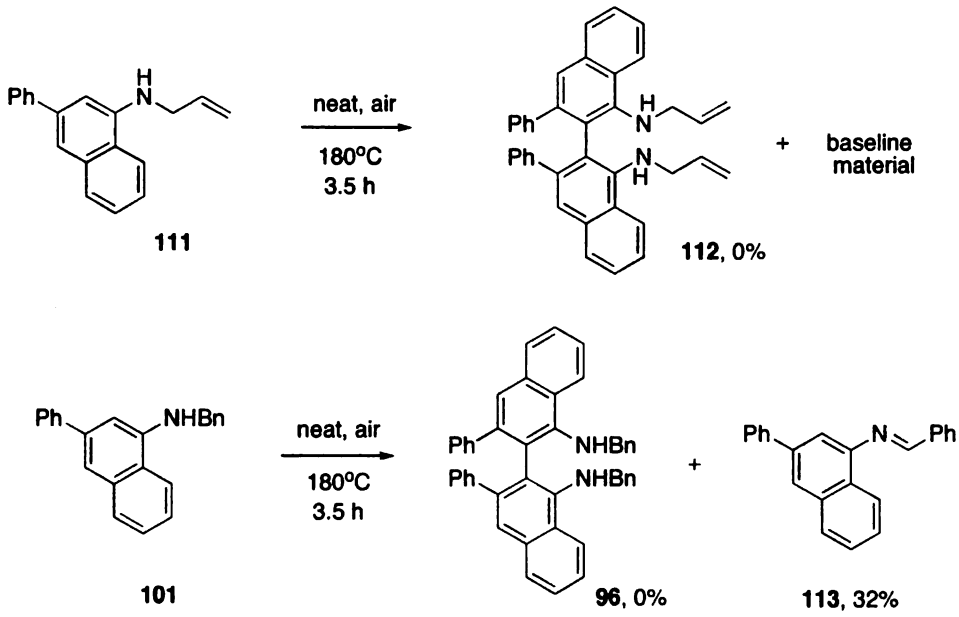


The allyl-protected substrate **111** was the compound of choice for testing this hypothesis. Compound **111** was synthesized from a Pd catalyzed coupling of **100** with allylamine **109**. This amination was a little more problematic than the one with benzylamine, since allylamine is a volatile compound and easily evaporates from the reaction mixture when using high temperatures, thus affording low yields (entry 1). This was solved when a larger excess of **102** was employed and higher catalyst loading was used to increase the rate. In this way a good yield of the desired product was obtained even when the reaction was scaled up to one gram of material.

It was disappointing to see that **111** did not give any product when its oxidative coupling was attempted (Scheme 42). Similar to **101**, the attempted reaction with **111** afforded a clean reaction mixture where surprisingly absolutely nothing had happened.

The failure of the $CuCl_2$ oxidation method turned our attention to alternative, and more forcing conditions for the oxidative coupling reaction. In specific, oxidative coupling under neat conditions using high temperature and air was considered. This has been a standard method for the synthesis of the chiral ligand VAPOL in our laboratories[3], and we thought it might turn out to be successful for the arylamine coupling as well. The coupling under neat conditions was tried both for **101** and **111**. The solids were put in a flask and subjected to high temperature for 3.5 hours under the flow of air. The results are shown in Scheme 43. Perhaps not surprisingly, the sensitive terminal double bond in **111** seems to be responsible for the considerable amount of baseline material observed in the oxidation of **111**. Concerning **101**, the only product observed after 3.5 h of heating was

Scheme 43. Attempted oxidation under neat conditions

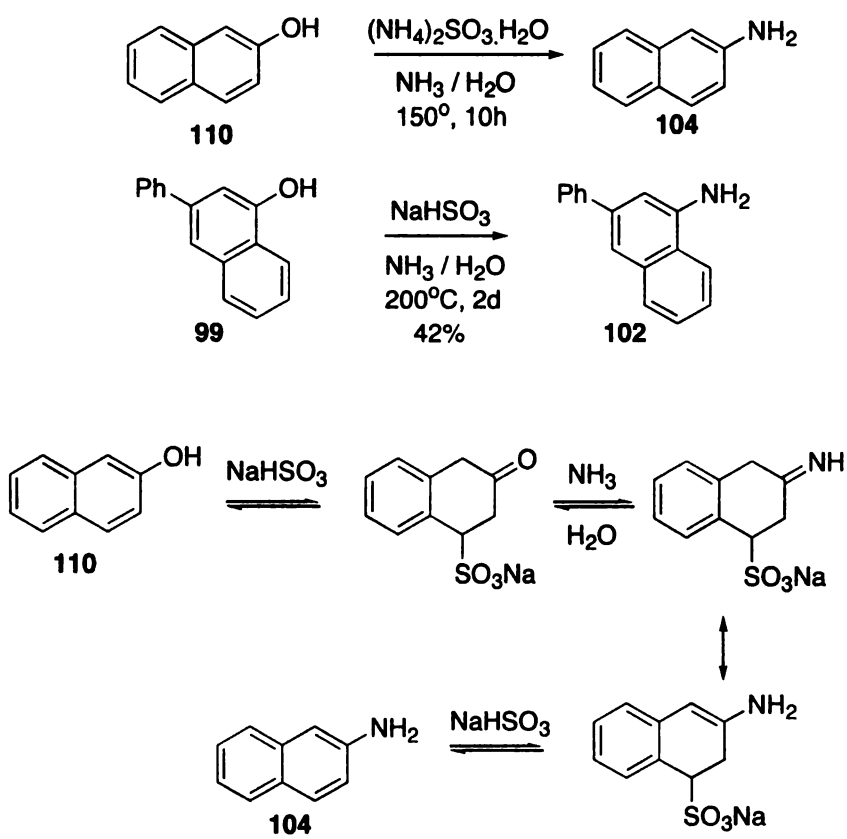


the imine **113** resulting from the oxidation of the benzyl moiety. These were the last attempts concerning this particular approach.

6.3. Attempts to synthesize 91 using the Bucherer reaction

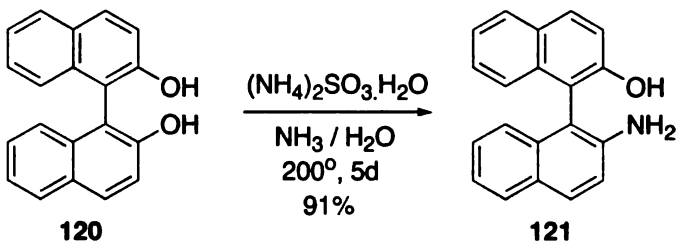
The last approach that was considered for the synthesis of **91** was the use of the Bucherer reaction, that is, the direct displacement in one step of the hydroxy groups with ammonia under forcing conditions[60]. The Bucherer reaction has been reported to transform 2-naphthol **110** and the VANOL monomer **99** to the arylamines **104** and **102** respectively[58], via the mechanism shown in Scheme 44.

Scheme 44. The Bucherer reaction for the synthesis of **104** and **102**



Despite the usefulness of the name reaction in the synthesis of simple naphthyl amines, there is no precedent for the synthesis of 1,1'-biaryl-2,2'-diamines using the above method. In fact, BINOL (**120**) has been reported to afford the monoaminated product **121** when subjected to the reaction conditions, but no BINAM was produced[61]. The difference in the reactivity of BINOL compared to its monomer **110** has been explained on the basis of an intramolecular H-bonding that stabilizes the monoaminated product **121** and "shuts down" any further reactivity, stopping the reaction and preventing the second hydroxyl group from getting displaced by ammonia (Scheme 45).

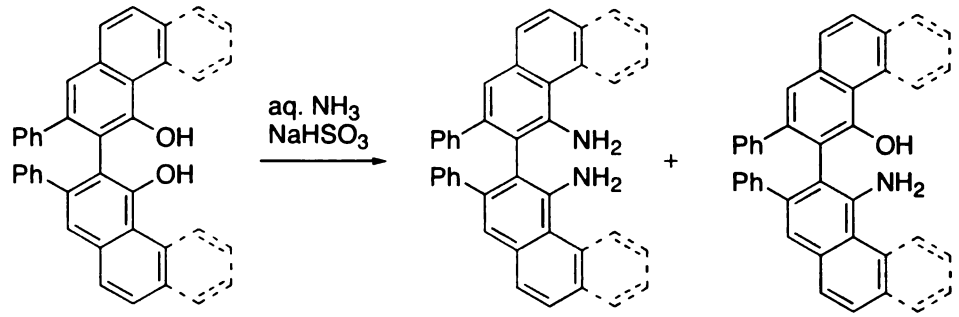
Scheme 45. Bucherer reaction of BINOL



120 **121**

Despite the unfavorable precedent with BINOL it was decided that an effort to test the VANOL (and VAPOL) ligand in the Bucherer conditions would be worthwile. VANOL and VAPOL thus were put in an aqueous solution of ammonia and heated at high temperatures in the presence of $NaHSO_3$. The results are shown in Table 42.

Table 42. Bucherer reactions of VANOL and VAPOL



116, VANOL
1, VAPOL

91
117

118
119

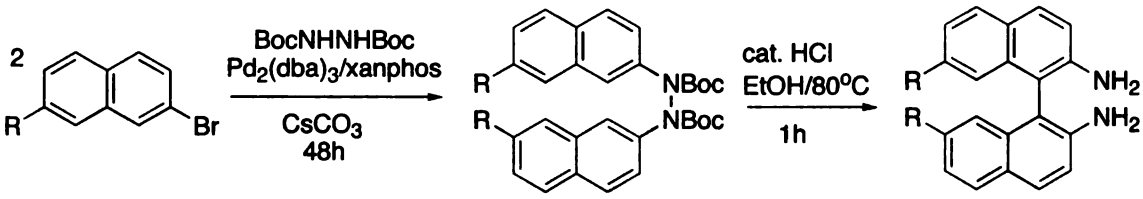
entry	ligand	scale	T(°C)	time (h)	%yield **91** or **117**	%yield **118** or **119**
1	**116**	217mg	200	60	0	50
2	**116**	2g	200	40	0	25
3	**1**	270mg	220	24	0	0

As can be seen, the reaction of VANOL **116** on a small scale (entry 1) produced compound **118** in 50% yield with no trace of the desired **91**. When the reaction was performed on a 2g scale though, the isolated yield dropped to 25% despite the almost complete conversion of the starting material. Finally, for the VAPOL ligand (entry 3) no reaction occurred at 220°C. Not surprisingly, the reactivity of VANOL resembles that of BINOL and the suspected intramolecular H-bond controls the reaction outcome here as well.

6.4. Future Work

In a recent report by Cho and coworkers it was shown that diaryl hydrazides **125-127** prepared from the Pd(0) catalyzed coupling reactions between aryl bromides **122-124** and di-*tert*-butyl hydrazidoformate (BocNHNHBoc) can undergo acid-catalyzed rearrangement to form 2,2'-diamino-1,1'-binaphthyls, according to the sequence shown in Scheme 46[62].

Scheme 46. Cho's synthesis of BINAM derivatives



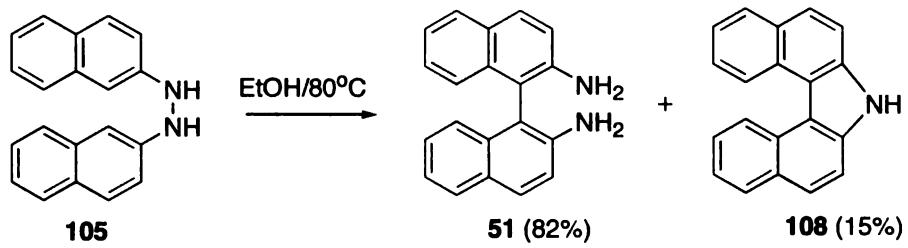
122 (R=H)
123 R=Br
124 (R=Me)

125, 81%
126, 37%
127, 65%

51, 75%
128, 81%
129, 81%

This type of rearrangement has been known for a long time to proceed either thermally or with acid catalysis for **105**, giving BINAM as a major product. For example, heating of **105** in boiling EtOH affords an 82% yield of **51** and a small amount (~15%) of the carbazole **108** (Scheme 47)[59b]. It seems that EtOH promotes the rearrangement by acting as a general acid catalyst.

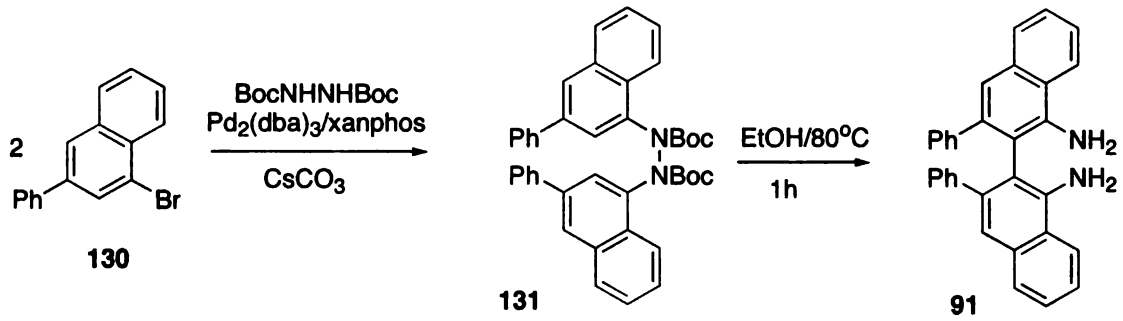
Scheme 47. Thermal rearrangement of **105** for the synthesis of BINAM



105 **51** (82%) **108** (15%)

It was envisioned that this synthetic sequence could be potentially used for the synthesis of VANAM **91**. An N-protected diaryl hydrazide **131** could hopefully rearrange to afford the desired product **91** without significant production of carbazole. If Kocovsky's proposed mechanism for the diamine versus carbazole formation is correct and the carbazole is produced through ammonia loss from the 3,3-rearrangement pathway intermediate **106**, then one would expect that in case of **131** the ammonia loss should be prevented *if the rearrangement occurred before the deprotection of nitrogen.* The mechanism for the reaction in Scheme 47 is not clear in every detail, but it could be argued that

Scheme 48. Proposed synthesis of **91** through hydrazide rearrangement

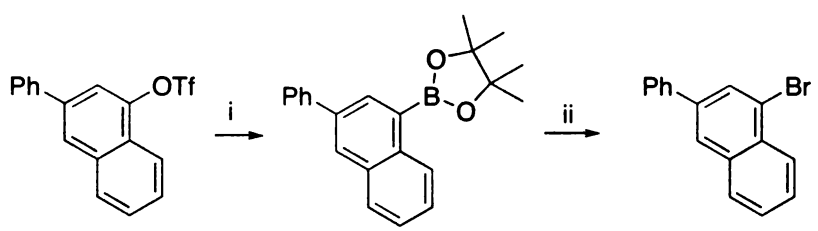


130 **131** **91**

avoiding the use of HCl in the rearrangement of **131** and performing the reaction under milder conditions (thermally, using only EtOH) might allow for the reaction to occur with the Boc groups still on, thus eliminating the issue of ammonia loss.

Compound **130** could be obtained from the triflate **100** through the intermediacy of a boronate ester **132** according to the method depicted in Scheme 49. This chemistry has been developed by Huffman's group and is known to afford very good yields of aryl halides[63]. For example, 2-naphthyl and 1-naphthyl bromides can be obtained in 77% and 84% overall yields from the starting triflate respectively. The reaction for the particular triflate **100** is not known, but it is expected that it will hopefully show similar behavior.

Scheme 49 Proposed synthesis of **130**



100 **132** **130**

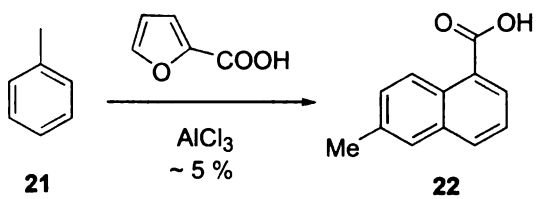
i. pinacolborane, $PdCl_2$, dppf, dioxane, NEt_3; ii. $CuBr_2$, MeOH, H_2O

In addition, the direct coupling of triflate **100** with BocNHNHBoc could be examined as an alternative way of accesing **131** in a fewer number of steps. Cho's method only concerns naphthyl bromides, but an extension of the methodology to include aryl triflates might be feasible. In this case the synthesis of **91** would be shorter and thus more attractive.

EXPERIMENTAL PROCEDURES

Experimental procedures for Chapter 2

6-Methylnapthoic acid 22

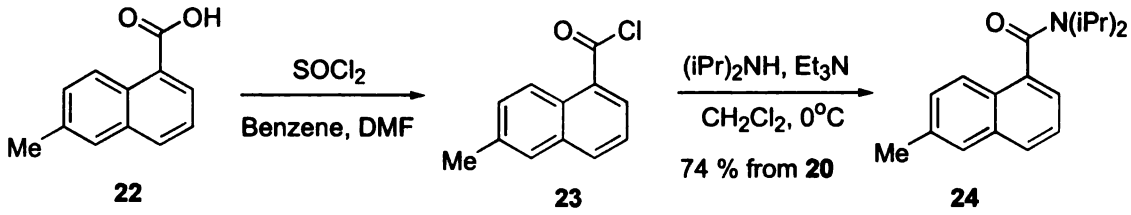


21 22

2-Furoic acid (120 g, 1071 mmol, 1.0 equiv) was added portionwise to a 3-necked flask containing toluene **21** (1000 mL), which was immersed in an ice bath and fitted with a mechanical stirrer. A bubbler was attached before $AlCl_3$ (300g, 2249 mmol, 2.1 equiv) was added in spatula portions over a 2 h period, maintaining a steady evolution of gas. The flask was removed from the ice and slowly heated to 60 °C and then stirred at this temperature for 18 h. The solution was then poured into an ice-cold HCl solution (550 ml of conc HCl in 2 litres of H_2O). This was then heated overnight (18 h) at 60 °C, to dissolve any solids. The two resulting layers were separated, and the organic layer was washed with H_2O (2 x 300 ml) before being heated with a 1.0 M $NaHCO_3$ solution (1000 mL) at 55 °C for 1 h. This was repeated once more and the combined aqueous layers (2000 mL) were heated to 55 °C before $Ba(OH)_2.8\ H_2O$ (315.0 g, 1000 mmol) was added and the resulting solution stirred for 2 h. The yellow precipitous solution was filtered and the red/brown aqueous layer collected and split into 3 x 1 litre fractions. Using pH paper these solutions were titrated with conc HCl to a pH of 7.0. The resultant yellow precipitate was

filtered and the green aqueous filtrate was further titrated with conc. HCl to a pH of 5.0-6.0. A paler yellow precipitate was filtered and collected, TLC analysis indicated that it was the desired product. The purity of the solid varied, with a solid orange contaminant being present. The material was crystallized to purity from either hot benzene or EtOAc to deliver bright yellow crystals of *6-methylnapthoic acid*, (16.7 g, 85.6 mmol, 8%). ^{1}H NMR (300 MHz, MeOD) δ 2.39 (s, 3H), 7.30-7.38 (m, 2H), 7.58 (s, 1H), 7.85 (d, 1H, J = 8.5 Hz), 8.00 (dd, 1H, J = 7.0, 1.2 Hz), 8.68 (d, 1H, J = 9.0 Hz).

Diisopropyl-6-methynapthamide 24

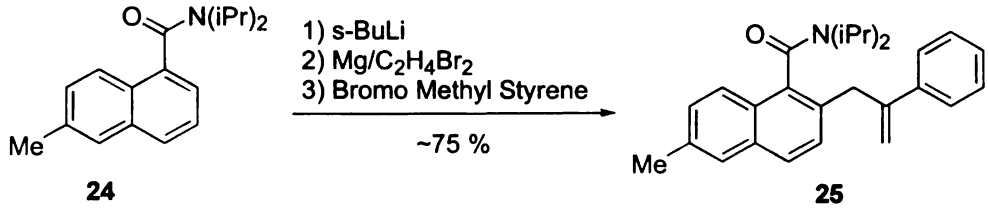


To a flask containing *6-methylnapthoic acid* **22** (8.27 g, 44.46 mmol, 1.0 equiv) under N_2 was added benzene (18.5 mL, 2.4 M) and the resulting slurry stirred for 5 min. $SOCl_2$ (3.5 mL, 48.11 mmol, 1.1 equiv) was added followed by the dropwise addition of DMF (1.5 mL, 19.36 mmol, 0.44 equiv). The resulting clear red solution was allowed to stir for 4 h, after which time the solution was concentrated on the rotary evaporator, removing any excess $SOCl_2$. The benzene/DMF solution was taken on into the next step.

The above reaction was assumed to have progressed in quantitative yield.

CH_2Cl_2 (10 mL) was added to a flask containing the acid chloride under N_2. This solution was stirred for 5 min before being added *via* canula to a flask containing a stirring solution of (*i*-Pr)$_2$NH (7.48 mL, 53.38 mmol, 1.2 equiv) and NEt_3 (7.44 mL, 53.38 mmol, 1.2 equiv) in CH_2Cl_2 (70 mL, 0.5M in **23**) under N_2. After stirring overnight, H_2O (50 mL) was added to the reaction, the layers separated and the aqueous layer extracted with CH_2Cl_2 (2*100 mL), and the combined organic fractions washed with 2M HCl (aq) (2*100 mL), sat $NaHCO_3$ (aq) (2*100 mL) and dried with Na_2SO_4. Concentration under reduced pressure and column chromatography (10% EtOAc:hexane) gave *diisopropyl-6-methynapthamide* (32.9 mmol, 8.85 g, 74 % for the two steps) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, 3H, *J* = 6.5 Hz), 1.05 (d, 3H, *J* = 6.5 Hz), 1.63 (d, 3H, *J* = 7.0 Hz), 1.69 (d, 3H, *J* = 7.0 Hz), 2.48 (s, 3H), 3.62-3.54 (m, 2H), 7.21-7.42 (m, 3 H), 7.60 (s, 1 H), 7.69-7.73 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.6, 20.6, 20.8, 21.6, 45.9, 51.0, 121.2, 124.7, 125.3, 127.1, 127.4, 127.8, 128.9, 133.7, 136.0, 136.4, 170.0, 1 sp_3 C not located; IR (neat) 3053m, 2976m, 1622s, 1332m, 1265s, 710s, 704s cm^{-1}; mass spectrum *m/z* (% rel. intensity) 269 [M^+] (16), 169 (100), 141.0 (43), 115 (11), 88 (17), 84 (16), calcd for *m/z* 269.1780, meas 269.1777. Anal calcd for $C_{18}H_{23}ON$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.02; H, 8.73; N, 5.18; White solid (EtOAc) mp = 140-142°C; R_f=0.19 (10% EtOAc:hexane).

Diisopropyl 6-methyl-2-(2-phenylallyl)naphthalen-1-amide 25.



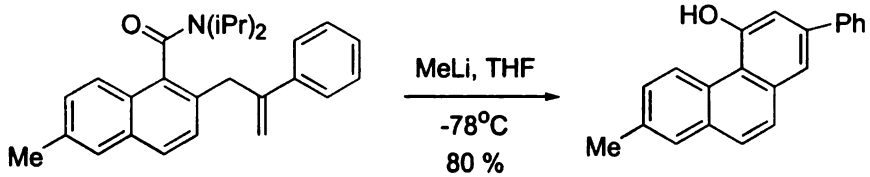
24 **25**

s-BuLi (6.43 mL, 8.99 mmol, 1.1 equiv) was added dropwise over 1 min to a solution of diisopropyl-6-methylnapthamide (2.2 g, 8.17 mmol, 1.0 equiv) in THF (80 mL, 0.08 M in **24**) under N_2 at –78 °C. The resulting orange solution was stirred for 1 h before the canular addition of the ethereal $MgBr_2$ solution, which was prepared *in situ* as described below.

Dibromoethane (2.1 mL, 24.51 mmol, 3.0 equiv) was added over a 1 h period to a flask, fitted with a condenser, containing magnesium turnings under N_2. The resulting reaction was stirred for 2 h before being added *via* canular to a solution containing the *ortho*-lithiated napthamide. The colour of the solution changed from orange to pale green and it was then stirred for a further 15 min before being allowed to warm to rt over a 1 h period. The solution was then cooled to –78 °C, followed by the dropwise addition of α-bromomethyl styrene and then allowed to warm to room temperature overnight. The reaction was quenched with sat NH_4Cl (100 mL), the layers separated and the aqueous fraction extracted with EtOAc (2*100 mL), washed with brine (2*50 mL) and dried with Na_2SO_4. Concentration under reduced pressure and column chromatography (10% EtOAc:hexane) gave the desired *diisopropyl 6-methyl-2-(2-phenylallyl)naphthalene-1-amide* (2.35 g, 6.12 mmol, 75%) as a pale yellow foam. ^1H NMR (300 MHz, $CDCl_3$) δ

1.03 (d, 3H, J = 6.5 Hz), 1.11 (d, 3H, J = 6.5 Hz), 1.69 (d, 3H, J = 6.5 Hz), 1.81 (d, 3H, J = 6.5 Hz), 2.51 (s, 3H), 3.54-3.72 (m, 2H), 3.88 (d, 1H, J = 16.5 Hz), 4.12 (d, 1H, J = 16.5 Hz), 5.07 (d, 1H, J = 1.5 Hz), 5.64 (s, 1H), 7.26-7.75 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.5, 20.6, 21.0, 21.3, 21.5, 38.0, 46.1, 50.9, 115.8, 124.7, 126.0, 126.9, 127.0, 127.3, 127.5, 128.0, 128.3, 128.6, 131.1, 132.3, 134.7, 135.3. 140.6. 145.9, 169.4; IR ($CDCl_3$) 3055, 2986, 2936, 1622, 1265 cm^{-1} ; mass spectrum m/z (% rel. intensity) 385 [M$^+$] (10), 285 (25), 269 (30), 249 (30), 226 (15), 169 (70), 141 (30), 88 (100), 71 (75), 57 (65), 51 (100), calcd for m/z 385.2406, meas 385.2416. R_f=0.45 (20% EtOAc:hexane).

7-Methyl-phenylphenanthren-4-ol 26

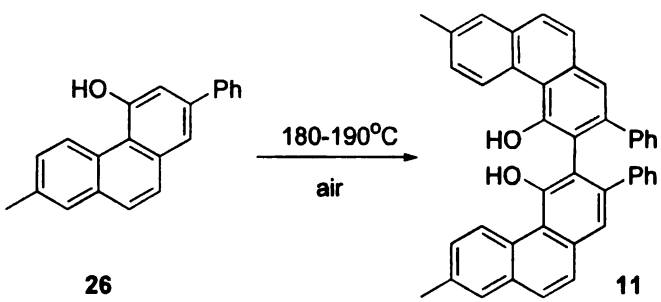


25 **26**

MeLi (5.52 mL, 5.52 mmol, 2.2 equiv) was added dropwise over a 5 min period, to a solution of diisopropyl 6-methyl-2-(2-phenylallyl)naphthalen-1-amide (0.966 g, 2.509 mmol, 1.0 equiv) in THF (50 mL, 0.05 M) at –78 °C, followed by stirring for 1 h before allowing the reaction to warm to room temperature overnight. The reaction was quenched with sat NH_4Cl (60 ml), the layers separated and the aqueous layer extracted with EtOAc (3 x 60 mL). The combined organic fractions were washed with brine (2 x 30 mL) and dried with Na_2SO_4. Concentration under reduced pressure and column chromatography (10% EtOAc:hexane), resulted in isolation of the desired *3-phenyl-8-methylphenanthrol*

as a brown solid (0.602 g, 2.00 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 1H, *J* = 1.5 Hz), 7.28 (s, 1H), 7.42 (d, 1H, *J* = 7.5 Hz), 7.51 (t, 3H, *J* = 7.5 Hz), 7.73 (t, 6H, *J* = 10 Hz), 9.53 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.3, 112.0, 118.6, 119.7, 127.1, 127.2, 127.4, 127.8, 128.1, 128.2, 128.3, 128.8, 132.7, 134.9, 135.6, 138.7, 140.2, 154.4, 1 sp_2 C not located; IR ($CDCl_3$) 3566, 3055, 2988, 1205, 710, 706 cm^{-1}; mass spectrum *m/z* (% rel intensity) 284 M^+ (100), 241 (10), 184 (50), 141 (60), 115 (20), 57 (30), calcd for *m/z* 284.1201, meas 284.1197. Brown solid (hexane), mp = 146-147°C, R_f=0.36 (20% EtOAc:hexane).

7,7'-Dimethyl-2,2'-diphenyl-(3,3'-biphenanthrene)-4,4'-diol 11



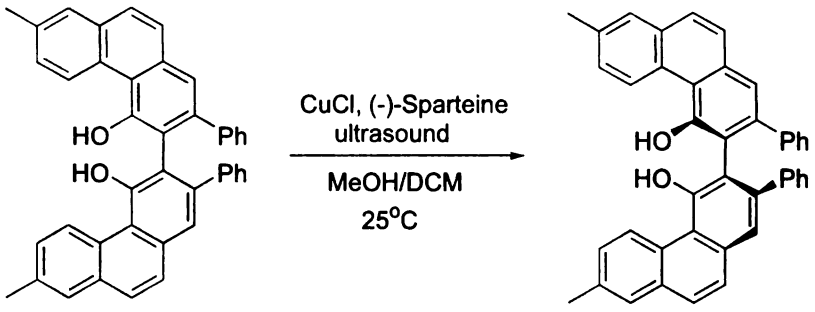
26 **11**

A round bottom flask containing 3-phenyl-8-methylphenanthrol (0.49 g, 1.33 mmol) was fitted with condenser. The flasks were then heated in an oil bath to 185 °C for 42 h. At 20 h interval, the black solid that was forming was dissolved with EtOAc, to ensure good mixing, and the polymer was filtered through celite, before the mixture was heated again. The reaction was monitored by TLC and ^{1}H-NMR. Work-up of the reaction involved dilution with EtOAc, filtration of insoluble polymeric material and column chromatography (4% EtOAc:pentane) leading to the isolation of name (164 mg, 0.438

mmol, 33.5%) as a slightly impure orange solid. Some starting material and a third compound was recovered - not characterized. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 6H), 6.65-7.64 (overlapping m, 22H), 9.63 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.3, 115.7, 118.1, 123.1, 126.7, 127.0, 127.5,128.03, 128.08, 128.68, 128.70, 128.8, 128.9, 133.0, 134.9, 136.1, 139.8, 141.1, 153.2; IR (neat) 3484w, 3026w, 2916w; mass spectrum *m/z* (% rel intensity) 566 M^+ (100), 384 (13), 283 (83), 244 (28), 154 (18), 105 (12), calcd for m/z 566.2246, meas 566.2245.

NOTE: The reaction using air flow is slower and generates more byproducts

(S)-7,7'-Dimethyl-2,2'-diphenyl-(3,3'-biphenanthrene)-4,4'-diol 11



11 (S)-**11**

(Typical procedure for deracemization of 7,7'-dimethyl VAPOL)

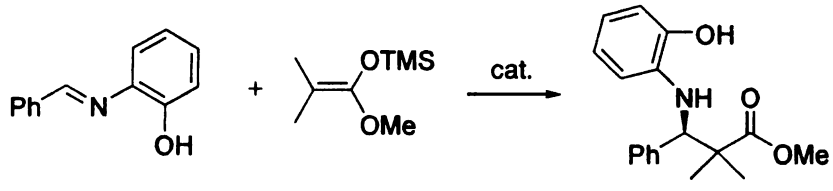
To a 50 mL round bottom flask was added 12 mL of MeOH, 64.7 g of CuCl (0.65 mmol) and 0.30 g of (-)-sparteine (1.30 mmol). The flask was sonicated in an ultrasonic bath with air sparged into the solution. The temperature was maintained at or below 25 oC by the addition of ice to the water in the bath. The flask was sealed with a septum after 45 minutes and then purged with argon for 60 minutes in the ultrasonic bath. The green

Cu(II)-sparteine solution was transferred via cannula to the solution of racemic 7,7'-dimethyl VAPOL (0.22 g, 0.38 mmol) in 50 ml of CH_2Cl_2 in a 250 ml round bottom flask which was had previously been purged with argon and sonciated for 60 minutes. The combined solution was sonicated for 10 minutes and then the flask was removed from ultrasonic bath, covered with aluminum foil and stirred at room temperature for 6 hours under a positive pressure of argon maintained by slow flow through the head space of the flask. The reaction was quenched by adding 5 mL of concentrated HCl and then stirring for 10 minutes. The two layers were separated. The lower CH_2Cl_2 layer was collected, the upper MeOH/H_2O layer was washed with 3*30 mL of CH_2Cl_2. The combined CH_2Cl_2 layer was dried over $MgSO_4$. Upon removal of solvent, the crude reaction mixture was loaded to silica gel column and eluted with a 1:1 mixture of CH_2Cl_2 / hexane to give 0.17 g (0.30 mmol, 79% yield) 26 as a white solid. The optical purity of 26 was found to be of $\geq$ 99 % by HPLC on a Pirkle D-Phenylglycine column with a 75:25 mixture of hexane/isopropanol (260 nm, flow rate: 2 mL/min). Under these conditions the retention time of (R)-25 was 14.8 min and that of (S)-25 was 19.8 min.

A typical experimental procedure for the reaction of aldimine with silyl ketene acetals.

To VAPOL (0.063 g, 0.11 mmol) and $Zr(O\text{-}i\text{-}Pr)_4.iPrOH$ (0.05 mmol) in toluene (0.9 mL) was added 1-methylimidazole (0.06 mmol) in toluene (0.1 mL) at room temperature. The mixture was stirred for 1 h at the same temperature. An aldimine (0.25 mmol in 1 mL) toluene solution was added to the catalyst and the mixture was stirred for an additional 5 min. Then the silyl ketene acetal (0.3 mmol) was added. The mixture was stirred for 15 h at room temperature. Aqueous $NaHCO_3$ was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was concentrated to give the crude product. The crude product was treated with THF and aqueous 1N HCl (10:1) at 0°C for 30 min. Then the reaction was quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine and concentrated. The desired product was obtained by chromatography on silica gel. The optical purity was determined by chiral HPLC analysis.

Methyl 3-(2-hydroxy-phenylamino)-3-phenyl-2,2-dimethyl-propionate 4.

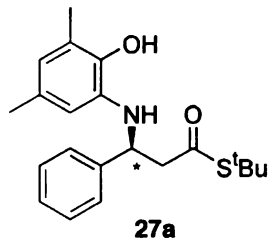


2 **3** **4**

The spectral data for this compound are the same as those previously reported for this compound (ref. 8). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3H), 1.23 (s, 3H), 3.67 (s, 3H), 4.53 (brs, 1H), 4.85 (brs, 1H), 5.29 (s, 3H), 6.37 (dd, J = 7.8, 1.1 Hz, 1H), 6.52 (dt, J = 7.0, 1.2 Hz, 1H), 6.59 (dt, J = 7.8, 1.1 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 7.20 -

7.27 (m, 5H). The optical purity was determined by chiral HPLC analysis (Daicel Chiralpak AD, Hexanes/i-PrOH = 9/1, flow rate 1.0 mL/min): R_t = 9.56 min (major enantiomer), R_t = 12.71 min (minor enantiomer).

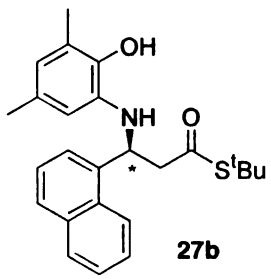
***tert*-Butyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-phenyl-propionthioate 27a.**



27a

White solid; R_f = 0.32 (9/1 hexanes/ethyl acetate); mp 90 – 92°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 2.05 (s, 3H), 2.17 (s, 3H), 2.85 (dd, *J* = 4.9, 14.8 Hz, 1H), 2.96 (dd, *J* = 8.8, 15.1 Hz, 1H), 4.17 (s, 1H), 4.68 (dd, *J* = 4.9, 8.8 Hz, 1H), 5.36 (s, 1H), 6.17 (s, 1H), 6.39 (s, 1H), 7.27–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 20.9, 29.6, 48.5, 51.7, 56.7, 115.0, 122.2, 122.7, 126.3, 127.2, 128.5, 129.3, 134.2, 141.8, 141.9, 198.6; MS (EI) *m/z* (relative intensity): 327 (9) [M^+], 227 (18), 226 (100), 148 (8), 136 (5), 131(2), 91 (12), 77 (5); Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.69; N, 4.28. Found: C, 71.19; H, 7.63; N, 4.09 (failed); HPLC (Daicel Chiralpak AD, hexanes/*i*-Pr= 9/1, flow rate = 1.0 mL/min): Rt = 11.7 min (minor enantiomer), R_t = 15.5 min (major enantiomer), (S)-VAPOL used as ligand.

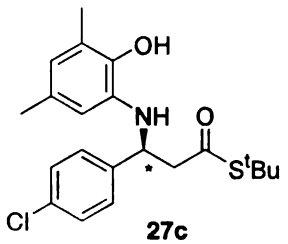
***tert*-Butyl-3-(2-hydroxy-3,5-dimethylphenylamino)-3-(1-naphthyl)-propionthioate 27b.**



27b

White solid; R_f = 0.31 (8/2 hexanes/ethyl acetate); mp 122 – 124°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 2.00 (s, 3H), 2.21 (s, 3H), 2.95 (dd, *J* = 9.3, 14.8 Hz, 1H), 3.12 (dd, *J* = 4.1, 14.8 Hz, 1H), 4.74 (br, 1H), 5.09 (br, 1H), 5.64 (dd, *J* = 4.1, 9.3 Hz, 1H), 6.13 (s, 1H), 6.35 (s, 1H), 7.38 – 7.65 (m, 4H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.90 (dd, *J* = 1.4, 8.2 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 15.8, 20.9, 29.7, 48.6, 51.2, 52.3, 113.3, 121.1, 122.3, 122.4, 123.1, 125.4, 125.5, 126.3, 127.8, 129.0, 129.8, 130.4, 133.9, 134.8, 137.1, 140.7, 198.4; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 9/1, flow rate = 1.0 mL/min): R_t = 12.9 min (minor enantiomer), R_t = 16.5 min (major enantiomer), (S)-VAPOL used as ligand.

***tert*-Butyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-(4-chlorophenyl)-propionthioate 14c.**



27c

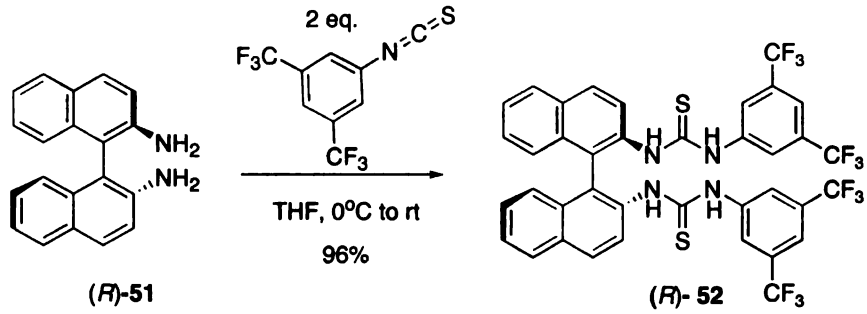
Yellow oil; R_f = 0.09 (9/1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 2.13 (s, 3H), 2.24 (s, 3H), 2.89 (dd, *J* = 5.4, 15.0 Hz, 1H), 2.99 (dd, *J* = 8.4, 15.0 Hz, 1H), 4.75 (m, 1H), 6.19 (s, 1H), 6.45 (s, 1H), 7.30 – 7.34 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) 15.7, 20.8, 29.6, 29.7, 48.7, 51.6, 55.9, 114.6, 122.2, 122.7, 127.8, 128.7, 129.6, 132.9, 134.1, 140.6, 141.6,198.3 ppm; IR (neat): 3410, 2964, 2922, 1672, 1601, 1516, 1491, 1456, 1385, 1199, 1151, 1091, 1030, 1014, 985, 827, 783 cm^{-1}; LRMS (FAB$^+$) *m/z* (relative intensity): 393 (33, ^{37}Cl) [M$^+$], 391 (76, ^{35}Cl) [M$^+$], 260 (20), 197 (20), 135 (60), 109 (24), 95 (40), 83 (40), 69 (60), 57 (100); HRMS (FAB$^+$) Calcd for $C_{21}H_{26}NO_2SCl$ 4391.1373, found 391.1375; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 9/1, flow rate = 1.0 mL/min): R_t = 17.3 min (minor enantiomer), R_t = 26.2 min (major enantiomer), (*S*-VAPOL as ligand).

Experimental Procedures for Chapter 4

General procedure for the preparation of the catalysts **52, 55**.

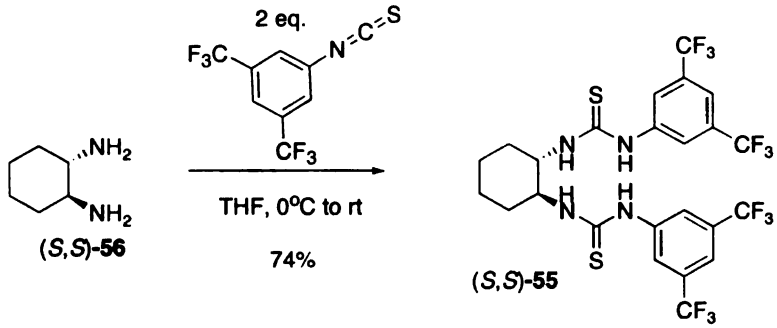
3,5-Bis-trifluoromethylphenyl isothiocyanate (8.12 mmol, 1.48 mL) was added to a solution of the appropriate diamine (4.06 mmol) in 7 mL THF at rt and the mixture was stirred overnight. The volatiles were evaporated and the crude mixtures were purified by crystallization.

Catalyst 52



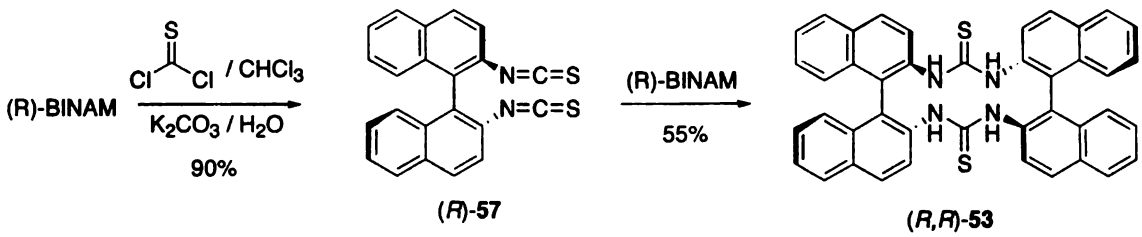
(*R*)-BINAM was used (1.26 g, 4.00 mmol). Purified by crystallization from dichloromethane/hexanes to afford 3.22g (3.89 mmol, 96%) isolated yield. White crystals, m.p. = 120-122°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.09 (d, J = 8.7 Hz, 2H), 7.26 (t, J = 6.9 Hz, 2H), 7.48 (m, 4H), 7.54 (m, 2H), 7.67 (br s, 4H), 7.81 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 8.10 (d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 119.2, 122.8 (q, J = 272.9 Hz), 124.6, 125.3, 125.6, 126.7, 127.5, 127.6, 128.5, 129.7, 131.7 (q, J = 33.7 Hz), 132.3, 132.8, 134.4, 139.1, 180.4 ppm; IR (neat) ν = 3265, 1688, 1498, 980 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{23}N_4F_{12}S_2$: 827.1179, found 827.1172; $[a]^{25}_D$ = +103.8 (c = 1.0, acetone).

Catalyst 55



Synthesized according to the general procedure using 468 mg (4.10 mmol) (*S*,*S*)-1,2-cyclohexyldiamine, purified by crystallization from EtOAc/hexanes to afford 1.99 g white crystals (3.03 mmol, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.35 (br s, 4H), 1.81 (br s, 2H), 2.20 (br s, 2H), 4.38 (br s, 2H), 7.07 (br s, 2H), 7.69 (s, 2H), 7.81 (s, 4H), 8.12 (br s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 24.4, 31.7, 59.4, 119.6, 122.7, 124.0, 132.9, 138.59, 180.54. The data agreed with the reported literature.[41a]

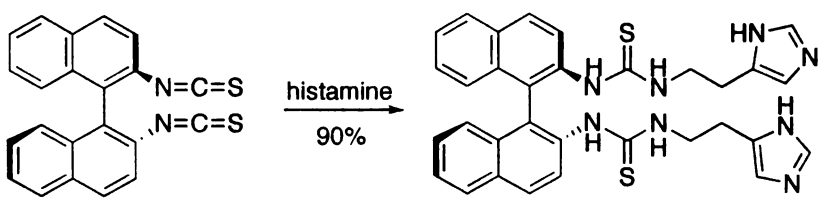
Catalyst 53



Synthesized using 365 mg (1 mmol) (R)-2,2'-bis(isothiocyonato)-2,2'-binaphthyl diamine[41b] and 281 mg (1 mmole) (R)-1,1'-binaphthyl-2,2'-diamine to afford 351 mg (55%) of white crystals (acetone/hexanes). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.68 (d, *J* = 8.7 Hz, 2H), 6.82 (s, 4H), 6.87 (s, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 6.9 Hz, 2H), 7.40 (q, *J* = 6.9 Hz, 6.9Hz, 4H), 7.57 (s, 2H), 7.67 (t, *J* = 6.9 Hz, 2H), 7.76 (d, *J* = 8.1Hz,

2H), 7.90 (d, J = 8.1Hz, 2H), 8.02 (d, J = 9.3 Hz, 2H), 9.41 (d, J = 9.3 Hz, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 300 MHz): δ = 119.8, 120.8, 123.1, 125.4, 125.5, 125.9, 127.1, 127.2, 127.8, 128.2, 128.6, 128.8, 129.3, 130.2, 131.1, 132.2, 132.3, 132.5, 133.7, 135.7, 177.6 ppm. IR (KBr) 3154, 1595 cm^{-1}; MS (FAB$^+$): m/z (%): 653 [M+H]$^+$ (18), 619 (4), 460 (5), 307 (40), 252 (45) 154 (100), 136 (84), 102 (38); m.p. 230-231°C.

Catalyst 54



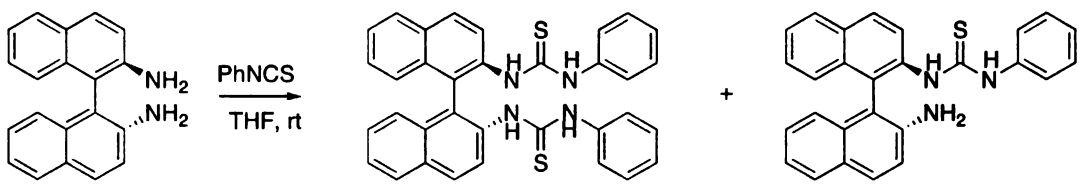
(*R*)-**57** (*R*)-**54**

Synthesized according to the general procedure using 0.5 g (1.3 mmol) (*R*)-2,2'-bis(isothiocyonato)-2,2'-binaphthyl and 302 mg (2.71 mmol) histamine to afford 540 mg (0.91 mmol, 100% from **57**) of an off-white solid. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 2.55 (br. s, 4H), 3.47 (br. s, 4H), 6.62 (br. s, 2H), 7.07-7.17 (m, 4H), 7.40 (m, 4H), 7.73 (m, 4H), 7.95 (t, J = 9.3, 4H), 8.61 (br. s, 2H), 11.71 (br. s, 2H); ^{13}C-NMR (DMSO-d_6, 300 MHz): δ = 27.0, 44.5, 55.4, 126.1, 126.2, 126.7, 127.2, 128.3, 128.7, 131.9, 133.1, 135.1, 136.4, 181.3; two carbons are not located. MS (FAB$^+$): m/z: 591 [M+H]$^+$ (17), 307 (14); IR (neat) 3150, 1595, 1490 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{32}H_{31}N_8S_2$: 591.2113, found 591.2117.

General procedure for the preparation of catalysts **56-61a**

Following the general procedure for **52** and **55**, the appropriate isothiocyanate (2 equiv.) was added to a solution of (*R*)-BINAM in THF (0.6M in BINAM) and the mixture was stirred overnight at rt. The volatiles were evaporated and the crude mixtures were purified by column chromatography on silica gel (always using 30% acetone in hexanes).

Catalyst **56a**, compound **56b**.



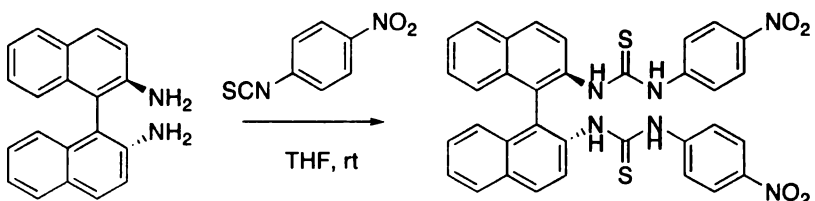
(*R*)-**56a** (50%) (*R*)-**56b** (50%)

Catalyst 56a

Synthesized from (*R*)-BINAM (300 mg, 1.05 mmol) and isolated as a white solid (277 mg, 0.50 mmol, 50%), m.p. = 128-130°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.12 (d, *J* = 7.2 Hz), 6.92 (t, *J* = 7.2 Hz, 4H), 7.03 (t, *J* = 7.5 Hz, 2H), 7.35-7.28 (m, 4H), 7.58-7.53 (m, 4H), 7.89 (d, *J* = 8.7 Hz, 2H), 8.01(d, *J* = 2.7 Hz, 4H), 8.04 (d, *J* = 2.7 Hz, 4H), 8.30 (br. s, 2H); three exchangeable H's do not show up. ^{13}C-NMR ($CDCl_3$, 300 MHz): δ = 125.30, 125.33, 126.4, 127.23, 127.29, 128.0, 128.1, 129.2, 129.5, 132.31, 132.33, 135.0, 135.6, 179.7; one C not located. IR (neat) 3159, 1593, 1535 cm^{-1}; MS (FAB$^+$): *m/z* (%): 555 [*M*+H]$^+$, (26), 462 (17), 307 (30), 154 (100), 136 (60); α^{25}_D = +60.0 (c = 1.0, dichloromethane).

Compound **56b.** White solid, 50% isolated (210 mg, 0.5 mmol) , m.p. = 108-110°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.46 (d, *J* = 9MHz, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 7.07-6.92 (m, 4H), 7.31-7.24 (m, 3H), 7.13 (td, *J* = 1.5, 6.9 Hz, 1H), 7.51-7.41 (m, 1H), 7.52 (br s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.4 MHz, 1H), 8.36 (d, *J* = 9 Hz, 1 H), 8.40 (br s, 1H); three exchangeable H's do not show up. ^{13}C-NMR ($CDCl_3$, 300 MHz): δ = 111.5, 118.3, 122.5, 122.9, 124.5, 125.6, 125.8, 126.0, 126.7, 126.7, 126.9, 127.2, 127.4, 127.9, 128.1, 129.6, 132.3, 132.4, 133.4, 135.2, 135.3, 142.7, 179.0 ppm; 2 C's not located. MS (FAB$^+$): *m/z* (%): 420 [*M*+H]$^+$ (40), 307 (30), 154 (100), 136 (65); IR (neat) 3352, 3186, 1626, 1510; α^{25}_D = +24.2 (c = 1.0, dichloromethane).

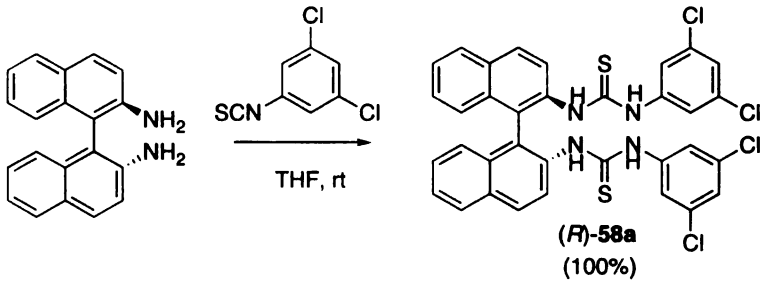
Catalyst 57a.



(*R*)-**57a**
(100%)

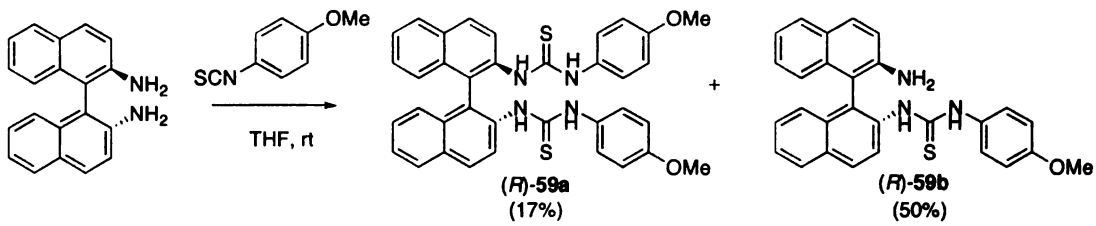
Synthesized from (*R*)-BINAM (300 mg, 1.05 mmol) and isolated as a white solid (644 mg, 1.00 mmol, 100%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.69 (d, *J* = 9 Hz, 4H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 8.0Hz, 2H), 7.82 (d, *J* = 9 Hz, 4H), 7.98 (d, *J* = 8.1 Hz, 2H), 8.06 (s, 4H) ppm; 4 exchangeable H do not show up. ^{13}C-NMR ($CDCl_3$, 300 MHz): δ = 112.8, 122.1, 124.7, 126.3, 126.6, 126.9, 127.1, 127.6, 128.5, 132.3, 133.1, 136.4, 142.9, 145.9, 180.0 ppm; MS (FAB$^+$): *m/z*: 645 [*M*+H]$^+$, 507, 460, 307, 154, 136; IR (neat) *v* = 3410, 1702, 1594, 1500, 1388, 1268 cm^{-1}; m.p. = 134-136°C; [a]$^{25}_D$ = -56.7 (c = 1.0, acetone).

Catalyst 58a



Synthesized from (*R*)-BINAM (300 mg, 1.05 mmol) and isolated as a white solid (692 mg, 1.00 mmol, 100%), m.p. = 116-120°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.50 (s, 4H), 7.04-7.03 (m, 2H), 7.30-7.22 (m, 4H), 7.55-7.48 (m, 2H), 7.74 (s, 2H), 7.88 (d, *J* = 9Hz, 2H), 8.00 (t, J = 9 Hz, 4H), 8.57 (br. s, 2H); ^{13}C-NMR ($CDCl_3$, 300 MHz): δ =179.8, 137.5, 135.2, 134.9, 132.12, 132.11, 128.9, 128.5, 128.2, 127.2, 127.0, 126.6, 126.3, 125.1, 123.6; IR (neat) 3434, 1644 cm^{-1}; MS (FAB$^+$): *m/z* (%): 693 [*M*+H]$^+$ (19, 3*^{35}Cl, 1*^{37}Cl), 691 [*M*+H]$^+$ (8, 4*^{35}Cl), 530 (11), 154 (100), 136 (60); [a]$^{25}_D$ = +106.8 (c = 1.0, dichloromethane).

Catalyst 59a, compound **59b**.

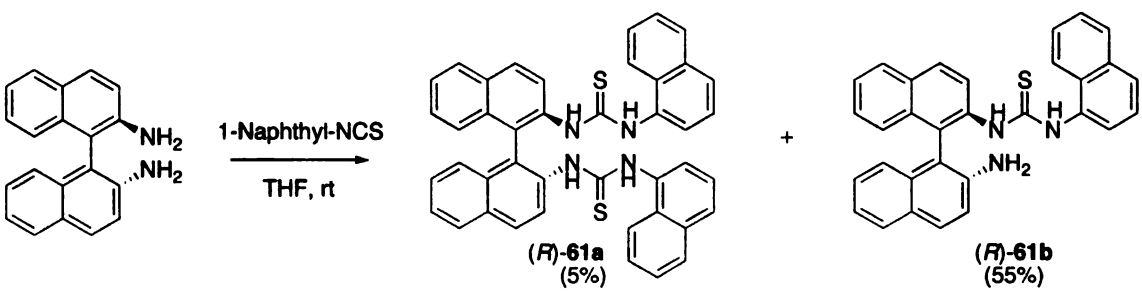


Catalyst **59a.** Synthesized from (*R*)-BINAM (300 mg, 1.05 mmol) and isolated as a white solid (104 mg, 0.17 mmol, 17%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 3.77 (s, 6H), 6.18 (d, 6.9 Hz, 4H), 6.47 (d, 6.9 Hz, 8H), 7.27-7.56 (m, 8H), 8.02-8.15 (m, 4H) ppm; ^{13}C-NMR ($CDCl_3$, 300 MHz): δ = 55.5, 114.9, 125.2, 126.4, 127.3, 127.6, 127.9, 128.1, 128.2,

132.3, 135.9, 158.9, 180.7 ppm; 3 C's not located. MS (FAB$^+$): *m/z*: 615 [*M*+H]$^+$, 492, 307, 154; m.p. = 124-125°C; IR (neat) ν = 3163, 2953, 1508, 1244, 860 cm^{-1}; $[a]^{25}_D$ = +15.3 (c = 1.0, acetone).

Compound **59b.** Synthesized from (*R*)-BINAM (300 mg, 1.05 mmol) and isolated as a white solid (224 mg, 0.50 mmol, 50%); m.p. = 114-116°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 3.68 (s, 3H), 6.45-6.38 (m, 4H), 6.81 (d, J = 8.4 Hz, 1H), 7.15-7.09 (m, 1H), 7.29-7.22 (m, 3H), 7.37 (br. s, 1H), 7.50-7.45 (m, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 8.15 (br. s, 1H), 8.49 (d, *J* = 8.7 Hz, 1H) ppm; 2 exchangeable H's do not show up; ^{13}C-NMR ($CDCl_3$, 300 MHz): δ = 55.6, 111.6, 115.5, 123.3, 125.6, 125.9, 126.3, 127.0, 127.1, 127.6, 127.8, 128.3, 128.43, 128.47, 128.5, 130.0, 132.6, 132.7, 133.7, 133.8, 135.8, 143.2, 158.7, 179.9, 122.7, 118.7 ppm; IR (neat) 3350, 3184, 3055, 2961, 2837, 1620, 1531 cm^{-1}; MS (FAB$^+$): *m/z* (%): 450 [*M*+H]$^+$ (98), 416 (20), 284, (100), 154 (70), 136 (50); $[a]^{25}_D$ = +66.2 (c = 1.0, dichloromethane).

Compounds **61a, 61b.**

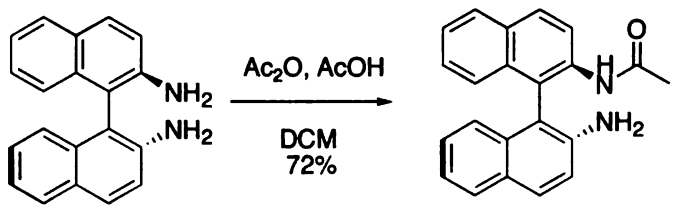


Compound **61a.** Synthesized from (*R*)-BINAM (300 mg, 1.05 mmol) and isolated as a white solid (32 mg, 0.05 mmol, 5%), not pure enough to characterize completely. ^{1}H-

NMR ($CDCl_3$, 300 MHz): δ = 5.91 (d, *J* = 7.2 MHz, 2H), 6.85 (t, *J* = 8.1 MHz, 2H), 7.59-7.14 (m, 16 H), 7.73 (dd, *J* = 8.7, 17.4 MHz, 4H), 7.88 (t, *J* = 8.4 MHz, 4 H); 2 exchangeable H's do not show up. R_f = 0.17 (30% acetone in hexanes); MS (FAB^+): *m/z* (%): 655 $[M+H]^+$ (40), 512 (37), 436 (20), 391 (18).

Compound **61b.** Synthesized from (*R*)-BINAM (300 mg, 1.05 mmol) and isolated as a white solid (259 mg, 0.55 mmol, 55%); m.p. = 126-128°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 3.1 (br. s, 2H), 6.42 (d, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 3H), 7.01 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 3H), 7.56-7.43 (m, 3H), 7.63 (d, *J* = 6.0 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 8.1Hz, 1H), 7.81 (d, *J* = 8.1Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = Hz, 1H), 8.53 (d, *J* = 9 Hz, 1H), 8.63 (br. s, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 300 MHz): δ = 110.9, 117.8, 122.0, 122.3, 122.7, 124.3, 125.00, 125.05, 125.5, 125.8, 126.5, 126.6, 126.9, 127.1, 127.6, 127.9, 128.03, 128.05, 128.4, 129.4, 129.5, 130.8, 132.1, 132.2, 133.0, 134.1, 135.3, 142.3, 179.9 ppm; 2 C's not located. MS (FAB^+): *m/z* (%): 470 (60) $[M+H]^+$, 307 (20), 284 (40); IR (neat) 3350. 2959, 1620, 1531 cm^{-1}; $[a]^{25}_D$ = +4.7 (c = 1.0, dichloromethane).

(*R*)-*N*-(1-(2-Aminonaphthalen-1-yl)naphthalen-2-yl)acetamide 63.

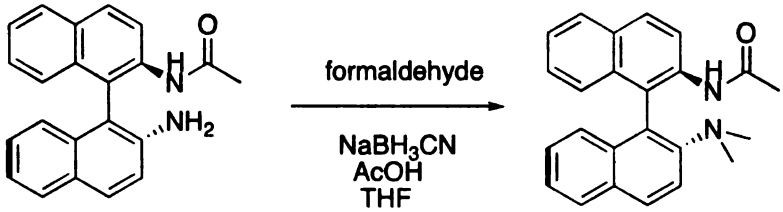


(*R*)-51 (*R*)-63

To a solution of (*R*)-(+)-1,1'-Binaphthyl-2,2'-diamine (284 mg, 1.0 mmol) and AcOH (0.6 mL, 10 mmol) in 10 mL of dried CH_2Cl_2 was added acetic anhydride (104 μL,

1.0 mmol) at 0 °C under N_2. The resulting solution was stirred overnight at room temperature, then 2*N* NaOH aqueous solution was added until pH ≈ 7. The reaction mixture was extracted by CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 2/1) to afford a colorless oil in 77% yield (0.25 g, 0.77 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.85 (s, 3H), 6.91-7.42 (m, 8H), 7.81-8.03 (m, 4H), 8.58 (d, *J* = 9.0 Hz, 2H). The data agreed with the reported literature[40b].

(*R*)-*N*-(1-(2-(Dimethylamino)naphthalen-1-yl)naphthalen-2-yl)acetamide 64

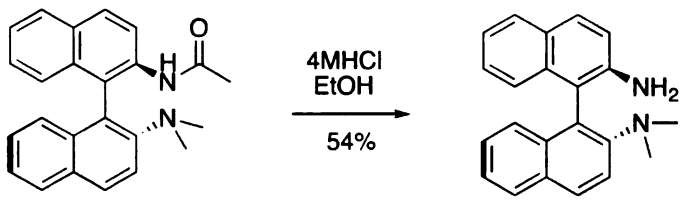


(*R*)-**63** (*R*)-**64**

N-(1-(2-Aminonaphthalen-1-yl)naphthalen-2-yl)acetamide **63** (0.25 g, 0.77 mmol) and aqueous formaldehyde (37%, 0.75mL, 9.0 mmol) were combined in 10 mL of THF and stirred for 15 min. $NaBH_3CN$ (200 mg, 5.3 mmol) was added, followed 15 min later by AcOH (1.0 mL). The resulting solution was stirred for 4 h at room temperature, then 1*N* NaOH aqueous solution was added until pH ≈ 7. The reaction mixture was extracted by CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with saturated brine and dried over MgSO4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 1/5) to afford a brown powder in quantitative yield (272 mg, 0.77 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz):

δ = 1.88 (s, 3H), 2.58 (s, 6H), 6.95 (d, *J* = 8.7 Hz, 1H), 7.12-7.55 (m, 6H), 7.84-7.80 (m, 4H), 8.49 (d, *J* = 9.0 Hz, 1H). 1 exchangeable H does not show up. The data agreed with the reported literature[40b].

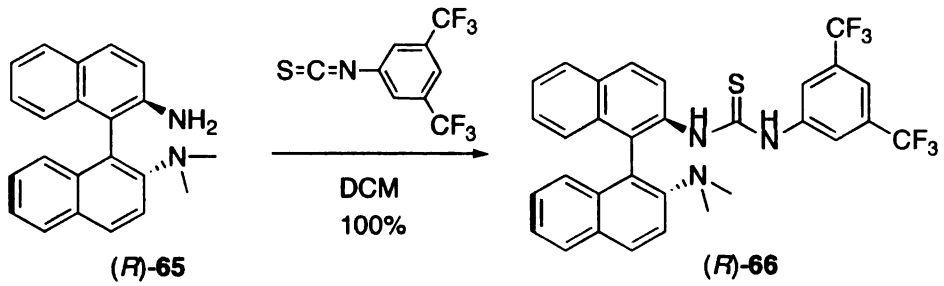
(*R*)-1-(2-(Dimethylamino)naphthalen-1-yl)naphthalen-2-amine 65



(*R*)-**64** (*R*)-**65**

To a solution of *N*-(1-(2-(dimethylamino)naphthalen-1-yl)naphthalen-2-yl)acetamide **64** (0.18 g, 0.51 mmol) in 15 mL of EtOH was added 4*M* HCl (6 mL). The resulting solution was stirred for overnight at room temperature, then 1*N* NaOH aqueous solution was added until pH ≈ 7. The reaction mixture was extracted by CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with saturated brine and dried over MgSO4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 1/10) to afford a colorless oil in 93% yield (148 mg, 0.47 mmol). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.59 (s, 2Me), 7.0-7.29 (m, 7H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.74-7.91 (m, 4H).

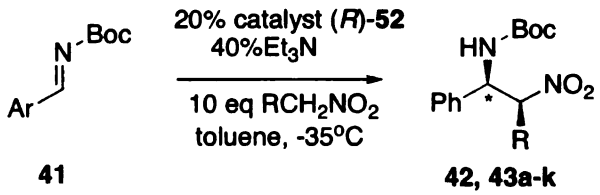
(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-(2-(dimethylamino)naphthalen-1-yl)naphthalen-2-yl)thiourea 66



(*R*)-65 (*R*)-66

To a solution of 1-(2-(dimethylamino)naphthalen-1-yl)naphthalen-2-amine **65** (36 mg, 0.12 mmol) in 2 mL of dried CH_2Cl_2 was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (22 mg, 0.132 mmol) at 0 °C under N_2. The resulting solution was stirred for overnight at room temperature. The reaction was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (ethylacetate/hexane = 1/10) to afford a slight yellow solid in 91% yield (64 mg, 0.11 mmol); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 6H), 6.90 (d, 1H, J = 7.5 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.26 (m, 2H), 7.36 (s, 2H), 7.41 (s, 1H), 7.56-7.50 (m, 4H), 7.71 (d, 1H, J = 8.5 Hz), 7.82 (d, 1H, J = 8.0 Hz), 7.98 (d, 2H, J = 9.0 Hz), 8.06 (d, 1H, J = 8.5 Hz), 8.37 (s, 1H); MS (FAB$^+$): *m/z* (%): 355 (100), 252 (30), 157 (37), 140 (47), 123 (37), 73 (60). The data matched the reported literature[40b].

General procedure for the asymmetric aza-Henry reaction (Table 20):

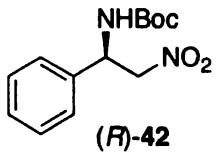


41 **42, 43a-k**

A flame-dried round bottom flask was loaded with 0.2 equiv. of catalyst **52** (0.2 mmoles, 160 mg) and 1 equiv of imine **41a-k** (1 mmol). The compounds were dissolved in 4 ml of toluene. $MeNO_2$ was added (10 equiv., 0.52 mL) at –35°C and after 5 minutes Et_3N was added (0.4 equiv, 56 μL). The mixture was stirred at –35°C for 17-36 hours and then the volatiles were evaporated. The crude mixture was purified by column chromatography on silica gel (always 20% acetone in hexanes) to afford products **42, 43a-k**.

For all the optimization studies of the aza-Henry reaction detailed in Chapter 4, the experimental procedures are the same as for the optimized reaction (described before), with slight modifications that are clarified in each Table. Whenever a % conversion is mentioned, that means the product was not purified, and the conversion was calculated from the integration of product peaks versus the imine C(=N)H proton, given that the only species observed in the crude ^{1}H-NMR was the catalyst, the desired product and imine, whenever some of it remained unreacted.

tert-Butyl (R)-2-nitro-1-phenylethylcarbamate 42

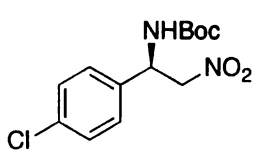


(*R*)-42

According to the typical procedure, imine **41a** (1 mmol, 205 mg) and $MeNO_2$ were stirred for 36 h and converted to the product **42** (146 mg, 0.55 mmol, 55%) as a white solid. HPLC analysis (Chiralpak OJ-H, hexane/2-PrOH 95/5, flow rate = 1.0 mL/min, l = 210 nm): t_r (minor) = 32.3, t_r (major) = 36.8 min; $[a]^{25}_D$ = -18.0 (86% ee, c = 1.0, $CHCl_3$); m.p. 107–108 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 ppm (s, 9H); 4.64–4.81 (m, 2 H), 4.80 (br s, 1H), 5.34 (br s, 1 H), 7.37-7.23 (m, 5 H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.3, 52.9, 78.9, 80.7, 126.4, 128.7, 129.2, 137.0, 154.9 ppm.

Palomo's group (ref. 27) reported the same absolute configuration (*R*) for **42** with a negative optical rotation, while Takemoto's group (ref. 37) assigned the same absolute configuration (*R*) to a positive optical rotation. While it is not clear which assignment is right, we assigned the absolute stereochemistry of **42** following Palomo's data (which agrees with the majority of the literature reports), and subsequently assigned the stereochemistry of the rest products (including **43k** and **43l**) using **42** as a reference.

1-(p-Chlorophenyl)-2-nitroethyl carbamic acid t-butyl ester 43a

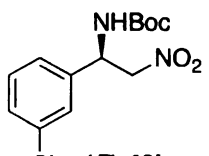


(*R*)-**43a**

Following the general procedure 239 mg imine were used (1 mmol) and compound **43a** was obtained as a white solid in 62% yield (0.62 mmol, 182 mg). The ee of the product was determined by HPLC using a Daicel Chiralpak OJ-H column (n-hexane/i-PrOH = 97/3, flow rate = 1 mL/min, t_r (minor)=68.6 min; t_r (major)=74.1 min, $[a]^{25}_D$ = -44.0 (c = 1.0, $CHCl_3$); 85% ee; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 4.72–4.90

(m, 1H), 4.73 (dd, J = 5.0, 12.6 Hz, 1H), 5.40 (br s, 2H), 7.28–7.30 (m, 2H), 7.34–7.41 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.2, 52.3, 78.7, 80.9, 127.8, 129.4, 134.6, 135.6, 154.8. The data agreed with the previously reported literature[27].

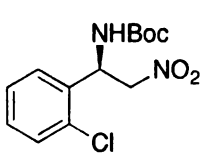
1-(m-Chlorophenyl)-2-nitroethyl carbamic acid t-butyl ester 43b.



(*R*)-**43b**

Following the general procedure, 239 mg imine were used (1 mmol) and compound **43b** was obtained as a white solid in 53% yield (161 mg, 0.53 mmol). The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (n-hexane/i-PrOH = 97/3, flow rate = 1 mL/min, t_r (minor) = 23.2 min; t_r (major) = 33.6 min, $[a]^{25}_D$ = -24.4 (c=1.0, acetone); 91% ee; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9H), 4.80–4.90 (br s, 1H), 4.72 (m, 1H), 5.42 (br s, 1H), 5.70 (br s, 1H), 7.21–7.35 (m, 4H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.2, 52.2, 78.6, 80.9, 124.6, 126.7, 128.8, 130.4, 135.0, 139.2, 154.9. MS (FAB$^+$): m/z (%): 303 $[M+H]^+$ (3, ^{37}Cl), 301 $[M+H]^+$ (10, ^{35}Cl), 245 (90), 184 (90) 154 (82); IR (neat): ν = 3370, 2980, 1686, 1556, 1368, 1165 cm^{-1}; m.p. 98-100°C.

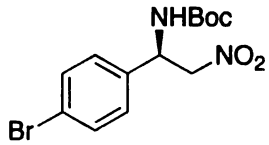
1-(o-Chlorophenyl)-2-nitroethyl carbamic acid t-butyl ester 43c.



(*R*)-**43c**

Following the general procedure, 239 mg imine were used (1 mmol) and compound **7d** was obtained as a white solid in 61% yield (179 mg, 0.61 mmol). The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (n-hexane/i-PrOH = 99/1, flow rate = 1 mL/min, t_r (major) = 69.1 min; t_r (minor) = 92.3 min, $[a]^{25}_D$ = +19.0 (c = 1.0, acetone); 74% ee; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 4.84 (m, 2H), 5.78 (m, 2H), 7.31-7.46 (m, 4H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.2, 50.6, 77.5, 80.8, 127.5, 128.0, 129.9, 130.3, 132.6, 134.4, 154.6. MS (FAB$^+$): *m/z* (%): 303 [*M*+H]$^+$ (3, ^{37}Cl), 301 [*M*+H]$^+$ (10, ^{35}Cl), 245 (90), 184 (90) 154 (82); IR (neat): 3355, 2982, 2935, 1712, 1685, 1555, 1367, 1253 cm^{-1}; m.p. 106-108°C.

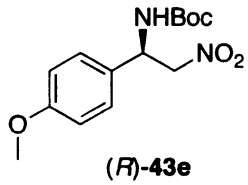
1-(p-Bromophenyl)-2-nitroethyl carbamic acid t-butyl ester 43d.



(*R*)-**43d**

Following the general procedure, compound **43d** was obtained as a white solid in 50% yield (172 mg). The ee of the product was determined by HPLC using a Daicel Chiralpak OJ-H column (n-hexane/i-PrOH = 95/5, flow rate = 1 mL/min, t_r (minor) = 51.1 min; t_r (major) = 54.9 min, 78% ee; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 4.75 (m, 1H), 4.76–4.90 (br s, 1H), 5.40 (br s, 2H), 7.23 (d, *J* = 6.9 Hz, 2H), 7.53 (d, *J* = 6.9 Hz, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.2, 52.2, 78.6, 80.9, 122.7, 128.1, 132.3, 136.1, 154.7; MS (FAB$^+$): *m/z* (%): 347 [*M*+H]$^+$ (10, ^{81}Br), 345 [*M*+H]$^+$ (10, ^{79}Br), 289 (60), 228 (65), 154 (100); IR (neat): 3338, 2981, 2935, 2363, 1687, 1527, 1166 cm^{-1}; m.p. = 140-142.

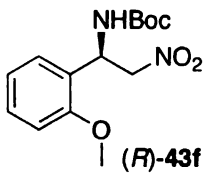
tert-Butyl (R)-2-nitro-1-(p-methoxyphenyl)ethylcarbamate 43e.



(*R*)-**43e**

According to the typical procedure, 235 mg imine were used (1 mmol) and the product **43e** was obtained in 49% (145 mg, 0.49 mmol) as a white solid. HPLC analysis (Chiralpak OJ-H, hexane/EtOH 95/5, flow rate=1.0 mL/min, l=210 nm): t_r (minor) = 65.8, t_r (major) = 72.0 min; $[a]^{25}_D$ = -31.0 (89% ee, c = 1.00, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 ppm (s, 9H), 3.82 (s, 3 H), 4.69 (dd, *J* = 12.0, 5.3 Hz, 1 H), 5.36 (m, 1H), 4.83 (s, 1H), 5.42 (s, 1 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2H) ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.3, 52.4, 55.3, 78.9, 80.6, 114.5, 127.7, 129.0, 154.9, 159.8 ppm. The data agreed with the previously reported literature[27].

tert-Butyl (R)-2-nitro-1-(o-methoxyphenyl)ethylcarbamate 43f.

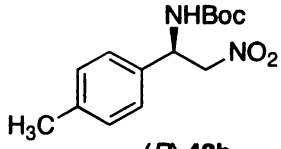


(*R*)-**43f**

According to the typical procedure, 235 mg imine were used (1 mmol) and the product **43f** was obtained in 40% yield (116 mg, 0.4 mmol) as a white solid. HPLC analysis (Chiralpak OJ-H, hexane/2-PrOH= 90/10, flow rate=1.0 mL/min,): t_r (major)= 17.2 min, t_r (minor)= 20.8.0 min; 65% ee; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 3.94 (s, 3 H), 4.72-4.78 (m, 1H), 4.84 (dd, *J* = 7.5 Hz, *J* = 7.2 Hz, 1H), 5.63 (br s, 1 H), 5.76 (br s, 1H), 6.95-7.00 (m, 2H), 7.28-7.38 (m, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ =

28.3, 51.0, 55.5, 77.9, 80.3, 111.0, 121.19, 129.1, 130.9, 154.8, 156.8 ppm; MS (FAB^+): *m/z* (%): 297 $[M+H]^+$ (5), 252 (100), 140 (100); IR (neat): ν = 3433, 2358, 2105, 1646 cm^{-1}; m.p. 138-140°C.

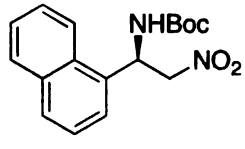
tert-Butyl (R)-2-nitro-1-(4-methylphenyl)ethylcarbamate 43h.



(*R*)-**43h**

According to the typical procedure, 219 mg imine were used (1 mmol) the product **43h** was obtained in 45% yield (134 mg) as a white solid. HPLC analysis (Chiralpak AD, hexane/2-PrOH 98/2, flow rate = 1.0 mL/min, l = 210 nm): t_r (minor)=50.5, t_r (minor)= 59.0 min; $[a]^{25}_D$ = -26.0 (86% ee, c = 1.00, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ =1.48 (s, 9H), 2.37 (s, 3H), 4.70 (dd, *J* = 12.4, 5.7 Hz, 1H), 4.83 (s, 1H),5.40 (br s, 1 H), 5.55 (m, 1H), 7.22 (s, 4 H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 21.1, 28.3, 52.7, 79.0, 80.5, 126.3, 129.8, 133.1, 138.5, 154.9 ppm. The data agreed with the previously reported literature[24].

tert-Butyl (R)-2-nitro-1-(1-naphthyl)ethylcarbamate 43i.

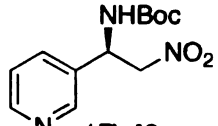


(*R*)-**43i**

According to the typical procedure 255 mg imine were used (1 mmol) and the product **43i** was obtained in 65% yield (165 mg, 0.65 mmol) as a white solid. HPLC analysis (Chiralpak OJ-H, hexane/2-PrOH 95/5, flow rate = 1.0 mL/min, l = 210 nm): t_r (minor) = 35.9, t_r (major) = 50.7 min; $[a]^{25}_D$ = -8.1 (85% ee, c = 0.5, $CHCl_3$); ^{1}H-NMR

(300 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 4.88 (br s, 2 H), 5.25 (m, 1H), 6.27 (m, 1H), 7.45 (m, 2H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.84 (dd, *J* = 5.7, 3.5 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1 H), 8.12 (d, *J* = 8.2 Hz, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.3, 49.3, 78.3, 80.7, 122.2, 123.3, 125.2, 126.3, 127.3, 129.3, 129.5, 130.3, 132.6, 134.1, 154.7 ppm; The rest of the data agreed with the previously reported literature[27].

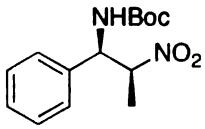
tert-Butyl (R)-2-nitro-1-(3-pyridyl)ethylcarbamate 43g.



(*R*)-**43g**

According to the typical procedure, 206 mg imine were used (1 mmol) and the product **43g** was obtained in 63% yield (168 mg, 0.63 mmol) as a white solid. HPLC analysis (Chiralpak AD, hexane/2-PrOH 90/10, flow rate = 1.0 mL/min, l = 210 nm): t_r (major) = 16.7, t_r (minor) = 17.9 min; $[a]^{25}_D$ = -33.5 (81% ee, c = 1.00, acetone); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 4.76 (d, J=8.9 Hz, 1H), 4.90 (s, 1 H), 5.40 (s, 2H), 7.32 (dd, *J* = 7.5, 4.7 Hz, 1 H), 7.65 (d, *J* = 7.9 Hz, 2H), 8.62 (d, *J* = 21.4 Hz, 2H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 28.2, 50.7, 78.3, 81.0, 123.8, 133.1, 134.2, 148.1, 149.9, 154.8 ppm; The data agreed with the previously reported literature[37] except for the sign of the optical rotation (see discussion on data for **42**).

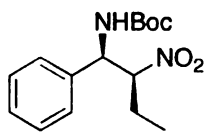
tert-Butyl (1R,2S)-2-nitro-1-phenylpropylcarbamate 43j.



(1*R*, 2*S*)-**43j**

According to the typical procedure, 205 mg imine were used (1 mmol) and the product **43j** was obtained in 59% yield (165 mg, 0.59 mmol) as a white solid and a 77/23 mixture of diastereomers by ^{1}H-NMR. The major diastereomer was determined to have 70% ee by chiral HPLC analysis and identification of enantiomeric pairs by UV absorption spectrum (Chiralpak AD, hexane/iPrOH 92/8 0.8 mL/min, l = 210 nm): *Syn* isomer: t_r (minor) = 13.8 min, t_r (major) 15.9 min; *anti* isomer: t_r (major) = 17.8 min, t_r (minor) = 21.8 min;); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9H), 1.50 (d, *J* = 6.7 Hz, 3H), 4.91 (br s, 1 H), 5.18 (dd, *J* = 8.8, 5.8 Hz, 1 H), 5.32 (br s, 1H), 7.18–7.24 (m, 2H), 7.37–7.34 (m, 3 H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 154.9, 136.7, 129.0, 128.7, 128.5, 126.8, 126.4, 85.8, 80.0, 57.7, 28.3, 15.2 ppm. The data agreed with the previously reported literature[37].

tert-Butyl (1R,2S)-2-nitro-1-phenylbutylcarbamate 43k.

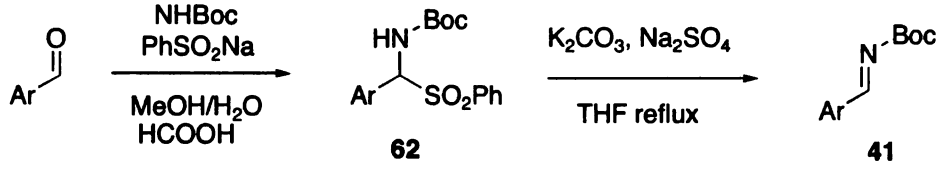


(1*R*, 2*S*)-**43k**

According to the typical procedure, 205 mg imine were used (1 mmol) the product **43l** was obtained as white solid in 63% yield (185 mg, 0.62 mmol) and a 80/20 mixture of diastereomers by HPLC analysis (enantiomeric pairs identified by comparison with a

racemic sample). The ee of major diastereomer **7k** was determined to be 80% by chiral HPLC analysis (Chiralpak OJ-H, hexane/2-PrOH 97/3, 0.8 mL/min, l = 210 nm). *Syn* isomer: t_r (major) = 28.1 min, t_r (minor) = 50.1 min; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.96–1.03 (t, *J* = 3.5 Hz, 3H), 1.43 (s, 9 H), 1.84–1.92 (m, 2H), 5.10–5.14 (m, 1 H), 4.74 (br s, 1H), 5.14–5.20 (br s, 1H), 7.22–7.26 (m, 2 H), 7.30–7.40 (m, 3H); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 10.4, 24.8, 28.2, 56.8, 80.0, 93.0, 126.9, 128.7, 129.0, 136.7, 154.9 ppm. The data agreed with the previously reported literature[37].

General procedure for the synthesis of aminosulfones **62** and imines **41**.

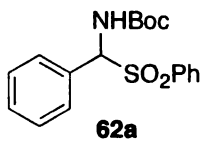


The appropriate aldehyde (1.2 eq, 20.48 mmol) was added to a mixture of 1 eq (2g, 17.07 mmol) of NHBoc and 2.0 eq. (5.6 g, 34.1 mmol) of $PhSO_2Na$ in 50 ml of water and MeOH (2:1 v/v) and stirred at rt for 3 days, after which time the resultant white suspension was filtered, washed with water and diethyl ether and then triturated with diethyl ether overnight. The product **62** was dried under vacuum.

Subsequently, 1 eq. of **62** (2 mmoles) was refluxed in THF for an overnight period in the presence of 1.60 g (12 mmol) K_2CO_3 and ~2g Na_2SO_4 (drying agent). The resulting mixture was filtered through a clean white frit funnel and the volatiles were evaporated. The resulting imine was transferred carefully under nitrogen to the pump where it was dried under high vacuum. Cautious handling of the procedure is required for preventing decomposition and hydrolysis of the imines, which were used in the aza-Henry reaction

without further purification. Imines **41a**, **e-f** and **h-j** are known in the literature and their preparation and data has been reported before.[28]

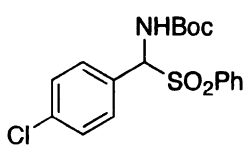
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)benzylamine 62a.**



62a

Synthesized using (2g, 17.07 mmol) of NHBoc to afford 5.89 g (17 mmol, 100%) of **62a** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.24 (9H, s), 5.72 (1H, br d, *J* = 10.3 Hz), 7.49-7.38 (5H, m), 5.90 (1H, br d, *J* = 11.0 Hz), 7.52 (2H, m), 7.62-7.60 (1H, m), 7.89 (2H, d, *J* = 7.3 Hz).

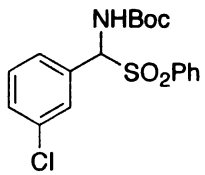
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-4-chlorobenzylamine 62b.**



62b

Synthesized using 2g (17.07 mmol) of NHBoc to afford 1.48 g (3.91 mmol, 23%) of **62b** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (9H, s), 5.63 (1H, br d, *J* = 10.1 Hz), 5.86 (1H, br d, *J* = 10.1 Hz), 7.36 (4H, s), 7.52 (2H, t, *J* = 7.8 Hz), 7.63 (1H, t, *J* = 7.5 Hz), 7.88 (2H, d, *J* = 8.4 Hz).

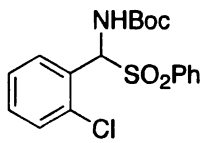
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-3-chlorobenzylamine 62c.**



62c

Synthesized using 2g (17.07 mmol) of NHBoc to afford 4.98 g (13.9 mmol, 77%) of **62c** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ =1.23 (9H, s), 5.69 (1H, br d, J = 10.5 Hz), 5.87 (1H, br d, J = 10.5 Hz),7.32-7.41 (4H, m), 7.54 (2H, t, J = 7.5 Hz), 7.62 (1H, t, J = 7.2 Hz), 7.90 (2H, d, J = 7.2 Hz).

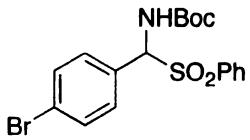
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-2-chlorobenzylamine 62d.**



62d

Synthesized using 2g (17.07 mmol) of NHBoc to afford 4.66 g (12.24 mmol, 77%) of **62d** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.32 (9H, s), 5.85 (1H, br d, J = 10.2 Hz), 6.65 (1H, br d, J = 10.2 Hz), 7.37-7.48 (3H, m), 7.55-7.58 (3H, m), 7.69 (1H, t, J = 6.9 Hz), 7.97 (2H, d, J = 7.5 Hz)

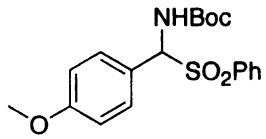
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-4-bromobenzylamine 62e.**



62e

Synthesized using 2g (17.07 mmol) of NHBoc to afford 2.24 g (5.27 mmol, 31%) of **62e** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (9H, s), 5.70 (1H, br d, *J* = 10.7 Hz), 5.89 (1H, br d, *J* = 10.7 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.58-7.51 (4H, m), 7.72-7.62 (1H, m), 7.91 (2H, d, *J* = 7.6 Hz).

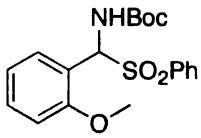
***N*-(*tert*-butoxycarbonyl)-α-(4-methylphenylsulfonyl)-4-methoxybenzylamine 62f.**



62f

Synthesized using 2g (17.07 mmol) of NHBoc to afford 5.83 g (14.28 mmol, 84%) of **62f** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (9H, s), 2.41 (3H, s), 3.81 (3H, s), 5.79 (1H, br d, *J* = 10.6 Hz), 5.85 (1H, br d, *J* = 11.0 Hz), 6.92 (2H, d, *J* = 8.8 Hz), 7.31 (2H, d, *J* = 8.1 Hz), 7.36 (2H, d, *J* = 8.8 Hz), 7.78 (2H, d, *J* = 7.7 Hz).

***N*-(*tert*-butoxycarbonyl)-α-(4-methylphenylsulfonyl)-2-methoxybenzylamine 62g.**

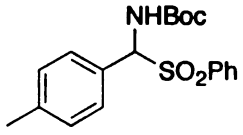


62g

Synthesized using 2g (17.07 mmol) of NHBoc to afford 5.76 g (15.3 mmol, 90%) of **62g** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.28 (9H, s), 2.37 (3H, s), 3.70 (3H, s), 6.16-6.27 (2H, m), 6.84 (1H, d, *J* = 8.1 Hz), 6.96 (1H, t, *J* = 7.2 Hz), 7.22-7.35 (4H, m), 7.68 (1H, d, *J* = 8.1 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 21.6, 28.1, 55.9, 71.1, 80.8, 111.5, 118.9, 120.9, 129.4, 129.5, 130.3, 131.1, 134.6, 144.6, 154.5, 157.9; MS

(FAB$^+$): *m/z* (%): 307 (10), 236 (100), 180 (100), 136 (90); IR ($CHCl_3$): ν = 3344, 2978, 2358, 1704, 1493, 1141; mp 160-162.

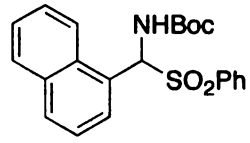
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-4-methylbenzylamine 62i.**



62i

Synthesized using 2g (17.07 mmol) of NHBoc to afford 4.54 g (12.58 mmol, 74%) of **62i** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.28 (9H, s), 2.40 (3H, s), 5.77 (1H, d, *J* = 10.6 Hz), 5.90 (1H, br d, *J* = 10.6 Hz), 7.27 (2H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 7.7 Hz), 7.53 (2H, t, *J* = 7.6 Hz), 7.64 (1H, t, *J* = 7.0 Hz), 7.93 (2H, d, *J* = Hz).

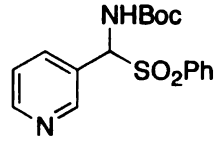
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-*C*-naphthalen-1-yl-methylamine 62k.**



62k

Synthesized using 2g (17.07 mmol) of NHBoc to afford 3.98 g (10.03 mmol, 59%) of **62k** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.27 (9H, s), 5.98 (1H, br d, *J* = 10.6 Hz), 6.88 (1H, br d, *J* = 10.6 Hz), 7.66-7.48 (6H, m), 7.79 (1H, d, *J* = 7.0 Hz), 7.88 (1H, d, *J* = 8.1 Hz), 7.94 (1H, d, *J* = 8.1 Hz,), 7.99 (2H, d, *J* = 7.7 Hz), 8.14 (1H, d, *J* = 8.4 Hz).

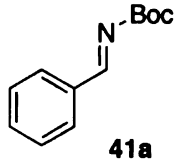
***N*-(*tert*-butoxycarbonyl)-α-(phenylsulfonyl)-*C*-pyridin-3-yl-methylamine 62h.**



62h

Synthesized using 2g (17.07 mmol) of NHBoc to afford 4.02 g (11.56 mmol, 68%) of **62h** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (9H, s), 5.97 (2H, br), 7.39-7.35 (1H, m), 7.57 (2H, t, *J* = 7.5 Hz), 7.68 (1H, t, *J* = 7.0 Hz), 7.86-7.83 (1H, m), 7.92 (2H, d, *J* = 8.3 Hz), 8.70-8.63 (2H, m).

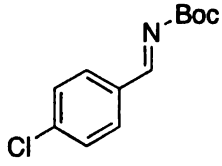
Benzaldehyde *N*-(*tert*-butoxycarbonyl)imine 41a.



41a

Synthesized from 5.89 g (17 mmol) of **62a** to afford 4.40 g (16.66 mmol, 98%) of **41a** as a colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.59 (9H, s), 7.49-7.43 (2H, m), 7.57-7.54 (1H, m), 7.93-7.90 (2H, m), 8.88 (1H, s).

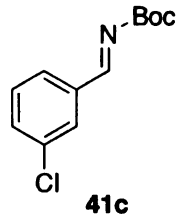
***p*-Chlorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine 41b.**



42b

Synthesized from 1.48 g (3.91 mmol) of **62b** to afford 0.91 g (3.83 mmol, 98%) of **41a** as a colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.57 (9H, s), 7.42 (2H, d, *J* = 8.4 Hz), 7.85 (2H, d, *J* = 8.4 Hz), 8.81 (1H, s).

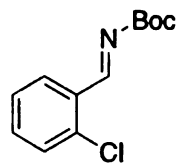
***m*-Chlorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine 41c.**



41c

Synthesized using 4.98 g (13.9 mmol) of **62c** to afford 3.32 g (13.76, 99%) **41c**. as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (9H, s) 7.39 (1H, t, *J* = 7.5 Hz), 7.48-7.52 (1 H, m), 7.73 (1H, dd, *J* = 1.2 Hz, *J* = 7.5 Hz), 8.77 (1H, s), 7.93 (1H, s).

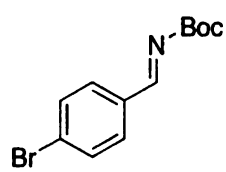
***o*-Chlorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine 41d.**



41d

Synthesized using 4.66 g (12.24 mmol) of **62d** to afford 2.86 g (11.99 mmol, 99%) **41d** as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.63 (9H, s), 7.37 (1H, t, *J* = 6.0 Hz), 7.47-7.50 (2H, m), 8.22 (1H, d, *J* =6.0 Hz), 9.31 (1H, s).

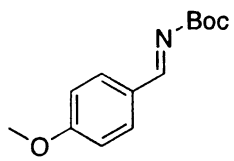
***p*-Bromobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine 41e.**



41e

Synthesized using 2.24 g (5.27 mmol) of **62e** to afford 0.95 g (3.37 mmol, 64%) **41e** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.57 (9H, s). 7.60 (2H, d, *J* = 8.4 Hz), 7.77 (2H, d, *J* = 8.4 Hz), 8.81 (1H, s).

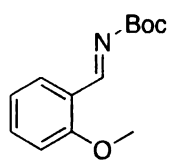
***p*-Methoxybenzaldehyde *N*-(*tert*-butoxycarbonyl)imine 41f.**



41f

Synthesized using 5.83 g (14.28 mmol) of **62f** to afford 2.58 g (10.99 mmol, 77%) **41f** as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (9H, s), 3.86 (3H, s), 6.96 (2H, d, *J* = 8.8 Hz), 7.88 (2H, d, *J* = 8.8 Hz), 8.88 (1H, s).

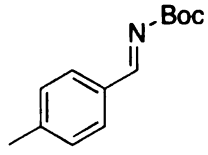
***o*-Methoxybenzaldehyde *N*-(*tert*-butoxycarbonyl)imine 41g.**



41g

Synthesized using 5.76 g (15.3 mmol) of **62g** to afford 3.41 g (14.53 mmol, 95%) **41g** as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (9H, s), 3.88 (3H, s), 6.90-7.00 (2H, m), 7.49 (1H, t, *J* = 9.0 Hz), 8.09 (1H, d, *J* = 7.8 Hz), 9.35 (1H, s); ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 27.9, 55.6, 81.9, 111.27, 120.77, 122.6, 128.3, 135.2, 160.9, 165.8, 163.2; MS (FAB$^+$): *m/z* (%): 236 $[M+H]^+$ (60), 180 (100), 136 (95); IR ($CHCl_3$): ν =2978, 1711, 1600, 1237, 1153.

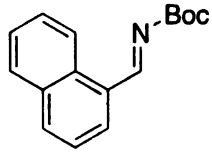
***p*-Tolualdehyde *N*-(*tert*-butoxycarbonyl)imine 41i.**



41i

Synthesized using 4.54 g (12.58 mmol) of **62i** to afford 2.67 g (12.20 mmol, 97%) **41i** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.58 (9H, s), 2.41 (3H, s), 7.26 (2H, d, *J* = 7.7 Hz), 7.81 (2H, d, *J* = 8.1 Hz), 8.87 (1H, s).

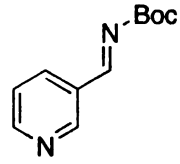
1-Naphthaldehyde *N*-(*tert*-butoxycarbonyl)imine 41k.



41k

Synthesized using 3.98 g (10.03 mmol) of **62k** to afford 2.55 g (10.00 mmol, 99%) **41k** as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61 (9H, s), 7.60-7.54 (2H, m), 7.68-7.63 (1H, m), 7.90 (1H, d, *J* = 7.7 Hz), 8.05 (1H, d, *J* = 8.4 Hz), 8.17 (1H, d, *J* = 7.0 Hz), 8.92 (1H, d, *J* = 8.4 Hz), 9.53 (1H, s).

3-pyridinecarboxaldehyde *N*-(*tert*-butoxycarbonyl)imine 41h.

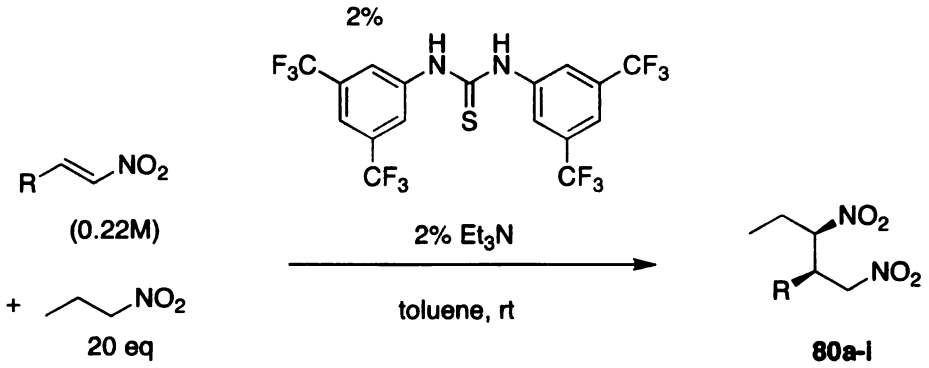


41h

Synthesized using 4.02 g (11.56 mmol) of **62h** to afford 2.32 g **41h** (11.3 mmol, 98%) as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.58 (9H, s), 7.40 (1H, dd, J = 4.8, 8.1 Hz), 8.25-8.28 (1H, dt, J = 1.8, 8.1 Hz), 8.76 (1H, dd, J = 1.83, 4.8 Hz), 8.87 (1H, s), 9.00 (1H, d, J = 2.2 Hz).

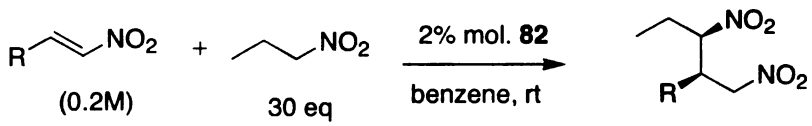
Experimental Procedures for Chapter 5

General procedure for the non-asymmetric addition of 1-nitropropane to nitrostyrene using catalyst 47 (Table 28).



A flame-dried round bottom flask was charged with 1 mmol of the appropriate nitrostyrene and 10 mg (0.02 mmol) of catalyst **47** and the solids were dissolved in 3 mL of toluene. 1-Nitropropane (1.6 ml, 20 mmol) was added followed by 3μL of Et_3N. The mixture was stirred at r.t. for the time indicated in the Table. The volatiles were evaporated and the crude product was purified with silica gel column chromatography to afford the racemate products **80a-i** as separated diastereomers. The syn/anti ratio was measured by the weight of the isolated products except in the case of **80a**, **80b** where it was determined by ^{1}H-NMR analysis.

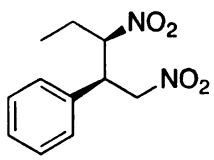
General procedure for the asymmetric addition of 1-nitropropane to nitrostyrene using catalyst (*R*)-82 (Table 39).



80a-i

A flame-dried round bottom flask was charged with 1 mmol of the appropriate nitrostyrene and 13.5 mg (0.02 mmol) of catalyst **82** and the solids were dissolved in 2.5 mL of benzene. 1-Nitropropane (2.5 mL, 30 mmol) was added and the mixture was stirred at r.t. for the time indicated in the Table 39. The volatiles were evaporated and the crude product was purified with silica gel column chromatography to afford the products **80a-i** as separated diastereomers. The syn/anti ratio was measured by the weight of the isolated products except in the case of **80a**, **80b**, **80c**, **80d** where it was determined by ^{1}H-NMR analysis.

2-Phenyl-1,3-dinitropentane 80a



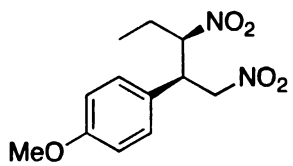
(2*R*, 3*R*)-**80a**

Prepared following the general procedures described above using 150 mg (1.00 mmol) nitrostyrene. Purified with silica gel column using 30% EtOAc/hexanes to afford 144 mg (60%, 0.60 mmol) of syn adduct as a clear oil and 47 mg (0.20 mmol, 20%) anti adduct from the asymmetric addition (Table 39). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ =1.00 (t, 3H, J = 7.1 Hz), 1.90-1.82 (m, 1H), 2.02-1.94 (m, 1H), 4.02 (q, 1H, J = 6.7 Hz), 4.78-4.71 (m, 2H), 4.86 (dd, 1H, J = 6.3, 13.9 Hz), 7.14-7.11 (m, 2H), 7.33-7.29 (m,

3H); ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.3, 24.4, 46.6, 76.4, 91.2, 127.9, 128.1, 129.3, 133.9 ppm; R_f = 0.30 (30% EtOAc/hexanes); HPLC analysis: Chiralpac OJ-H, hexane/2-PrOH 80/20, 1.5 mL/min, 95% ee, α^{25}_D = +7.2 (c=1.0, dichloromethane), t_r = 31.0 min (major), t_r = 42.0 min (minor). The data agreed with the reported literature[48].

The non-asymmetric addition (Table 28) afforded 178 mg (75%) of syn-**80a** adduct and 28 mg (0.12 mmol, 12%) anti adduct.

2-(4-Methoxyphenyl)-1,3-dinitropentane 80b

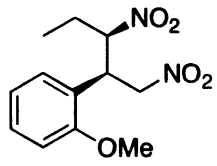


(2*R*, 3*R*)-**80b**

Prepared following the general procedures described above using 179 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 126 mg (47%, 0.47 mmol) of syn adduct as a clear yellow oil and 34 mg (13%, 0.13 mmol) anti adduct from the asymmetric addition (Table 39). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 0.99 (t, 3H, *J* = 7.1 Hz), 1.87-1.1.80 (m, 1H), 2.02-1.93 (m, 1H), 3.75 (s, 3H), 3.95 (q, 1H, *J* = 6.7 Hz), 4.72-4.71 (m, 2H), 4.83 (dd, 1H, *J* = 6.3, 13.9 Hz), 7.04 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 8.7 Hz, 2H); ^{13}C-NMR (300MHz), $CDCl_3$ δ =10.5, 24.6, 46.2, 55.5, 76.8, 91.5, 114.9, 125.8, 129.3, 160.2; R_f = 0.08 (20% EtOAc/hexanes); HPLC analysis: Chiralpac OD-H, hexane/2-PrOH 70/30, 0.5 mL/min, 94% ee, α^{25}_D = +22.0 (c=1.0, dichloromethane), t_r = 15.6 min (major), t_r = 31.1 min (minor). The data agreed with the reported literature[48].

The non-asymmetric addition (Table 28) afforded 197 mg (0.73 mmol, 73%) of syn-**80a** adduct and 24 mg (0.09 mmol, 9%) of the anti adduct.

2-(2-Methoxyphenyl)-1,3-dinitropentane 80c

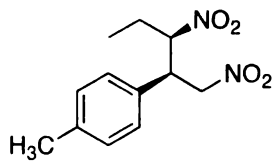


(2*R*, 3*R*)-**80c**

Prepared following the general procedures described above using 179 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 193 mg (72%, 0.72 mmol) of syn adduct as a clear oil and 58 mg (0.22 mmol, 22%) of the anti adduct from the asymmetric addition (Table 39). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 0.98 (t, 3H, *J* = 7.1 Hz), 1.93-1.82 (m, 1H), 2.03-1.94 (m, 1H), 3.85 (s, 3H), 4.24 (q, 1H, *J* = 7.5 Hz), 4.84 (dd, 2H, *J* = 5.1, 7.5 Hz), 5.00 (m, 1H), 6.88-6.86 (m, 2H), 7.04 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.28-7.25 (m, 1H). ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.6, 24.8, 43.9, 55.7, 75.6, 90.2, 111.6, 121.4, 122.4, 130.4, 130.5, 157.5 ppm; R_f = 0.20 (20% EtOAc/hexanes); HPLC analysis: Chiralpac OD-H, hexane/2-PrOH 80/20, 0.5 mL/min, 94% ee, α^{25}_D = +8.0 (c=1.0, dichloromethane), t_r = 11.9 min (major), t_r = 23.3 min (minor). The data agreed with the reported literature[48].

The non-asymmetric addition (Table 28) afforded 178 mg (0.66 mmol, 66%) of syn-**80c** adduct and 45 mg (0.17 mmol, 17%) of the anti adduct.

4-Methyl-1,3-dinitropentane 80d

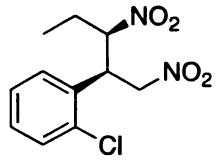


(2*R*, 3*R*)-**80d**

Prepared following the general procedure described above using 163 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 146 mg (58%, 0.58 mmol) of syn adduct as a clear oil and 35 mg (0.14 mmol, 14%) from the asymmetric addition (Table 39). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 0.98 (t, J = 7.2 Hz, 3H), 1.80-1.84 (m, 1H), 2.02-1.96 (m, 1H), 2.29 (s, 3H), 3.97 (q, J = 8.1 Hz, 1H), 4.75-4.68 (m, 2H), 4.80 (dd, J = 13.5, 6.3 Hz, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H); ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.3, 21.1, 24.4, 46.2, 76.5, 91.2, 127.8, 129.9, 130.8, 138.9 ppm; R_f = 0.17 (20% EtOAc/hexanes); MS (FAB$^-$): *m/z* (%): 251 [M-H]$^-$ (60), 239 (25), 204 (60); IR (neat) 3028, 2978, 2926, 2883, 1552, 1510, 1460, 1435, 1377, 1318, 1122 cm^{-1}; HPLC analysis: Chiralpac OD-H, hexane/2-PrOH 70/30, 0.5 mL/min, 94% ee, α^{25}_D = +11.0 (c=1.0, dichloromethane), t_r = 14.8 min (major), t_r = 45.7 min (minor).

The non-asymmetric addition (Table 28) afforded 142 mg (0.56 mmol, 56%) of syn-**80d** adduct and 40 mg (0.16 mmol, 16%) of the anti adduct.

2-(2-Chlorophenyl)-1,3-dinitropentane 80e



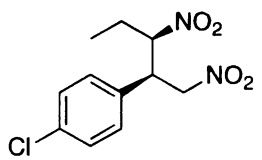
(2*R*, 3*R*)-**80e**

Prepared following the general procedure described above using 183 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 15% EtOAc/hexanes to afford 175 mg (0.62 mmol, 62%) of syn adduct as a clear oil and 60 mg (0.22 mmol, 22%) of the anti adduct from the asymmetric addition (Table 39). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 1.06 (t, *J* = 7.2 Hz, 3H), 2.08-2.04 (m, 2H), 4.70-4.67 (m, 1H), 4.90 (dd, *J* = 5.9, 8.3 Hz, 2H), 5.02-5.07 (m, 1H), 7.17-7.20 (m, 1H), 7.29-7.45 (m, 2H), 7.49-7.46 (m, 1H); ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.6, 24.3, 43.0, 75.4, 90.2, 127.9, 128.8, 130.4, 130.9, 132.0, 134.5; R_f = 0.22 (15% EtOAc/hexanes); HPLC analysis: Chiralpac OJ-H, hexane/2-PrOH 70/30, 0.5 mL/min, 92% ee, α^{25}_D = +6.7 (c=1.0, dichloromethane), t_r = 48.4 min (major), t_r = 74.9 min (minor). The data agreed with the reported literature[48] except for the sign of the optical rotation.

The non-asymmetric addition (Table 28) afforded 185 mg (68%) of syn-**80e** adduct and 32 mg (0.12 mmol, 12%) of the anti adduct.

Data for anti-**80e**: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 0.93 (t, *J* = 7.5 Hz, 3H), 1.61-1.69 (m, 1H), 1.95-2.00 (m, 1H), 4.55-4.62 (m, 1H), 4.69 (dd, *J* = 3.9 Hz, 13.5 Hz, 1H), 4.80-5.00 (m, 1H), 7.14-7.44 (m, 4H); ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.2, 25.4, 42.6, 75.0, 90.76, 103.9, 127.9, 130.2, 130.9, 131.9; one C not located; α^{25}_D = +8.0 (c=0.8, dichloromethane).

2-(4-Chlorophenyl)-1,3-dinitropentane 80f

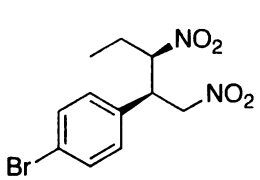


(2*R*, 3*R*)-**80f**

Prepared following the general procedure described above using 183 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 168 mg (0.62 mmol, 62%) of syn adduct as a clear oil and 35 mg (0.13 mmol, 13%) anti adduct from the asymmetric addition (Table 39). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 0.99 (t, J = 7.2 Hz, 3H), 1.80-1.90 (m, 1H), 1.96-1.99 (m, 1H), 4.00 (q, J = 7.8 Hz, 1H), 4.75-4.67 (m, 2H), 4.83 (dd, J = 13.5, 6.0 Hz, 1H), 7.08 (dd, J = 6.6, 2.4 Hz, 2H), 7.31 (dd, J = 6.6, 2.4 Hz, 2H). ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.2, 24.5, 45.9, 76.2, 90.9, 129.3, 129.5, 132.3, 135.1; MS (FAB$^-$): *m/z* (%): 273 [M-H]$^-$ (27, ^{37}Cl), 271 [M-H]$^-$ (80, ^{35}Cl) 224 (100); IR (neat) 3406 (H_2O), 2980, 1554, 1493, 1460, 1435, 1377, 1095, 1014 cm^{-1}; HPLC analysis: Chiralpac OD-H, hexane/2-PrOH 70/30, 0.5 mL/min, 92% ee, α^{25}_D = +10.9 (c=1.0, dichloromethane), t_r = 13.7 min (major), t_r = 24.8 min (minor). For the anti adduct α^{25}_D = +23.2 (c=1.0, dichloromethane).

The non-asymmetric addition (Table 28) afforded 157 mg (58%) of syn-**80a** adduct and 40 mg (0.15 mmol, 15%) of the anti adduct.

2-(4-Bromophenyl)-1,3-dinitropentane 80g.

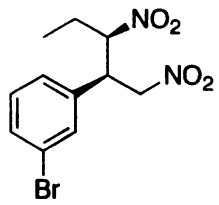


(2*R*, 3*R*)-**80g**

Prepared following the general procedure described above using 228 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 207 mg (0.65 mmol, 65%) of syn adduct as a clear oil and 31 mg (0.10 mmol, 10%) of the anti adduct from the asymmetric addition (Table 28). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 1.00 (t, J = 7.2 Hz, 3H), 1.88-1.81 (m, 1H), 2.03-1.96 (m, 1H), 3.99 (q, 6 Hz, 1H), 4.67-4.76 (m, 2H), 4.83 (dd, J = 19.5, 6 Hz, 1H), 7.02 (d, J = 9 Hz, 2H), 7.46 (d, J = 9 Hz, 2H). ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.2, 24.4, 46.0, 76.0, 90.8, 123.3, 129.6, 132.5, 132.8 ppm; R_f = 0.11 (20% EtOAc/hexanes); IR (neat) 3451(H_2O), 2112, 1653, 1558, 1375; MS (FAB$^-$): m/z (%): 317 [M-H]$^-$ (98, ^{81}Br), 315 [M-H]$^-$ (97, ^{79}Br), 268 (100); HPLC analysis: Chiralpac OD-H, hexane/2-PrOH 70/30, 0.5 mL/min, t_r = 14.8 min (major), t_r = 31.8 min (minor), 93% ee, $\alpha^{25}{}_D$ = +10.2 (c=1.0, dichloromethane).

The non-asymmetric addition (Table 28) afforded 180 mg (0.57 mmol, 57%) of syn-**80a** adduct and 28 mg (0.09 mmol, 9%) of the anti adduct.

2-(3-Bromophenyl)-1,3-dinitropentane 80h.



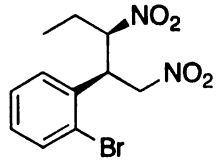
(2*R*, 3*R*)-**80h**

Prepared following the general procedure described above using 228 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 197 mg (0.62 mmol, 62%) of syn adduct as a clear yellow oil and 22 mg (0.07 mmol, 7%) of the anti adduct from the asymmetric addition (Table 39). Syn adduct: ^{1}H-

NMR (300MHz), $CDCl_3$ δ = 1.00 (t, *J* = 7.5 Hz, 3H), 1.88-1.81 (m, 1H), 2.03-1.94 (m, 1H), 3.97 (q, 6 Hz, 1H), 4.77-4.70 (m, 2H), 4.83 (dd, *J* = 13.5, 6 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.30 (t, 1.8 Hz, 1H), 7.47 (dq, *J* = 8.1 Hz, *J* = 1.2 Hz, 1H). ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.2, 24.5, 46.1, 76.0, 90.9, 123.2, 126.5, 130.9, 131.2, 132.3, 136.3; MS (FAB$^-$): *m/z* (%): 317 $[M-H]^-$ (98, ^{81}Br), 315 $[M-H]^-$ (97, ^{79}Br), 268 (100); IR (neat) 3451 (H_2O, 2112, 1653, 1558, 1375, 1010; HPLC analysis: Chiralpac OD-H, hexane/2-PrOH 70/30, 0.5 mL/min, 94% ee, α^{25}_D = +4.3 (c=1.0, dichloromethane), t_r = 14.5 min (major), t_r = 69.6 min (minor).

The non-asymmetric addition (Table 28) afforded 217 mg (0.69 mmol, 69%) of syn-**80h** adduct and 19 mg (0.06 mmol, 6%) of the anti adduct.

2-(2-Bromophenyl)1,3-dinitropentane 80i



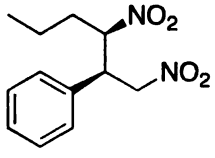
(2*R*, 3*R*)-**80i**

Prepared following the general procedure described above using 228 mg (1.00 mmol) of the nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 185 mg (0.58 mmol, 58%) of syn adduct as a clear oil and 63 mg (0.20 mmol, 20%) of the anti adduct from the asymmetric addition (Table 39). Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 1.00 (t, *J* = 7.5 Hz, 3H), 1.94-2.04 (m, 2H), 4.62-4.70 (m, 1H), 4.82-4.91 (m, 2H), 4.95-5.04 (m, 1H), 7.11-7.21 (m, 2H), 7.29 (td, *J* = 7.5, 1.2 Hz, 1H), 7.61 (dd, *J* = 8.1, 1.5 Hz, 1H); ^{13}C-NMR (300MHz), $CDCl_3$ δ = 10.4, 24.0, 44.8, 75.3, 90.0, 128.3, 130.4, 133.4, 134.1; MS (FAB$^-$): *m/z* (%): 317 $[M-H]^-$ (98, ^{81}Br), 315 $[M-H]^-$

(97, ^{79}Br), 268 (100); IR (neat) 3451(H_2O), 2112, 1653, 1558, 1375, 1010; HPLC analysis: Chiralpac OD-H, hexane/2-PrOH 70/30, 0.5 ml/min, t_r = 11.8 min (major), t_r = 38.5 min (minor), 92% ee, $\alpha^{25}{}_D$ = -6.8 (c=1.0, dichloromethane). For the anti adduct $\alpha^{25}{}_D$ = +6.6 (c=1.0, dichloromethane).

The non-asymmetric addition (Table 28) afforded 191 mg (60%) of syn-**80i** adduct and 19 mg (0.06 mmol, 6%) of the anti adduct.

2-Phenyl-1,3-dinitropentane 80j

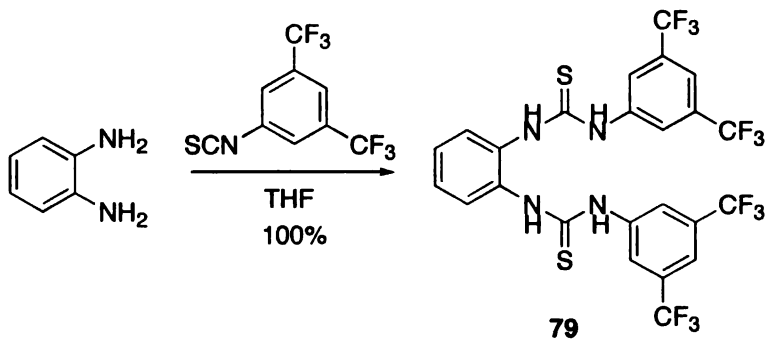


(2*R*, 3*R*)-**80j**

Prepared following the general procedure described above, using 50 mg (0.33 mmol) of nitrostyrene. Purified with silica gel column using 20% EtOAc/hexanes to afford 63 mg (0.23 mmol, 70%) of syn adduct as a white solid and 20 mg (0.08 mmol, 8%) of the anti adduct. Syn adduct: ^{1}H-NMR (300MHz), $CDCl_3$ δ = 0.94 (t, *J* = 7.2Hz, 3H), 1.34 (tq, *J* = 7.2 Hz. 2H), 1.74-1.68 (m, 1H),2.00-1.91 (m, 1H), 4.00 (t, *J* = 6.9 Hz, 1H), 4.92-4.72 (m, 3H), 7.15-7.11 (m, 2H), 7.34-7.31 (m, 3H) ppm; ^{13}C-NMR (300MHz), $CDCl_3$ δ = 13.3, 19.1, 32.7, 46.7, 76.2, 89.3, 127.8, 129.0, 129.2, 133.7 ppm; HPLC analysis: Chiralpac OJ-H, hexane/2-PrOH 80/20, 1.5 ml/min, t_r = 26.2 min (major), t_r = 31.9 min (minor), 91% ee, $\alpha^{25}{}_D$ = --(c=1.0, dichloromethane); The data agreed with the reported literature[48].

Thioureas **47** and **76-78** were prepared according to literature procedures[41c] and their spectroscopic data matched those of the literature.

Thiourea **79**.



79

Synthesized using the same procedure as for catalysts **52**, **55** (Chapter 4). 162 mg (1.50 mmol) *o*-phenylene diamine and 0.54 mL (813 mg, 3.00 mmol) 3,5-trifluoromethylphenyl isothiocyanate were used, to afford **79** as a red solid in 100% yield (975 mg, 1.50 mmol); ^{1}H-NMR (300MHz, CD_3CN) δ = 7.60 (s, 2H), 7.60-7.48 (m, 4H) 8.13 (s, 4H), 8.65 (s, 2H), 8.74 (s, 2H); IR (neat): 3240, 2993, 1705, 1539, 1471, 1381, 1280, 1180, 1136, 1045, 983, 889, 700, 682; R_f = 0.42 (50% EtOAc in hexanes), mp = 176-178°C; MS (FAB$^+$): *m/z* (%): 651 (50) $[M+H]^+$, 617 (20), 378 (20), 362 (24), 346 (100), 272 (24), 151(44), 119 (17), 109 (26).

General experimental procedure for the rate acceleration study using thioureas 47, 76, 77 (Scheme 26). *trans*-β-Nitrostyrene (20 mg, 0.13 mmoles) and the appropriate thiourea (10 mol.%) were dissolved in 1 mL $CDCl_3$ at r.t. and 1-nitropropane was added (0.060 mL, 5 eq.). The mixture was put in an NMR tube and was let stand for a

2h period, during which several ^{1}H-NMR spectras were obtained. The yield of the product **80a** was determined by integration of the quartet of the product at 4.02 ppm and the aromatic peaks of the thiourea catalysts, that were used as internal standards.

General procedure for the study of the non-asymmetric addition of 1-nitropropane to nitrostyrene using thiouras 47, 76-79 (Table 26). *trans*-β-Nitrostyrene (100 mg, 0.66 mmoles) and thiourea **47** were put in a flame-dried flask and dissolved in 2 mL toluene. The appropriate nitroalkane was added (10 eq.) followed by triethylamine (10 mol%, 0.010 ml) and the mixture was stirred overnight at r.t. followed by evaporation of the volatiles. The crude mixture was subjected to column chromatography purification (20% ethyl acetate in hexanes) and the product **80a** was obtained as a mixture of diastereomers. The diastereomeric ratio of the product was determined by injection of the crude reaction mixture (passed through a pippete with silica gel) to HPLC, using Chiracel OJ-H, hexane/2-PrOH 80/20, 1.5 mL/min. Retention times of syn adduct: 31.5 min, 44.4 min. Retention times of the anti adduct: 20.0 min, 26.4 min.

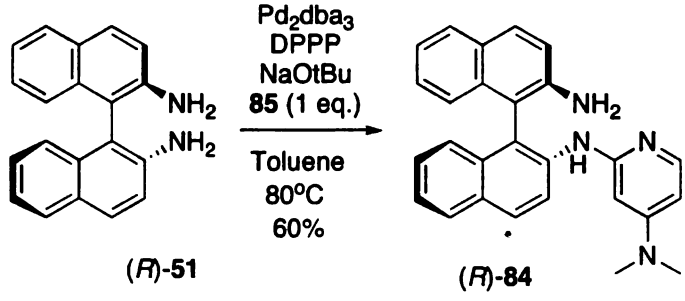
General procedure for the optimization of the non-asymmetric addition of 1-nitropropane to nitrostyrene using thiourea 47 (Table 27). Nitrostyrene and thiourea **47** were put in a flame-dried flask and dissolved in various solvents. The appropriate nitroalkane was added followed by triethylamine and the mixture was stirred overnight at r.t. followed addition of 50 mol.% triphenylmethane (internal standard) and evaporation of the volatiles. The yield was determined from the crude ^{1}H-NMR spectrum by integration of the quartet of the product at 4.02 ppm and the singlet of triphenylmethane at 5.6 ppm.

The diastereomeric ratio was determined by injection of the crude reaction mixture (passed through a pippete with silica gel) to HPLC, using Chiracel OJ-H, hexane/2-PrOH 80/20, 1.5 mL/min. Retention times of syn adduct: 31.5 min, 44.4 min. Retention times of the anti adduct: 20.0 min, 26.4 min.

For the rest of the tables in Chapter 5, the experimental procedures were the same as for the ones described before for the optimum conditions, with slight variations that are clarified in each table.

Preparation of catalyst 82.

Synthesis of compound **84**.

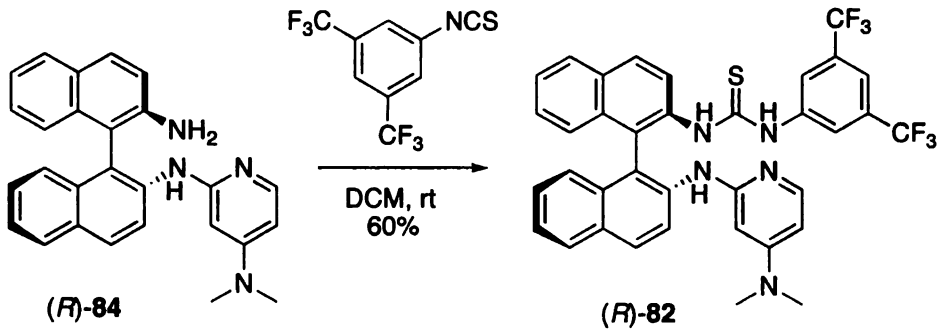


(*R*)-**51** (*R*)-**84**

Compound **51** (1.077 g, 3.79 mmol) was put in a Schlenck flask along with Pd_2dba_3 (262 mg, 0.28 mmol), diphenylphosphinopropane (DPPP) (238 mg, 0.57 mmol), NaOtBu (549 mg, 5.71 mmol). Toluene (30 mL) and 1 equivalent of 2-chloro-4-dimethylaminopyridine **85** (595 mg, 3.79 mmol) were added and the mixture was freeze-thawed twice. The flask was then put in an oil bath at 80°C and stirred at that temperature for 36h. Filtration of the reaction mixture through Celite and evaporation of toluene under reduced pressure followed. The dark residue was extracted with dichloromethane and water and the dichloromethane layer was dried with $MgSO_4$. The crude product was

purified by column chromatography (SiO_2) using 50% ethylacetate in hexanes to afford 982 mg **84** as a yellow solid (2.27 mmol, 60%). ^{1}H-NMR (300MHz), $CDCl_3$ δ =2.88 (s, 6H), 3.69 (br s, 2H), 5.87 (d, *J* = 1.2 Hz, 1H), 6.07 (dd, *J* = 6.0, 0.9 Hz, 1H), 6.24 (br s, 1H), 7.44-7.01 (m, 7H), 7.85-7.75 (m, 3H), 7.91 (d, *J* = 9.3Hz, 1H), 8.24 (d, *J* = 9.0 Hz, 1H); 1 exchangeable H did not show up. ^{13}C-NMR (300MHz), $CDCl_3$ δ = 39.2, 91.1, 101.2, 111.9, 118.3, 119.1, 120.4, 122.3, 123.8, 123.9, 124.9, 126.6, 126.8, 128.0, 128.1, 128.3, 128.8, 129.7, 130.0, 133.4, 133.9, 138.1, 142.7, 147.8, 155.9, 156.1 ppm; R_f = 0.36 (5% Et_3N/EtOAc); MS (FAB$^+$): *m/z* (%): 405 (100) $[M+H]^+$, 387 (40), 267 (18); IR (neat) 3389, 3194, 3053, 2924, 1607, 1487, 1290; α^{25}_D = +75.9 (c=1.0, dichloromethane).

Catalyst **82**:

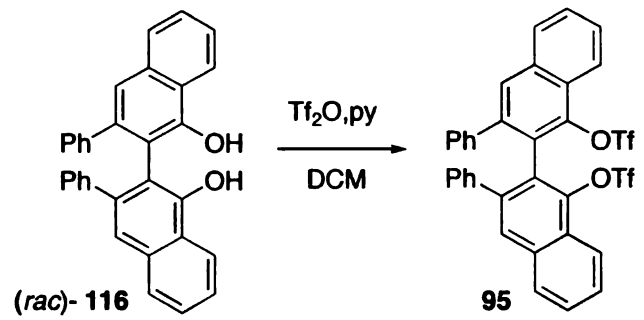


In a typical procedure, 982 mg (2.43 mmol) of compound **84** was put in a round bottom flask and dissolved in THF (10 mL). 3,5-Bis(trifluoromethyl) phenylisothiocyanate (2.43 mmol, 0.443 mL) was added and the mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the crude mixture was subjected to silica gel column chromatography purification (50% EtOAc in hexanes followed by 10% MeOH in dichloromethane) to afford 986 mg (60%) of the catalyst **82** as a yellow solid, m.p. = 130°C; R_f = 0.47 (10%

MeOH/dichloromethane); ^{1}H-NMR (300MHz), $CDCl_3$ δ = 2.82 (s, 6H), 5.89 (d, *J* = 5.7 Hz, 1H), 6.00 (s, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.40-7.18 (m, 4H), 7.54-7.49 (m, 3H), 7.63 (br s, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 1H); 3 exchangeable H's did not show up. ^{13}C-NMR (300MHz), $CDCl_3$ δ = 39.1, 91.7, 101.6, 117.6, 117.7, 121.2, 121.4, 122.6, 124.7, 124.8, 124.9, 125.5, 125.9, 126.4, 127.1, 127.33, 128.3, 128.34, 128.7, 129.3, 129.5, 130.3, 130.9, 131.4, 132.5, 133.2, 133.5, 134.2, 137.9, 140.3, 146.4, 155.6, 156.1, 179.8 ppm; IR (neat) 3308, 1610, 1489, 1385, 1277, 1132 MS (FAB$^+$): *m/z* (%): 676 (100) $[M+H]^+$, 642 (40), 447 (30), 388 (10), 267 (7); α^{25}_{D} = +129.9 (c=1.0, dichloromethane).

Experimental Procedures for Chapter 6

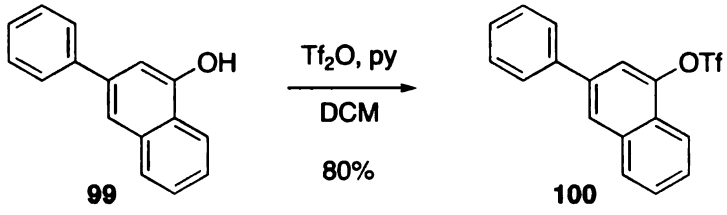
Preparation of VANOL triflate **95**



(*rac*)- **116** **95**

In a typical experiment, 150 mg (0.34 mmol) of (*rac*)-**116** were put in a flame-dried flask and were dissolved in 3 mL of dichloromethane. Dry pyridine was added (82.9 μL, 1.03 mmol) followed by triflic anhydride (126 μL, 0.75 mmol). The mixture was stirred overnight at room temperature and then washed with 10 mL 2N HCl, 4 mL saturated $NaHCO_3$ and 4 mL water. The organic layer was filtered through silica gel and the silica was washed with dichloromethane/EtOAc (10/1). The volatiles were evaporated to afford 220 mg (0.30 mmol) **95** as a yellow solid (91%), m.p. = 228-230°C; ^{1}H-NMR (300 MHz), $CDCl_3$ δ = 6.57 (d, *J* = 7.8 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 2H), 7.06 (t, *J* = 7.2 Hz, 2H), 7.74-7.61 (m, 6H), 7.88 (d, *J* = 8.1 Hz, 4H), 8.29 (d, *J* = 8.4 Hz, 4H)ppm; ^{13}C-NMR (300 MHz), $CDCl_3$ δ = 115.8, 120.1, 121.8, 124.3, 126.5, 126.8, 127.9, 128.3, 128.5, 128.9, 130.4, 134.6, 139.0, 140.5, 144.7 ppm; IR (neat): 3057, 2928, 1414, 1217, 1134, 1010, 812, 765, 702; MS (FAB$^+$): *m/z* (%): 702 (90) [M$^+$], 570 (42), 436 (78), 402 (100), 154 (45), HRMS (FAB$^+$): calcd for $C_{34}H_{20}F_6O_6S_2$ m/z 702.0605, meas 702.0602.

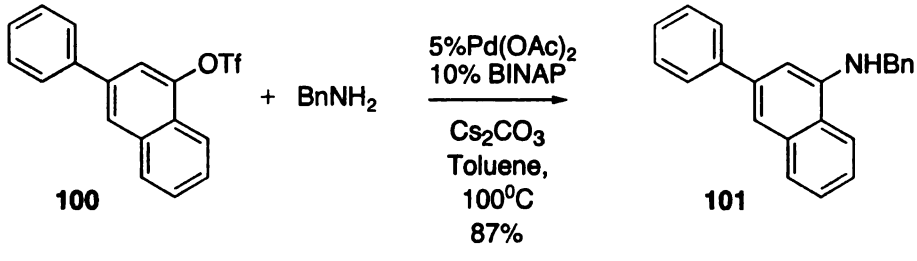
3-Phenyl-1-naphthyl triflate 100



99 100

The procedure was identical to the one for preparing VANOL triflate **95**. In a typical experiment 1.50 g VANOL (3.40 mmol) were employed affording 1.90 g (2.72 mmol) of **100** (80%) as a brown oil (turned to a solid at 4°C). ^{1}H-NMR (300 MHz), $CDCl_3$ δ = 7.96-7.93 (m, 1H), 7.44-7.39 (m, 1H), 8.07-8.05 (m, 2H), 7.52-7.47 (m, 2H), 7.71-7.60 (m, 5H); ^{13}C-NMR (300MHz), $CDCl_3$ δ = 117.5, 120.6, 120.9, 125.2, 125.9, 127.2, 127.71, 127.73, 128.1, 128.3, 129.1, 134.9, 138.4, 139.1, 145.9 ppm; IR (neat): 3063, 3036, 1637, 1599, 1496, 1421, 1213, 1142, 1062, 1010, 924, 879, 819, 783, 696, 650 cm^{-1} MS (FAB^+): *m/z* (%): 352 (100) [M^+], 219 (40), 154 (23), HRMS (FAB^+): calcd for $C_{17}H_{11}F_3O_3S$ *m/z* 352.0381, meas 352.0378.

3-Phenyl-1-(N-benzyl) naphthylamine 101

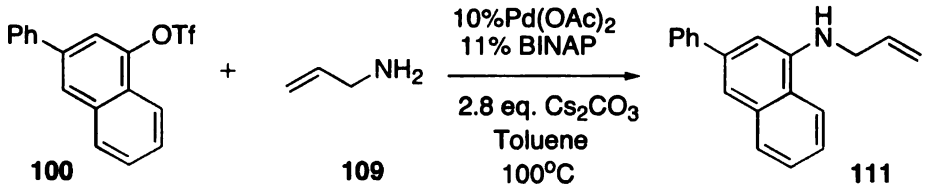


100 101

A flame-dried Schlenk flask was charged with 150 mg (0.42 mmol) **100**, 4.7 mg (0.021 mmol) $Pd(OAc)_2$, 14.5 mg (0.023 mmoles) BINAP and 193.8 mg (0.59 mmol) Cs_2CO_3. The solids were dissolved in 3 ml toluene and 55.7 μl (0.51 mmoles) $BnNH_2$ was added. The resulting mixture was deoxygenated by the freeze-thaw method three times

and put in an oil bath at 100°C. The mixture was stirred at that temperature for 17h and then the volatiles were evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using 10% EtOAc in hexanes to afford 114 mg (0.36 mmol, 87%) of **101** as a yellow solid, m.p.=110-112°C; ^{1}H-NMR (300MHz), $CDCl_3$ δ = 4.55 (s, 2H), 4.75 (br s, 1H), 6.96 (s, 1H), 7.54-7.35 (m, 11H), 7.74 (d, *J* = 6.0 Hz, 2H), 7.84 (d, *J* = 6.9 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H). ^{13}C-NMR (300 MHz), $CDCl_3$ δ = 48.6, 104.4, 115.8, 119.8, 122.6, 124.7, 126.1, 127.1, 127.3, 127.4, 127.8, 128.64, 128.67, 128.7, 128.9, 134.5, 138.9, 139.3, 141.9, 143.5 ppm; IR (neat): 3445, 3061, 3030, 1626, 1593, 1581, 1525, 1495, 1412, 1257, 775, 698 cm^{-1}; MS (FAB$^+$): *m/z* (%): 309 (100) [M$^+$], 252 (75), 140 (70), 123 (50); HRMS (FAB$^+$): calcd for *m/z* $C_{23}H_{19}N$ 309.1517, meas 309.1515.

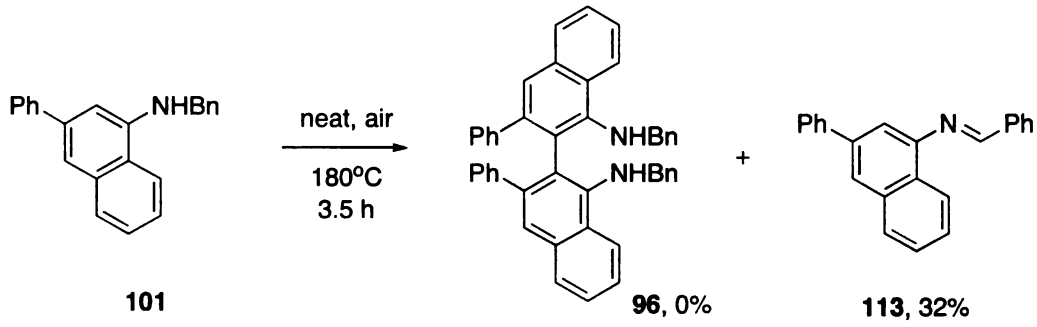
3-Phenyl-1-(N-allyl) naphthylamine 111



The procedure was the same as for the synthesis of **101**, only more catalyst (10 mol%) was used. For 1g scale reaction (2.8 mmol **100**) 416 mg (1.59 mmol, 57%) of **111** were obtained as a yellow oil after column chromatography purification on silica gel using 10% EtOAc/hexanes. ^{1}H-NMR (300MHz), $CDCl_3$ δ = 4.02 (d, *J* = 4.8 Hz, 2H), 4.54 (br s, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 5.41 (d, *J* = 16.8 Hz, 1H), 6.87 (s, 1H), 6.20-6.05 (m, 1H), 7.49-7.35 (m, 6H), 7.73-7.68 (m, 2H), 7.84 (t, *J* = 7.2 Hz, 2H). ^{13}C-NMR (300MHz), $CDCl_3$ δ = 46.6, 104.2, 115.5, 116.4, 119.4, 122.4, 124.4, 125.8, 126.8, 127.1, 128.3,

128.7, 134.2, 134.7, 139.0, 141.7, 143.1; IR (neat): 3443, 3061, 1626, 1583, 1525, 1496, 1414, 1235, 920, 839, 761, 698 cm^{-1} ; MS (FAB^+): *m/z* (%): 259 (100) [M^+], 232 (8), 219 (10), 191 (5); HRMS: calcd for $C_{19}H_{17}N$ *m/z* 259.1361, meas 259.1363.

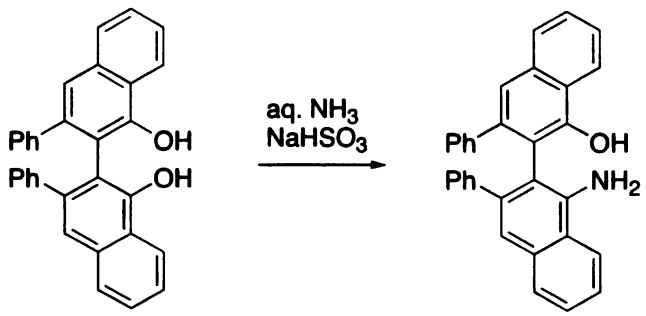
Benzaldehyde N-(3-phenyl-1-naphthyl) imine 113



101 **96**, 0% **113**, 32%

Obtained as a major product from the attempted synthesis of **96** from **101** through oxidative coupling under neat conditions. Compound **101** was heated at 180°C in an oil bth for 6 h, after which time it was let to cool down. The product **113** was purified with column chromtography on silica gel using 5% EtOAc/hexanes, and in this way 50 mg (0.16 mmol, 32%) **113** were obtained s a white solid. ^{1}H-NMR (300 MHz), $CDCl_3$ δ = 7.24 (s, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.50-7.40 (m, 7H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.85-7.82 (m, 2H), 7.96 (br s, 2H), 8.26 (d, *J* = 7.5 Hz, 1H), 8.54 (s, 1H); ^{13}C-NMR (300MHz), $CDCl_3$ δ = 112.5, 123.6, 123.9, 125.8, 126.9, 127.4, 127.5, 128.0, 128.9, 129.1, 131.6, 134.2, 136.4, 138.9, 141.1, 149.9, 160.7; two C's not located; MS: *m/z* (%): 307 (100) [M^+], 230 (25), 202 (85).

Compound 118



116 **118**

VANOL **116** (2.00 g, 4.56 mmol) was put in a Parr reactor with 11.5 g (110 mmol) $NaHSO_3$ and 87 mL of 30% aq. NH_3 was added. The mixture was heated at 200°C and stirred with a mechanical stirrer for 40h. The resulting mixture was cooled down and extracted with dichloromethane, the volatiles were evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using 10% EtOAc/hexanes to afford 498 mg (0.91 mmol, 25%) of **118** as a light brown solid; m.p. = 220-224°C; ^{1}H-NMR (300MHz), $CDCl_3$ δ = 4.45 (br. s, 2H), 6.00 (br. s, 1H), 6.53 (d, *J* = 7.5 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 2H), 7.04-6.84 (m, 6H), 7.10 (s, 1H), 7.22 (s, 1H), 7.48-7.44 (m, 4H), 7.73-7.68 (m, 2H), 7.87-7.84 (m, 1H), 8.34-8.26 (m, 1H). ^{13}C-NMR (300 MHz), $CDCl_3$ δ = 116.3, 120.5, 121.2, 121.6, 122.1, 122.7, 123.0, 125.3, 125.4, 125.5, 126.3, 126.4, 126.8, 126.9, 127.2, 127.3, 127.6, 128.1, 128.4, 128.8, 128.9, 134.2, 140.6, 140.7, 140.9, 141.5, 149.7 ppm; one C not located; IR (neat): 3491, 3383, 3053, 3028, 1608, 1588, 1493, 1383, 1265, 758, 738, 702 cm^{-1}; MS: *m/z* (%): 437 (100) [M$^+$], 307 (10), 219 (20), 154 (40), 136 (22), HRMS: calcd for $C_{32}H_{23}NO$ *m/z* 437.1779, meas 437.1777.

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9. As was reported in previous work (ref. 5), the reaction of VAPOL with 0.5 equivalents of zirconium tetraisopropoxide in the presence of two equivalents of NMI produces the clean formation of a single C_2-symmetrical species which is tentatively assigned by ^{1}H NMR spectroscopy as **8**: ^{1}H- NMR ($C_6D_5CD_3$): δ 1.60 (br s, 6 H), 4.37 (br s, 2H), 5.57 (br s, 2 H), 5.87 (br s, 2 H), 6.79 - 6.84 (m, 12H), 6.98 - 7.01 (m, 8H), 7.05 (s, 4 H), 7.14 (d, 4H, J = 8.7 Hz), 7.19 (d, 4H, J = 8.7 Hz), 7.22 (td, 4H, J = 8.1, 1.1 Hz), 7.41 (dd, 4H, J = 8.1, 1.2 Hz), 7.84 (td, 4H, J = 8.1, 1.5 Hz), 11.33 (d, 4H, J = 8.4 Hz). The ^{1}H-NMR spectrum shows that a number of species are generated when a 1:1 stoichiometry of VAPOL to zirconium is employed.

10. As reported with the BINOL - Zr catalyst[8], the induction falls off with a catalyst prepared with a 1:1 stoichiometry of zirconium to VAPOL (to 60%ee for the reaction at room temperature in toluene).

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