# CHIRAL PROTON CATALYSIS: DEVELOPMENT OF DIASTEREO- AND ENANTIOSELECTIVE SYNTHESES OF *VICINAL* DIAMINES AND α,β-DIAMINO ACIDS

By

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# *CHAPTER I*

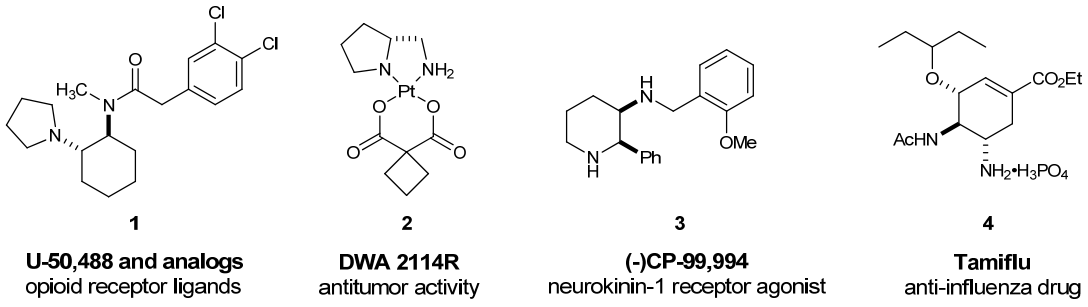
## *INTRODUCTION*

### *1.1 Vicinal-Diamines in Organic Chemistry: Significance and Synthetic Approaches*

#### *1.1.1 Biologically Active Molecules and Synthetic Catalysts Containing the vic-Diamine Functionality*

1,2-Diamines form an important class of compounds, some members of which are valuable for their medicinally relevant biological activity. Figure 1 depicts these molecules with a recently well publicized member being the neuramidinase inhibitor

**Figure 1.** Biologically Active *vic*-Diamines



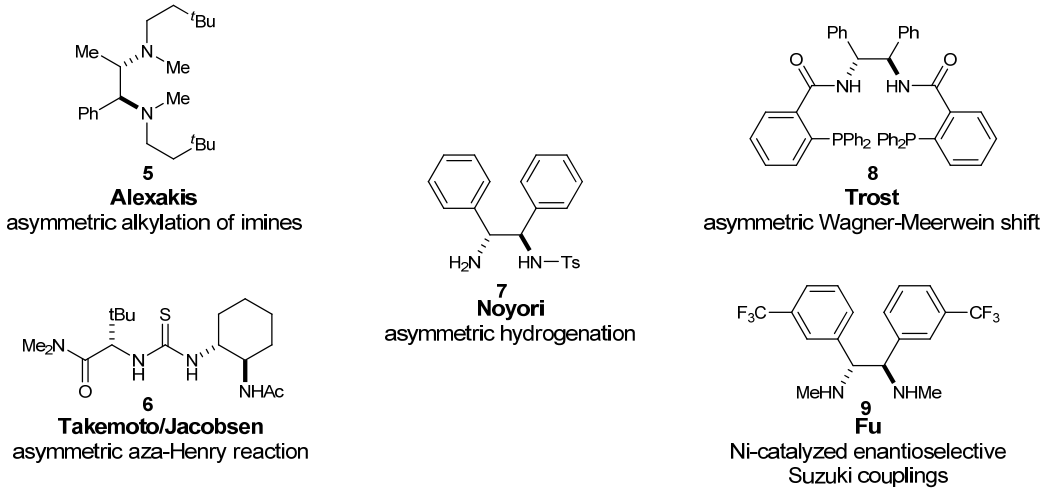

Tamiflu which is prescribed to treat the H5N1 avian influenza and the H1N1 swine influenza.

Chiral, non-racemic 1,2-diamines have emerged as one of the most important class of ligands for enantioselective catalysis. They have been used as ligands in conjunction with metals to catalyze many reactions, an example of which is the Noyori hydrogenation catalyst derived from a stilbene diamine.[1] *Vicinal* diamines have also been a driving force behind the explosive growth of organocatalysis in the last decade as seen

[1] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

by their use as precursors for versatile catalysts such as the thioureas and bis-amidine class of molecules.[2,3,4,5,6,7]

**Figure 2.** Diamines Used in Asymmetric Catalysis



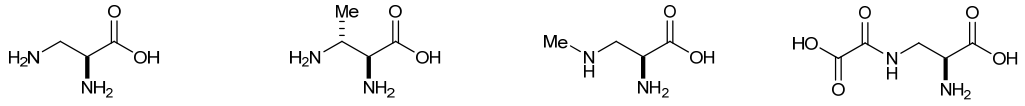

### *1.1.2 Diamines as Constituents of α,β-Diamino Acids*

α,β-Diamino acids are nonproteinogenic amino acids which have garnered interest due to their existence in Nature either in the free form or as motifs in complex molecules. These atypical amino acids often display interesting and useful biological properties. Furthermore, these molecules have been used as building blocks for the synthesis of amino acid surrogates to modulate their structural profile and biological behavior.[8]

Examples of free α,β-diamino acids in nature include the simplest member α,β-diaminopropionic acid which is found in protein free extracts from Bombyx insects.[9] α,β-

[2] Perron, Q.; Alexakis, A. *Tetrahedron Asymmetry* **2007**, *18*, 2503.
[3] Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.
[4] Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466.
[5] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466.
[6] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694.
[7] Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 103.
[8] Viso, A.; Pradilla, R. F.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
[9] Corrigan, J. J.; Srinivasan, N. G. *Biochemistry* **1966**, *5*, 1185.

**Figure 3.** Free α,β-Diamino Acids in Nature



**10** α,β-diaminopropionic acid

**11** α,β-diaminobutanoic acid

**12** L-β-methylaminoalanine (neurotoxin)

**13** L-β-methylaminoalanine (neurotoxin)

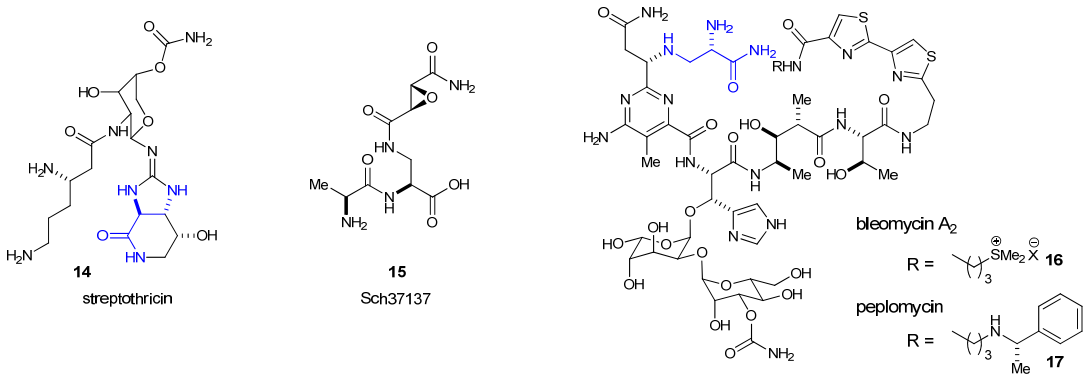
Diaminopropionic acid has been isolated from the root nodules of *Lotus tennius* inoculated with *Rhizobium* strain NZP2213.[10] Some α,β-diamino acids found in plants display neurotoxic activity towards animals. Examples of these include L-β-methylaminoalanine (BMAA) and 3-(*N*-oxalyl)-L-2,3-diaminopropionic acid (β -ODAP). BMAA is currently of interest due to its link to neurodegenerative diseases such as amytrophic lateral sclerosis, Alzheimer's disease, and Parkinsonism dementia.[11,12] β-ODAP is an ionotropic glutamate receptor agonist which causes latyrism (paralysis of the lower limbs). This condition occurs mainly in humans and less frequently in animals. The staple crop grass-pea contains β–ODAP[13,14] which limits its utility and hence methods have been devised to either eliminate the neurotoxin[15] or to convert it to the non-toxic enantiomer α–ODAP. [16]

In addition to the above mentioned free α,β-diamino acids, many complex natural products have been isolated which contain the diamino acid functionality in slightly modified form. Among the most useful of these is the bleomycin family of antitumor antibiotics. The bleomycins were isolated from *Streptomyces verticillus* and are clinically used for the treatment of Hodgkin's lymphoma, tumors of testis, and carcinomas of head,

[10] Shaw, G. J.; Ellingham, P. J.; Bingham, A.; Wright, G. J. *Phytochemistry* **1982**, *21*, 1635.
[11] Murch, S. J.; Cox, P. A.; Banack, S. A.; Steele, J. C.; Sacks, O. W. *Acta Neurol. Scand.* **2004**, *110*, 267.
[12] Cox, P. A.; Banack, S. A.; Murch, S. J. *Proc. Natl. Acad. Sci.* **2003**, *100*, 13380.
[13] Ross, S. M.; Roy, D. N.; Spencer, P. S. *J. Neurochem.* **1989**, *53*, 710.
[14] Sabri, M. I.; Lystrup, B.; Roy, D. N.; Spencer, P. S. *J. Neurochem.* **1995**, *65*, 1842.
[15] Yigzaw, Y.; Gorton, L.; Solomon, T.; Akalu, G. *J. Agric. Food Chem.* **2004**, *52*, 1163.
[16] Bruyn, A.; Becu, C.; Lambien, F.; Kebede, N.; Abegaz, B.; Nunn, P. B. *Phytochemistry* **1994**, *36*, 85.

neck, and skin.[17,18] Peplomycin is a member of this family which is less toxic and displays a wide antitumor spectrum.[19]

**Figure 4.** Complex Natural Products Containing the *vic*-Diamine Functionality



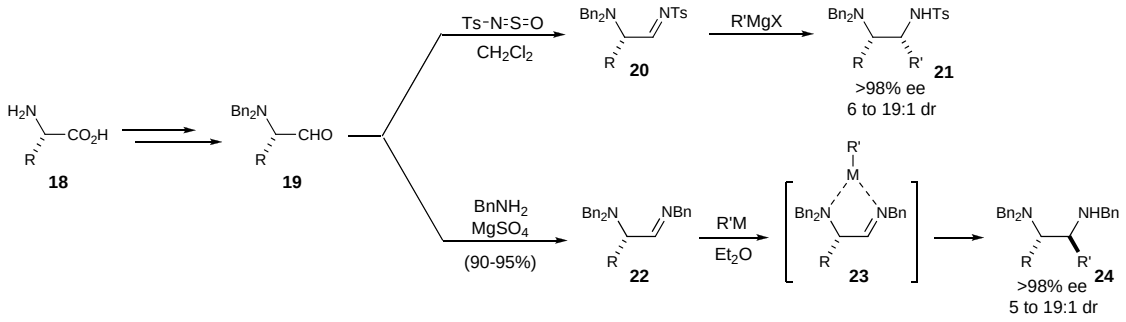

### *1.1.3 Synthetic Approaches Towards Enantioenriched 1,2-Diamines*

Since vicinal diamine containing compounds are of broad interest to the scientific community, an appreciable amount of effort has been devoted to their synthesis. Among the oldest methods is the resolution of a racemic mixture. The process of resolution is not only limited by the availability of an effective chiral, non-racemic resolving agent, but also suffers from lack of generality towards substrates since they must be solids for recrystallization based approaches. Since this document pertains to the development of enantioselective reactions, resolution based approaches will not be discussed.

[17] Umezawa, H.; Maeda, K.; Takeuchi, T.; Okami, Y. *J. Antibiotics*, **1966**, *19*, 200.
[18] Galm, U.; Hager, M. H.; Van Lanen, S. G. V.; Ju, J.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739.
[19] Yamamoto, T.; Yoneda, K.; Ueta, E.; Osaki, T. *Jpn. J. Pharmacol.* **2001**, *87*, 41.

Naturally occurring enantiopure amino acids are an obvious source for the

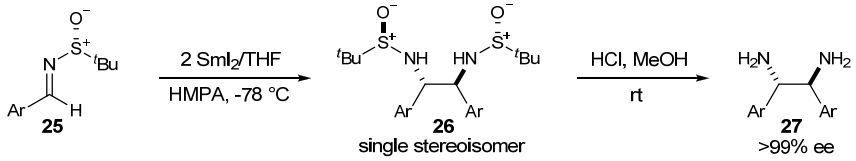
**Scheme 1**




synthesis of chiral, non-racemic *vicinal*-diamines, and they have been demonstrated to be suitable precursors for this purpose. Reetz's synthesis of both *syn* and *anti*-1,2-diamines starting from various *L*-amino acids is a good example of this approach. This approach, however, is limited by the availability of the amino acid precursor.[20]

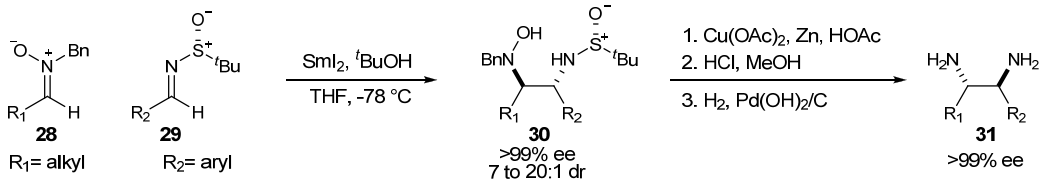
Reductive homocoupling[21] of imines has been explored as a viable route towards

**Scheme 2**




enantiopure diamines by Xu and Lin who utilized aryl *N*-sulfinyl imines in a

**Scheme 3**

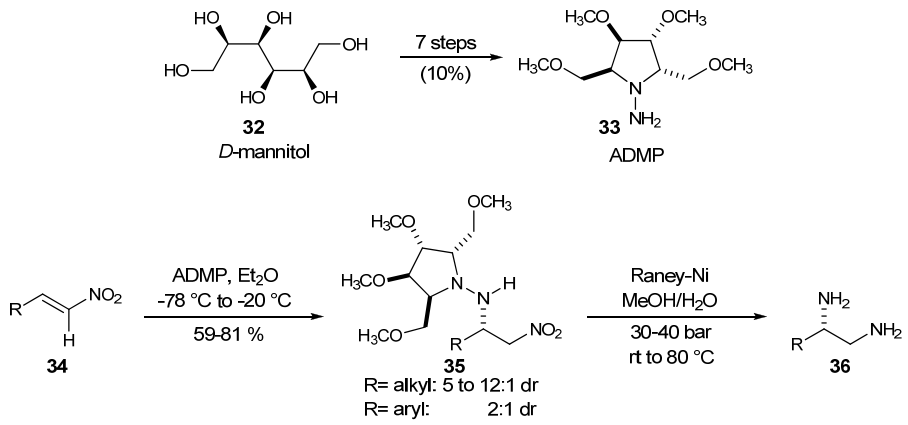



[20] Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 103.
[21] Zhong, Y.; Izumi, K,; Xu, M.; Lin, G. *Org. Lett.* **2006**, *4*, 4747.

samarium(II) mediated coupling. The resulting diamine was obtained as a single stereoisomer which was subsequently deprotected to reveal the free diamine in >99% ee. In order to arrive at a diamine with different alkyl/aryl groups, a cross-coupling between nitrones and imines was employed. The use of enantiopure sulfinyl imine ultimately led to the synthesis of enantioenriched, unsymmetrical 1,2-diamines.[22]

A diastereoselective Michael addition of an ammonia equivalent to nitroalkenes has been developed by Enders as a means to access 1,2-diamines.[23] A mannitol derived

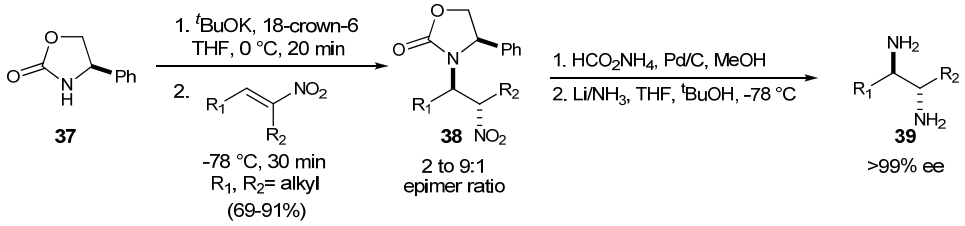
**Scheme 4**




auxiliary was the source of chirality in these reactions. However, the tedious and low yielding synthesis of this auxiliary was a limitation to the usefulness of this methodology. The same principle was used by Mioskowski who demonstrated the use of an oxazolidinone chiral auxiliary to effect a distereoselective Michael addition of a cyclic carbamate to nitroalkenes.[24]

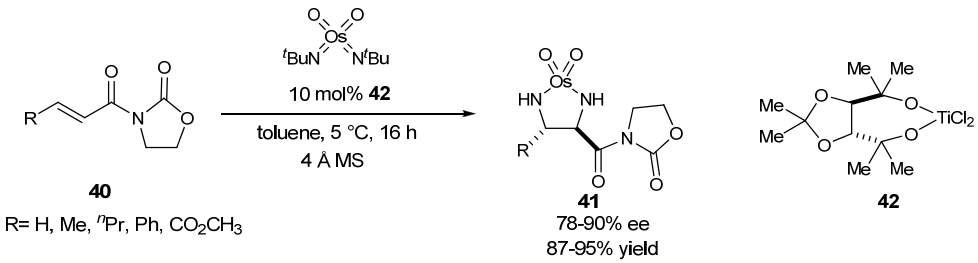
[22] Lin, G.; Xu, M.; Zhong, Y.; Sun, X. *Acc. Chem. Res.* **2008**, *41*, 831.
[23] Enders, D.; Wieldemann, J. *Synthesis* **1996**, 1443.
[24] Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580

**Scheme 5**



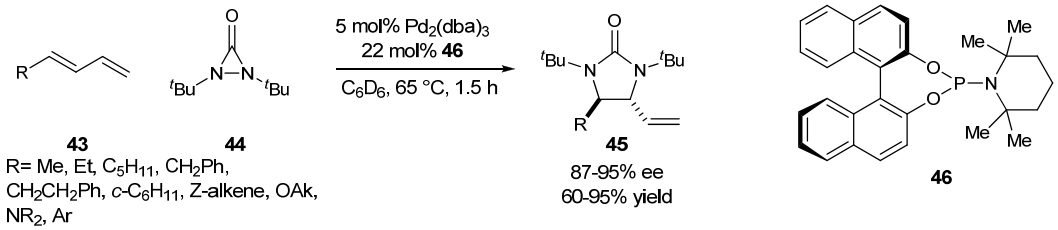

Olefin diamination is conceptually a straightforward solution to this problem. However, only two groups have reported such a reaction which was catalyzed by metals. Muniz has demonstrated that alkenes can be diaminated using osmium nitride and a titanium TADDOL catalyst in up to 90% ee.[25]

**Scheme 6**




Shi has shown that dienes can be diaminated with high enantioselection using a

**Scheme 7**

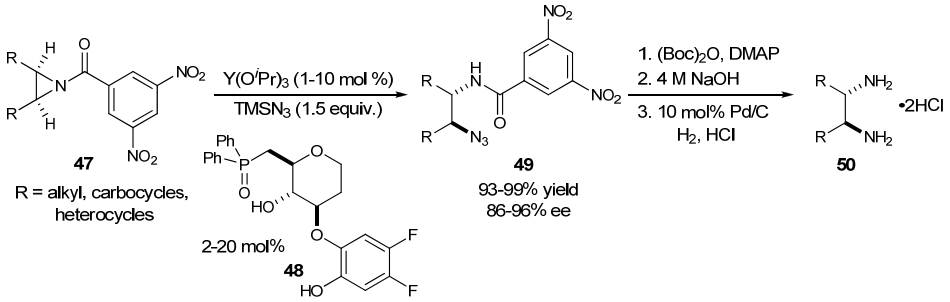



[25] Almodovar, I.; Hövelmann, C. H.; Streuff, J.; Nieger, M.; Muñiz, K. *Eur. J. Org. Chem.* **2006**, 704.

palladium-BINOL derived catalyst. The resulting urea can be converted to a 1,2-diamino acid or a diamine with a vinyl substitution.

Ring opening of aziridines has been shown to be a viable route towards 1,2-diamines by Shibasaki who used desymmetrization of *meso*-aziridines to synthesize a variety of syn-

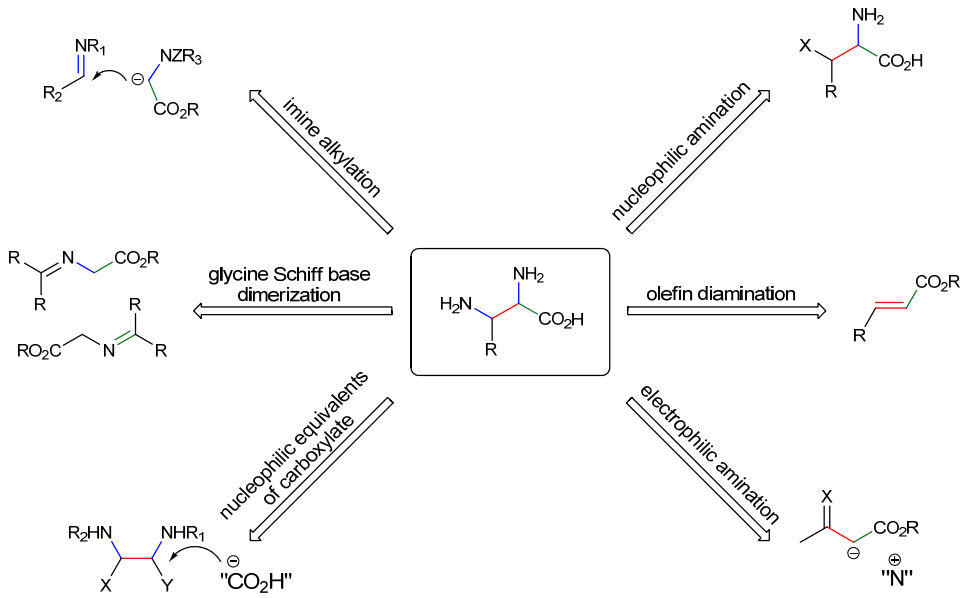
**Scheme 8**




1,2-diamines. This methodology was applied to the synthesis of the antiviral compound Tamiflu.[26]

For the synthesis of α,β-diamino acids, some of the strategies mentioned above

**Figure 5.** Strategies for the Synthesis of α,β-Diamino Acids




[26] Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

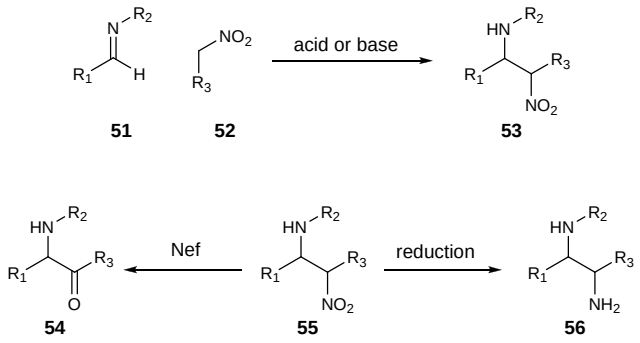
are applicable and have been reported in the literature. Retrosynthetically, approaches to α,β-diamino acids can be classified into two categories: one that builds C-C bond(s) and the other that starts from the requisite carbon skeleton and builds the C-N bonds. Figure 5 depicts these scenarios and provides illustrative examples of the combinations that might be utilized. A detailed discussion about the synthesis of these molecules will be undertaken in Chapters 3 and 4.

One of the most concise and straightforward methods to synthesize a 1,2-diamine (including the corresponding diamino acids) is the aza-Henry reaction which has been widely utilized for the same and is discussed in section 1.2.

### *1.2 The Aza-Henry Reaction*

The aza-Henry reaction is an important carbon-carbon bond forming process in which a nitroalkane nucleophile adds to an imine. These reactions are typically

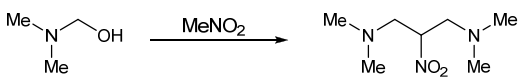
**Scheme 9**




performed under acidic or basic catalysis. The products of this reaction are α-nitro amines which can be transformed into a variety of useful compounds such as *vicinal* diamines or α-amino acids.

The origins of the aza-Henry reaction can be traced back to the discovery of the Henry reaction, which is the addition of nitroalkanes to aldehydes.[27,28] Concurrently with the report of the Henry reaction, Henry described the double addition of nitromethane to the hemiaminal **57**. The scope of the early form of aza-Henry reaction was extended by Cerf who erroneously claimed that only two equivalents of the hemiaminal **57** will react with nitromethane and only one equivalent of **57** will react with higher nitroalkanes.[29] Cerf's claims were proved to be incorrect by Senkus who published his findings describing the use of primary amines and formaldehyde.[30] Concurrent with Senkus's report, Johnson reported an independent study describing the use of secondary amines to form hemiaminal precursors.[31]

**Scheme 10**




**57** **58**

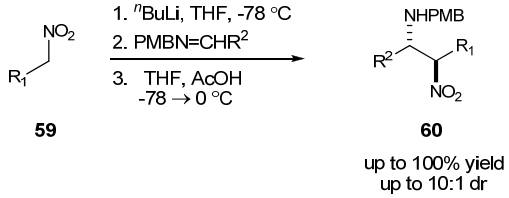
The first report of an aza-Henry reaction using a traditional imine and nitroalkane was published in 1950.[32] In the reaction, nitromethane was added into *N*-phenyl benzylimine affording the product in 64% yield. The authors were also able to use nitroethane as the nucleophile, albeit with low yield (35%). However, there was no comment about diastereoselectivity. Along similar lines, Kozlov and Fink used

[27] Henry, L. *Bull. Acad. Roy. Belg.* **1896**, *32*, 33.
[28] Henry, L. *Chem. Ber.* **1905**, *38*, 2027.
[29] Cerf de Mauney, C. D. *Bull. Soc. Chim. France* **1937**, *4*, 1451.
[30] Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10-12.
[31] Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12-14.
[32] Hurd, C. D.; Strong, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4813.

nitropropane with the same imine to yield the α-nitro amine product in 35% yield with no comment on diastereoselectivity.[33]

The aza-Henry was reaction was revisited by Anderson in 1998 as a viable route for the stereoselective synthesis of *vicinal* diamines. They were able to synthesize a

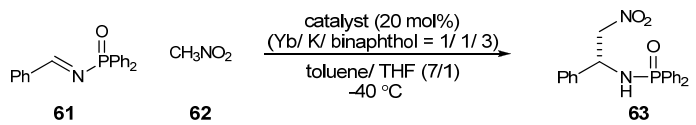
**Scheme 11**




variety of *vic*-diamines in high yields and with good diastereoselection.[34] In the continuation of this work, Anderson reported a Lewis acid catalyzed variant of this reaction using $Sc(OTf)_3$. To improve the rate of the reaction, they employed preformed silyl nitronates. Their best result was a 99% yield after 2 hours at 0 °C, with a diastereomeric ratio of 9:1.[35]

Shibasaki reported a significant advancement in this area by achieving the first catalytic enantioselective aza-Henry reaction. The catalyst employed was a heterobimetallic complex prepared from $Yb(O^iPr)_3$, $KO^tBu$ and (*R*)-binaphthol and the product was obtained with up to 91% ee (Scheme 12).[36] This catalyst system was unable

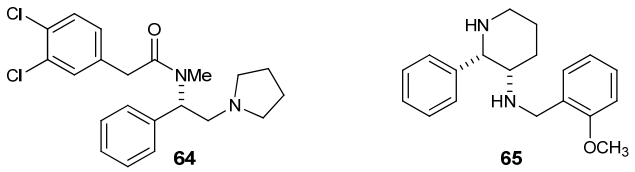
**Scheme 12**




[33] Kozlov, L. M.; Fink, E. F. *Trudy Kazan. Khim. Tekhnol. Inst. Im. S. M. Kirova* **1956**, *21*, 163.
[34] Adams, H.; Anderson, J. C.; Peace, S.; Pennel, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.
[35] Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, *6*, 850.
[36] Yamada, K.; Harwood, S. J.; Groger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.

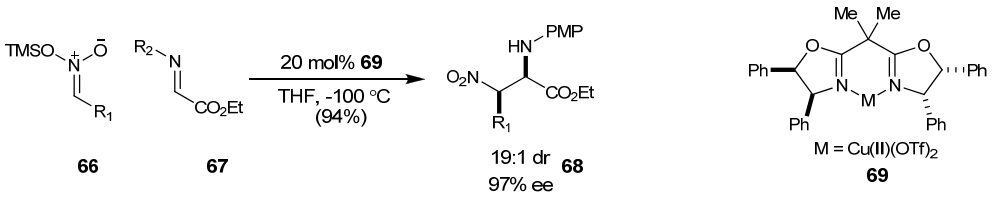
to catalyze the addition of higher nitroalkanes for which an aluminum-lithium complex was developed to provide adducts with up to 7:1 dr and 83% ee.[37,38] In addition to showcasing the generality of the catalyst system, Shibasaki used this chemistry to improve the synthesis of two biologically active compounds, ICI-199441 and CP-99994.[39] The new route utilizing the aza-Henry reaction was more concise than the previous route which started from an amino acid.

**Figure 6**




In 2001, Jørgensen published the first catalytic asymmetric aza-Henry reaction of silyl nitronates with α-imino esters. The reaction proceeds well with a variety of Cu(II)

**Scheme 13**

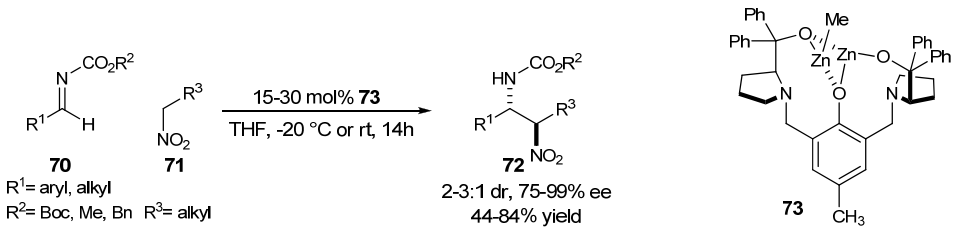



Box salts affording products in high yields and with high diastereo and enantioselectivities (Scheme 13).[40] Shortly after this work, Jørgensen reported a direct variant of this reaction in which an external base was added in addition to the chiral

[37] Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980.
[38] Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511.
[39] Tsuritani, N. Y. K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, *31*, 276.
[40] Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.

Cu(II) Box catalyst. The base allowed the use of nitroalkanes as nucleophiles instead of preforming the nitronates. As in the previous case, the conversion and stereoselection were excellent.[41] A recent example by Trost exemplifies the effectiveness of a dinuclear zinc complex in catalyzing aza-Henry reactions with good enantioselectivity albeit with low diastereoselection (Scheme 14).[42]

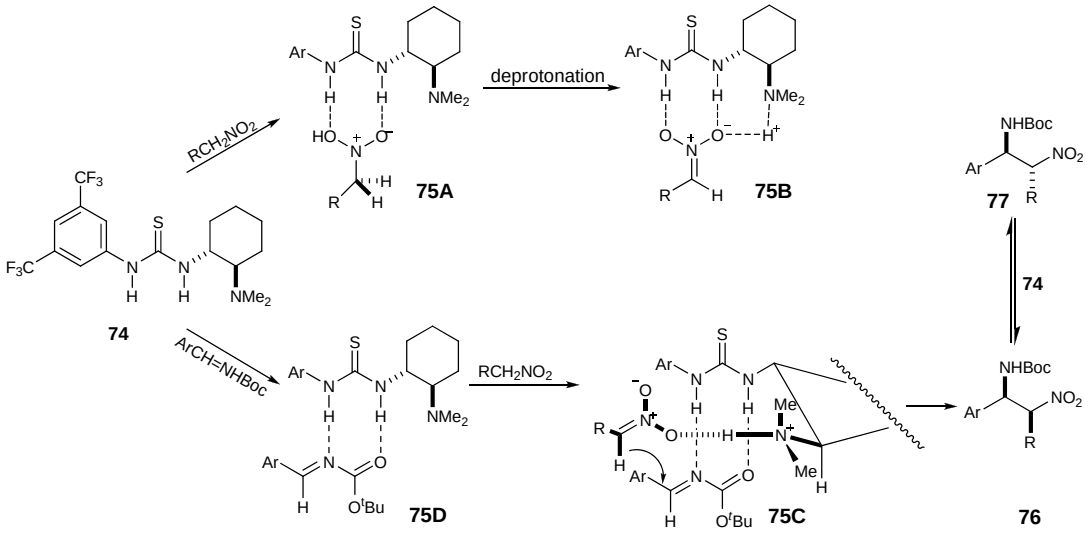
**Scheme 14**




Various organocatalytic variants of the aza-Henry reaction have been reported.[43,44] Takemoto published an enantioselective aza-Henry reaction catalyzed by a bifunctional organocatalyst (**74**). The reaction yielded products in good yield and up to 76% ee.[45] A few years later, Takemoto reported improved results for the same transformation when *N*-Boc imines were used as substrates. To account for the stereoselectivity, the authors proposed the formation of a ternary complex between the catalyst, imine and the nitronate (formed by deprotonation of the nitroalkane by the catalyst). Thus, the catalyst activates both the imine and the nucleophile and also orients them in a way that leads to the observed stereoselectivity (Scheme 15).

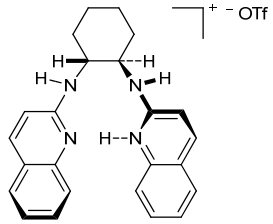
[41] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992.
[42] Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023.
[43] Sgarzani, V.; Ricci, A.; Herrera, R. P; Fini, F.; Bernardi, L. *Tetrahedron*, **2006**, *62*, 375.
[44] Ricci, A.; Fochi, M.; Franchini, M. C.; Dessole, G.; Capito, E.; Bonini, B. F.; Bernardi, L. *J. Org. Chem.* **2004**, *69*, 8168.
[45] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.

**Scheme 15.** Proposed Modes of Activation for the Thiourea Catalyzed aza-Henry Reaction




As illustrated in Figure 7, Johnston and co-workers have reported a "chiral

**Figure 7.** Chiral Proton Catalyst Reported by Johnston



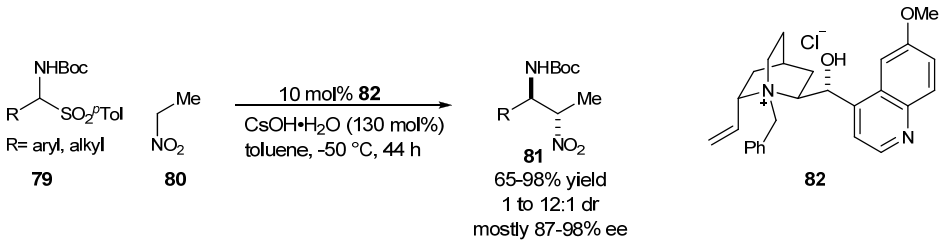

**78**
H,Quin-BAM•HOTf

proton" catalyzed aza-Henry reaction.[46] The corresponding products were obtained with high diastereo- and enantioselectivity. Although a stereochemical model has not been proposed yet, it was stated that initial experiments indicate that the proton plays a key role in both substrate activation and orientation, leading to asymmetric induction.

[46] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

A phase-transfer catalyst has been developed by Palomo which utilizes the combination of a cinchona alkaloid based catalyst and an exogenous base (CsOH). In contrast to earlier examples which used imine as the substrate, Palomo uses an α-amido sulfone which forms the amine *in situ*.[47] Hence, this method constitutes a two step, one-pot transformation. The circumvention of the imine forming step as a discreet reaction

**Scheme 16**



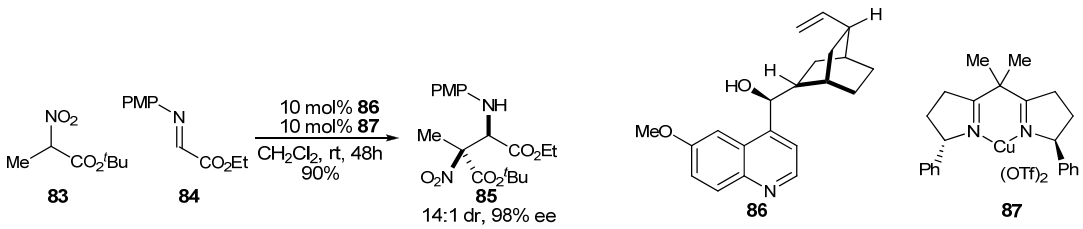

and the use of bench stable[48] α-amido sulfones provide two practical advantages over the conventional strategy. *N*-Boc imines derived from aliphatic and aromatic aldehydes provided adducts with high ee and low to good dr.

Prior to our efforts to apply the aza-Henry reaction to the synthesis of unnatural α,β-diamino acids, only two reports in the literature described the use of α-nitroacetates in enantioselective reactions.[49,50] Jorgensen described the use of a copper-Box catalyst in tandem with a chincona alkaloid base to effect the addition of α-methyl nitroacetate to glyoxyl imine in good dr and ee. However, only one example was provided in their report. The role of the copper complex was to activate the electrophile, and the exogenous base catalyst was used to activate the nucleophile.

---

[47] Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc* **2008**, *130*, 7955.
[48] Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.
[49] Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed.* **2005**, *44,* 105.
[50] Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.

**Scheme 17**




Since our work in this area, many reports have been published describing the use of nitroacetates (including α-substituted derivatives) in enantioselective aza-Henry reactions. These will be discussed in Chapters 3 and 4.

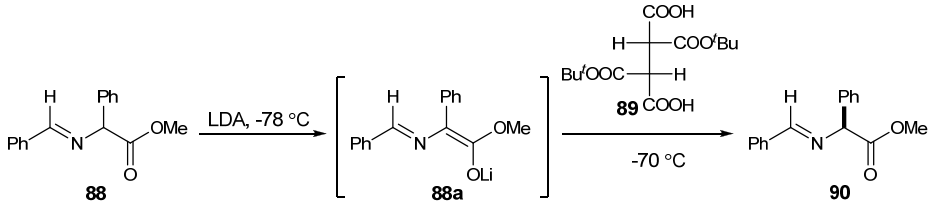
### *1.3 Asymmetric Brønsted Acid Catalysis*

The use of protic acids in asymmetric catalysis has received much attention in recent years. The interest in such organic protic acids arises from their ability to accelerate reactions and induce asymmetry without the use of metals that are often expensive and toxic. Brønsted acids have been known to catalyze many reactions but their use in asymmetric catalysis is fairly recent. The rapid developments in this area reflect the increased appreciation of the potential impact of this concept.

In 1977, Duhamel reported the enantioselective protonation of lithium enolate **88a** using the chiral Brønsted acid **89** (Scheme 18).[51] Although asymmetric protonations have been the subject of many studies, the focus of this work will be Brønsted acid *catalyzed* reactions. Hydrogen bonding has been utilized to effect several asymmetric transformations. While some of these reactions use hydrogen bonding only as a secondary control element, there are several new reports describing the use of hydrogen bonds as a primary source of asymmetric induction.

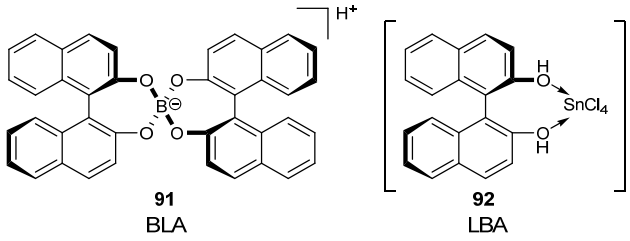
[51] (a) Duhamel, L.; Plaquevent, J. *Tetrahedron Lett.* **1977**, *26*, 2285-2288. (b) Duhamel, L; Plaquevent, J. *J. Am. Chem. Soc.* **1978**, *100*, 7415.

**Scheme 18**




The concept of Brønsted acid "assisted" catalysis was pioneered by Yamamoto in mid-1990's when he employed Lewis acid assisted chiral Brønsted acids (LBA) to effect enantioselective transformations (Figure 8). This work was a complement to his earlier work in which he employed Brønsted acid assisted chiral Lewis acids (BLA). The two complexes demonstrate the different ways in which hydrogen bonding is used in conjunction with Lewis acid activation. In the case of BLA, the chiral Lewis acid is responsible for the activation of the substrate and the selectivity while the Brønsted acid

**Figure 8.** BLA and LBA Complexes Developed by Yamamoto

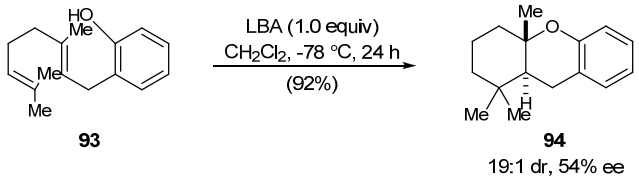



acts as a secondary control element. In contrast, an LBA activates the substrate through the Brønsted acid, while the Lewis acid serves only as a means by which the Brønsted acid is activated. The LBA concept was used by Yamamoto to develop biomimetic polyprenoid cyclizations. Using this methodology, polycyclic terpenoids were constructed stereoselectively in a single step (Scheme 19).[52] This work was extended to

[52] Ishihara, K,; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.

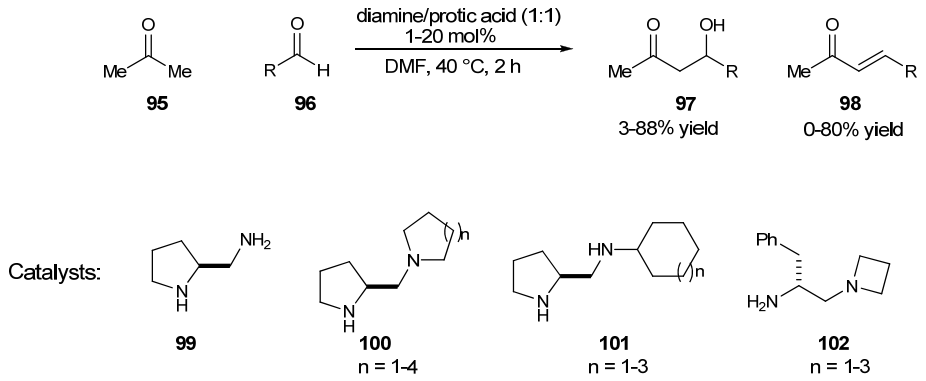
achieve elegant syntheses of various naturally occurring targets with excellent enantioselection.[53]

**Scheme 19**




In 2001, Yamamoto and co-workers described the development and use of protic

**Scheme 20**



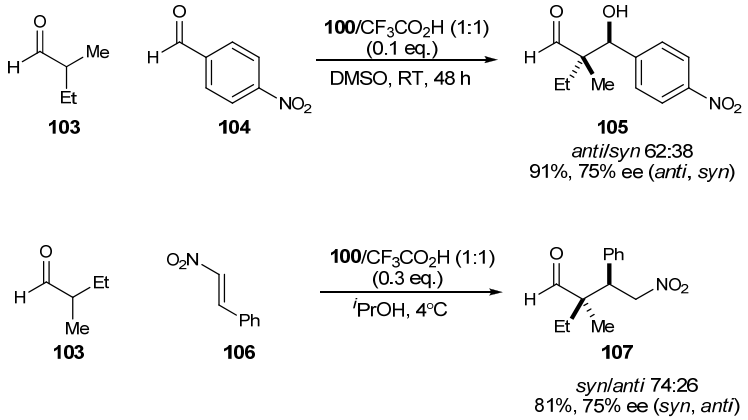

acid-diamine catalysts for the direct asymmetric aldol reaction between acetone and some aromatic and aliphatic aldehydes (Scheme 20).[54] The authors suggest that the catalyst plays two roles: a) increase the rate of enamine formation, and b) orient the substrates by hydrogen bonding.

Barbas and co-workers described an efficient asymmetric aldol reaction using the trifluoroacetate salt of the diamine **100**. They were able to generate β-hydroxy aldehydes

[53] (a) Ishihara, K,; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (b) Nakamura, S.; Ishihara, K,; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (c) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (d) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Chem. Rec.* **2002**, 177. (e) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551.
[54] Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett*, **2001**.

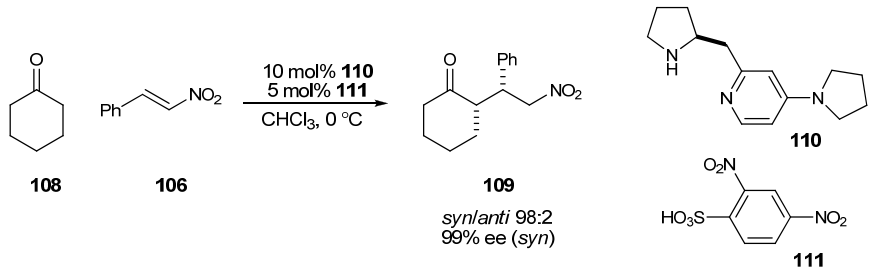
with quaternary stereogenic carbon centers by the use of α,α-disubstituted aldehydes as aldol donors (Scheme 21).[55] The same catalyst was also effective in the direct asymmetric Michael reaction between α,α-disubstituted aldehydes and β-nitrostyrene (Scheme 21).[56]

**Scheme 21**




The direct asymmetric Michael reaction was also studied by Kotsuki and co-

**Scheme 22**



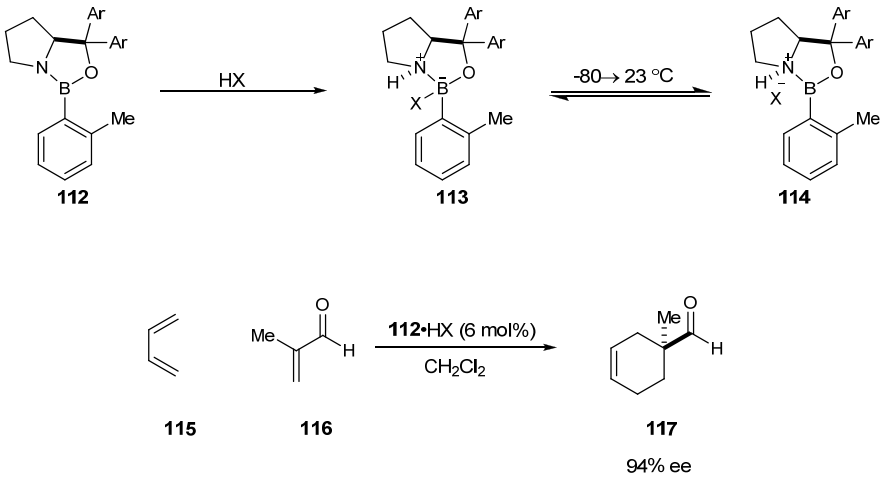

workers, who employed cyclohexanone as the Michael donor with β-nitro olefin acceptors.[57] Excellent diastereoselectivity and enantioselectivity was achieved by

[55] Mase, N.; Tanaka, F.; Barbas, C.F. *Angew. Chem. Int. Ed.* **2004**, *43* 2420.
[56] Mase, N.; Thayumanavan, F.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2004**, *6*, 2527.
[57] Takaaki, I.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.

employing a catalyst which was a pyrrolidine-pyridine base in combination with a protic acid (Scheme 22).

A slightly different type of Brønsted acid catalyst was used by Corey and co-workers to catalyze Diels-Alder reactions with high enantioselectivities.[58] The catalyst was derived from protonated oxazaborolidines of type **113**. Treatment of **112** with anhydrous TfOH led to the formation of the protonated species **113** which exists in equilibrium with **114,** which was understood to be highly Lewis acidic at the boron owing to its cationic character. α,β-Unsaturated carbonyl compounds were found to be

**Scheme 23**



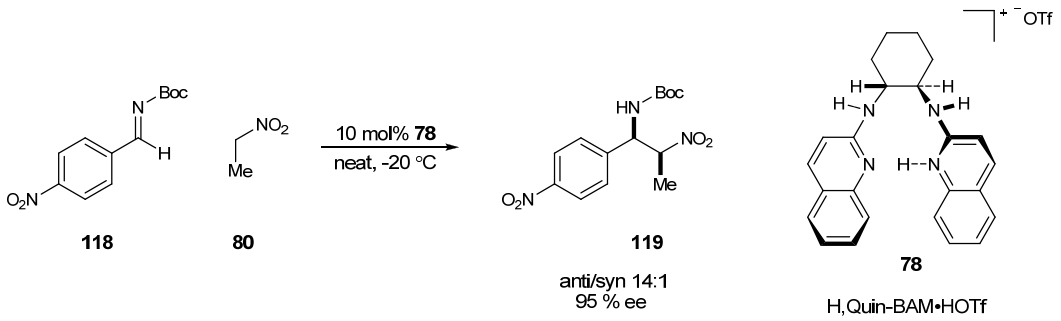

efficiently activated by such protonated oxazaborolidines to react even with unreactive dienes such as butadiene to afford adducts with high enantioselectivities (Scheme 23). In all the cases mentioned to this point, hydrogen bonding is only a secondary control element. Significant development has been made in designing catalysts which utilize

[58] (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (c) Ryu, D. H.; Corey. E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

hydrogen bonding as a primary source of asymmetric induction in addition to catalyzing the reaction.

Recently, Johnston and co-workers have reported a Bis-(AMidine) (BAM) catalyst for the highly diastereo and enantioselective aza-Henry reaction. The catalyst is a bench stable salt generated by protonating a bis(amidine) derived from a chiral diamine

**Scheme 24**




**118** **80** **119**

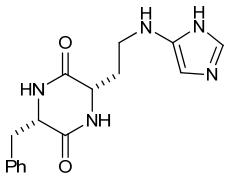
anti/syn 14:1
95 % ee

**78**

H,Quin-BAM•HOTf

using triflic acid (Scheme 24).[59] The authors believe that the coordination of the imine to the catalyst *via* hydrogen bonding is responsible for both the activation and asymmetric induction. In addition to the use of protonated amines as catalysts, various research groups have reported the application of small, neutral molecules for catalysis. In 1981,

**Figure 9.** Inoue's Dipeptide Catalyst

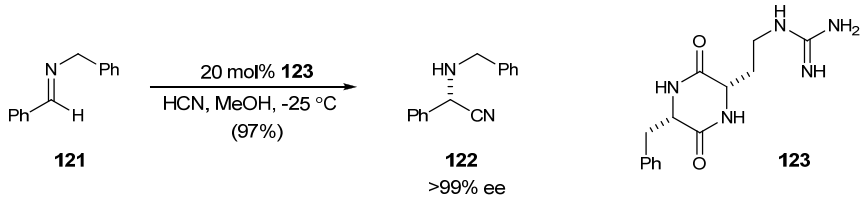



**120**

[59] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

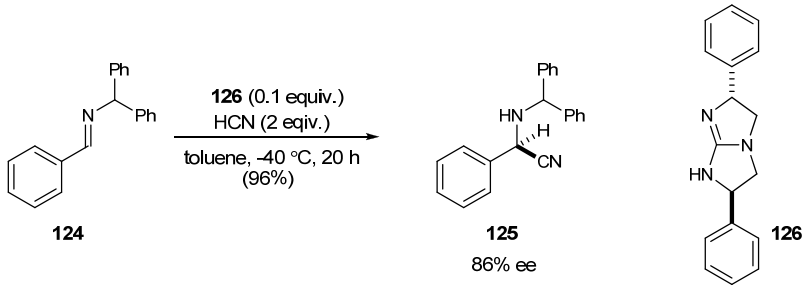
Inoue reported the catalytic asymmetric addition of hydrogen cyanide to benzaldehyde using dipeptide **120**.[60] The enantioselectivity observed for the product after 30 minutes was 90% but it was found that longer reaction times led to racemization. After Inoue's work, Lipton *et al.* reported the enantioselective Strecker reaction using dipeptide **123** as the catalyst.[61] Excellent enantioselectivities were obtained for some substrates but the reaction was not very general (Scheme 25).

**Scheme 25**




In the following years, the Strecker reaction again succumbed to enantioselective

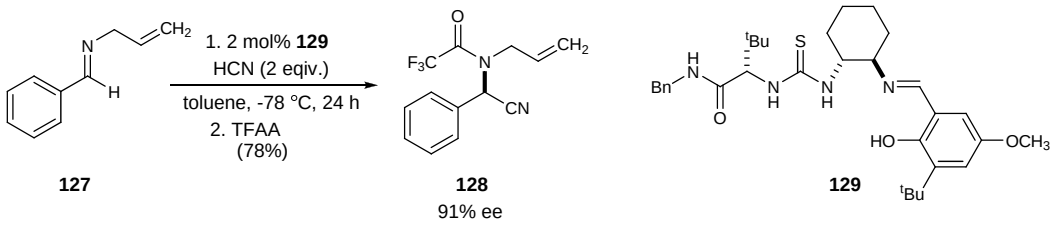
**Scheme 26**




catalysis when Corey[62] (Scheme 26) and Jacobsen[63] (Scheme 27) reported guanidine and thiourea catalysts to achieve this transformation using hydrogen bonding catalysis.

[60] (a) Oku, J.; Inoue, M. *J. Chem. Soc. Chem. Commun.* **1981**, 229. (b) Tanaka, K.; Mori, A.; Inoue, M. *J. Org. Chem.* **1990**, *55*, 181.
[61] Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910.
[62] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.
[63] (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Sigman, M.S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279.

**Scheme 27**

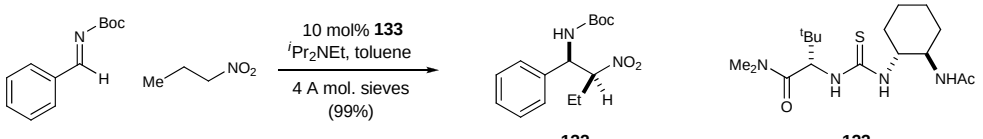



Further studies by Jacobsen and Vachal extended the scope of the catalyst **129** from aldimines to ketimines.[64] Investigation into the structural changes revealed that the thiourea moiety was critical to the activation and selectivity. These studies also led to the identification of an improved catalyst (**140**) for the Strecker reaction.[65] In the ensuing years, the use of thiourea based organocatalysts was successfully extended to many asymmetric reactions such as the Mannich reaction,[66] hydrophosphonylation,[67] acyl-Pictet-Spengler reaction,[68] nitro-Mannich reaction (Scheme 28),[69] acyl-Mannich reaction,[70] conjugate additions to nitroalkenes,[71] cyanosilylation of ketones,[72] and the aza-Baylis-Hillman reaction (Scheme 29).[73]

[64] Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.
[65] Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.
[66] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
[67] Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.
[68] Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
[69] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466.
[70] Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700.
[71] (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (b) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 6366.
[72] Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.
[73] Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.

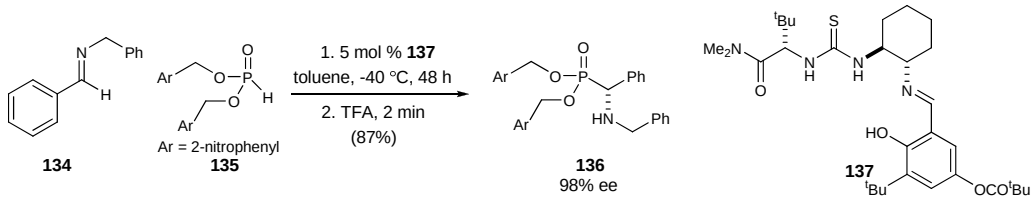
**Scheme 28**

Nitro-Mannich Reaction:



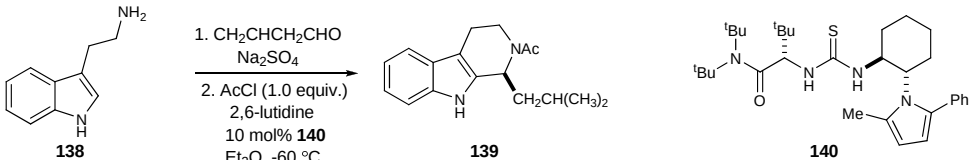

**130** **131** **132** 7:1 dr (*syn*/*anti*) 95% ee **133**

Hydrophosphonylation:



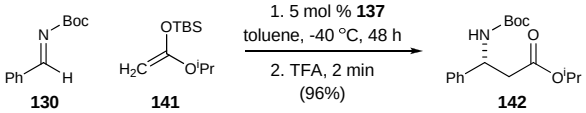

**134** **135** **136** 98% ee **137**

Acyl Pictet-Spengler Reaction:



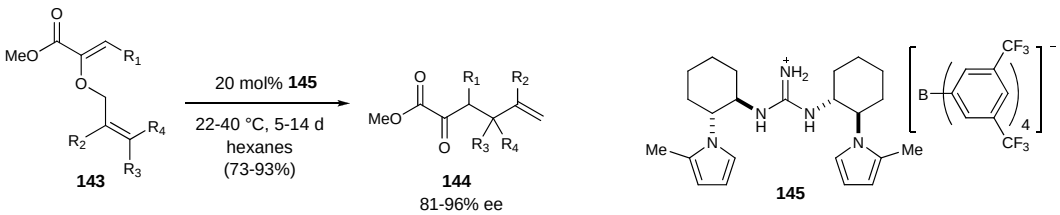

**138** **139** 95% ee **140**

Mannich Reaction:




**130** **141** **142** 97% ee

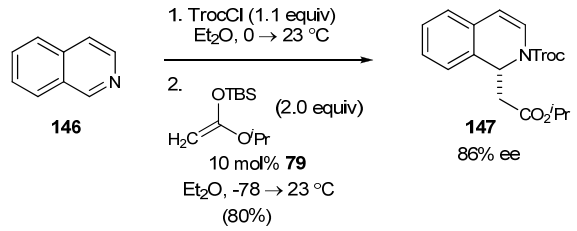
Claisen Rearrangement:




**143** **144** 81-96% ee 19 to >20:1 dr **145**

**Scheme 29**

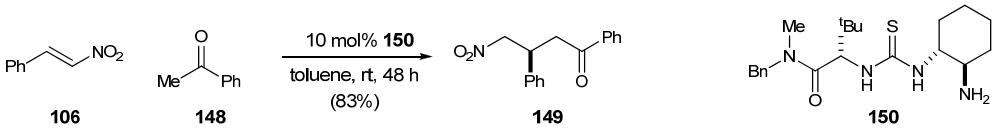
Acyl-Mannich Reaction:




**146** **147**

86% ee

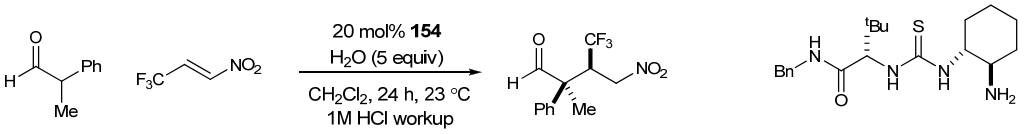
Conjugate Addition of Ketones to Nitroalkenes:




**106** **148** **149** **150**

99% ee

Conjugate Addition of α,α-disubstituted Aldehydes to Nitroalkenes:

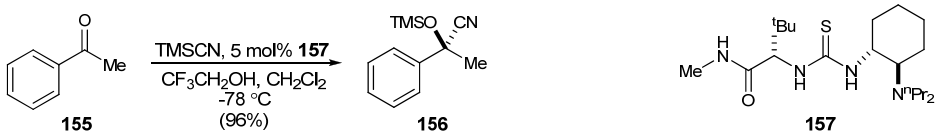



**151** **152** **153** **154**

> 50:1 dr (*syn*:*anti*)

97% ee

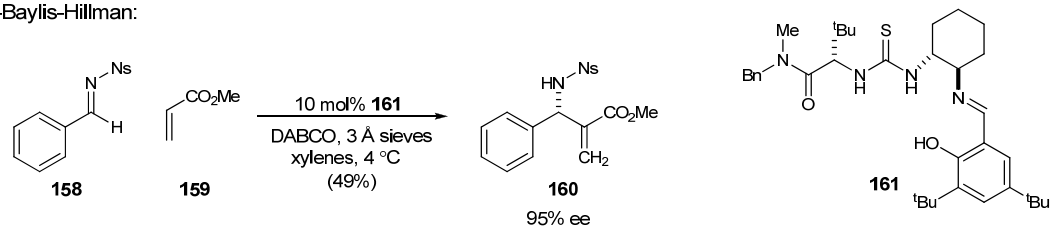
Cyanosilylation of Ketones:




**155** **156** **157**

97% ee

Aza-Baylis-Hillman:

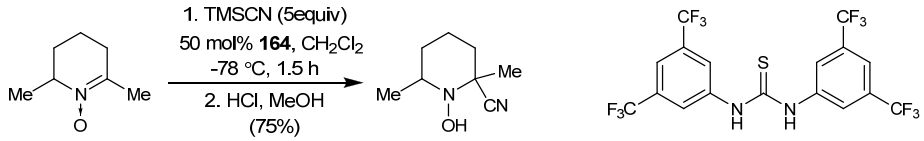



**158** **159** **160** **161**

95% ee

Shortly after Jacobsen's initial reports on the use of thioureas in asymmetric catalysis, Takemoto and co-workers reported an achiral thiourea (**164**) which was used to catalyze the addition of cyanides to nitrones (Scheme 30).[74]

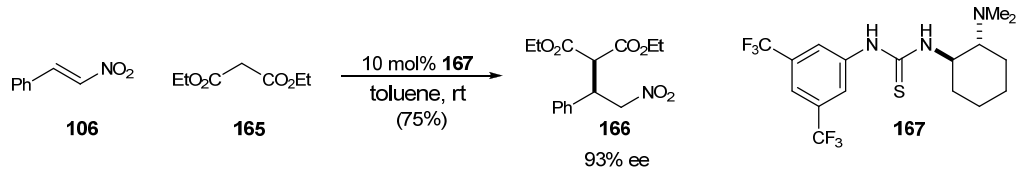
**Scheme 30**




**162** **163** **164**

Shortly thereafter, a related chiral thiourea was developed which was used effectively in the addition of malonates to nitroolefins. Good yields and high enantioselectivities were

**Scheme 31**



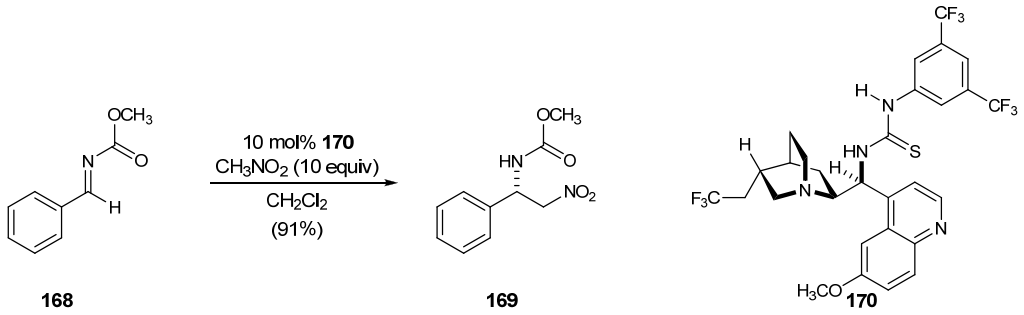

**106** **165** **166** 93% ee **167**

observed for a broad range of substrates (Scheme 31).[75] The same catalyst **167** was shown to catalyze the aza-Henry reaction. The authors suggest that the catalyst serves a bifunctional role of activating both the electrophile and the nucleophile.[76]

[74] Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817.
[75] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
[76] (a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett*. **2004**, *6*, 625. (b) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466.

Recently, Schaus has reported that a hydroquinine derived thiourea is a very

**Scheme 32**

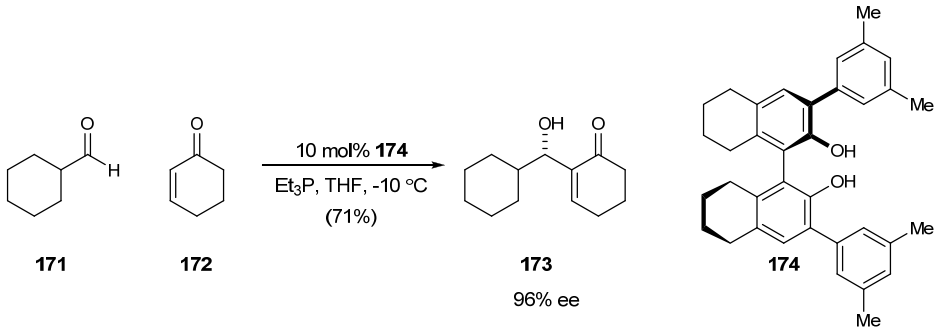



**168** **169** 93% ee **170**

effective general catalyst for the addition of stabilized nucleophiles to acyl imines. The nucleophiles studied included nitromethane, nitroethane, and dimethyl malonate (Scheme 32).[77]

Various chiral alcohols have also been used to effect asymmetric transformations. In 2003, Schaus reported an asymmetric Morita-Baylis-Hillman reaction using a chiral Brønsted acid (Scheme 33).[78]

**Scheme 33**

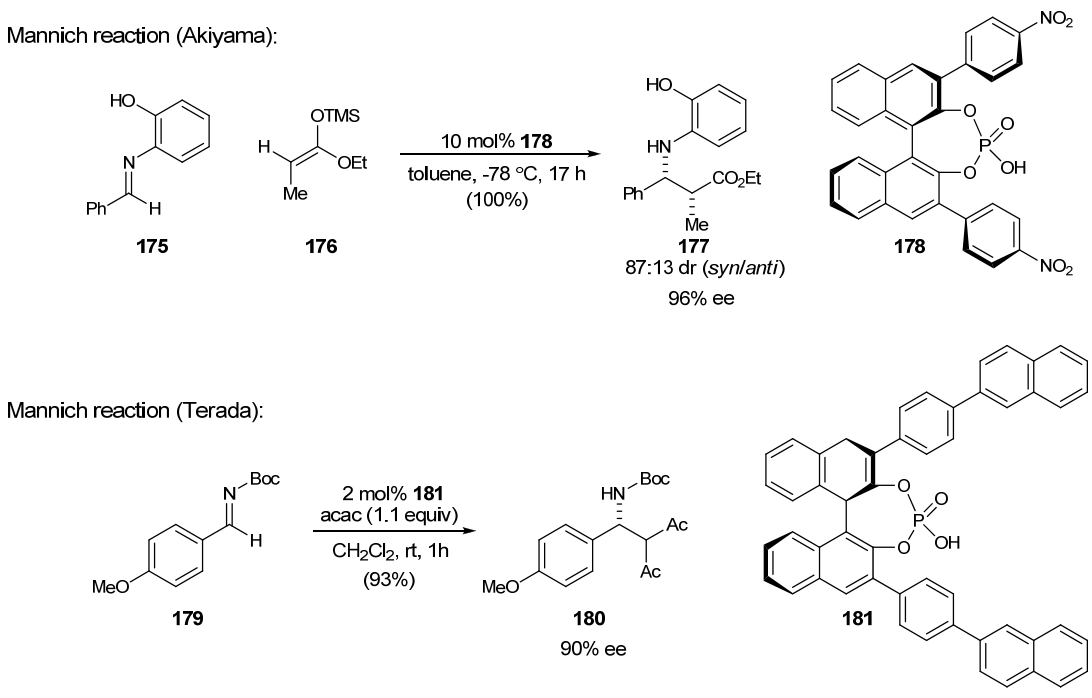



**171** **172** **173** 96% ee **174**

[77] Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499.
[78] (a) McDougal, N. T.; Schaus, S. E.; *J. Am. Chem. Soc.* **2003**, *125*, 12094. (b) McDougal, N. T.; Travellini, W.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231.

A novel phosphoric acid catalyst derived from the BINOL framework was discovered independently by Akiyama[79] and Terada[80] in 2004 (Scheme 34). In contrast to the other Brønsted acid catalysts mentioned herein, their catalysts are more acidic.

**Scheme 34**

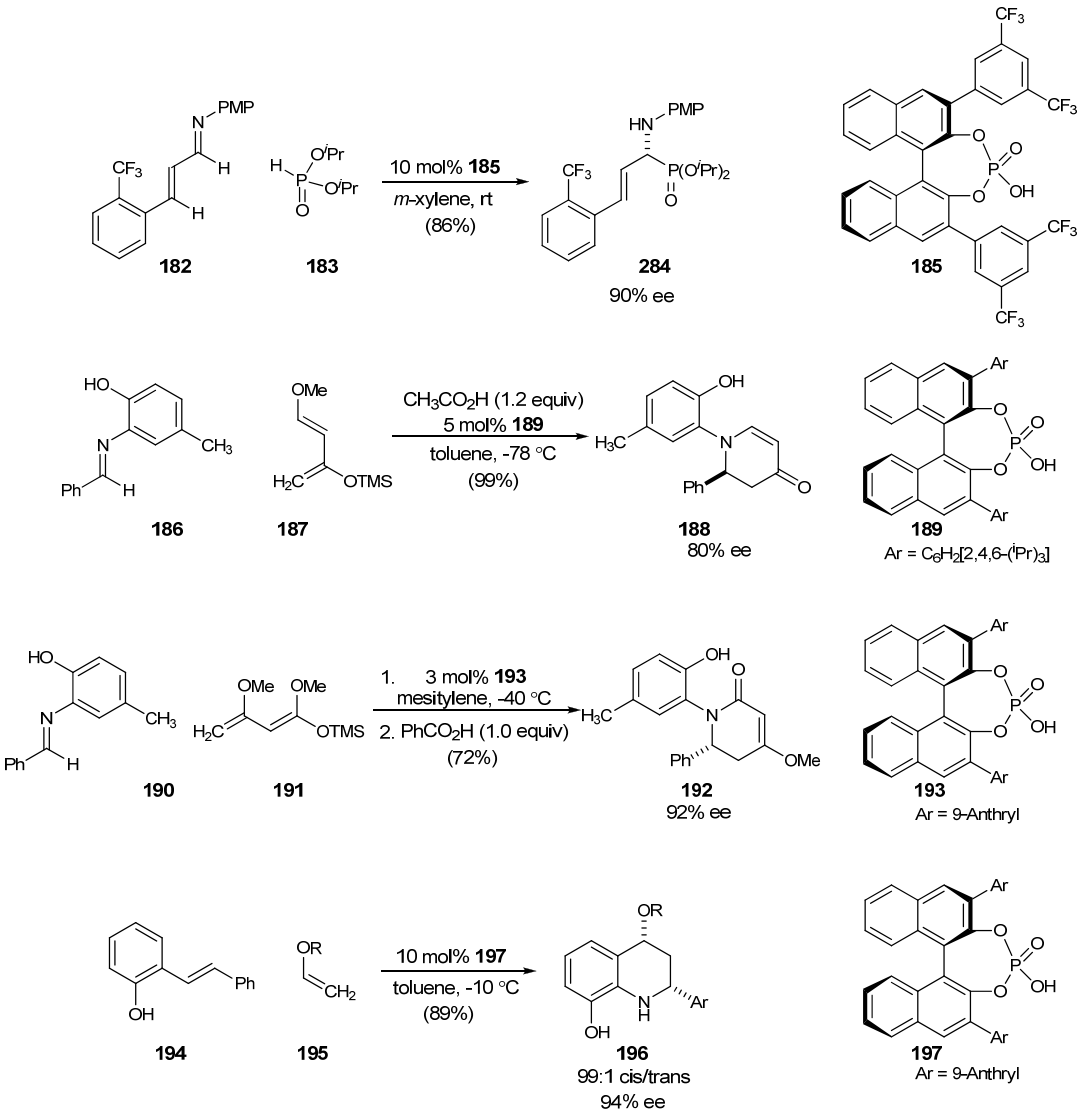



[79] Akiyama, T.; Itoh, J.; Yokata, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
[80] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

In the following years, Akiyama was able to extend the use of the chiral phosphoric acid catalysts to phosphonylation and Diels-Alder reactions by making minor structural changes (Scheme 35).[81]

[81] (a) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, *1*, 141. (b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796. (c) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (c) Akiyama, T, Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth Catal.* **2005**, *347*, 1523.

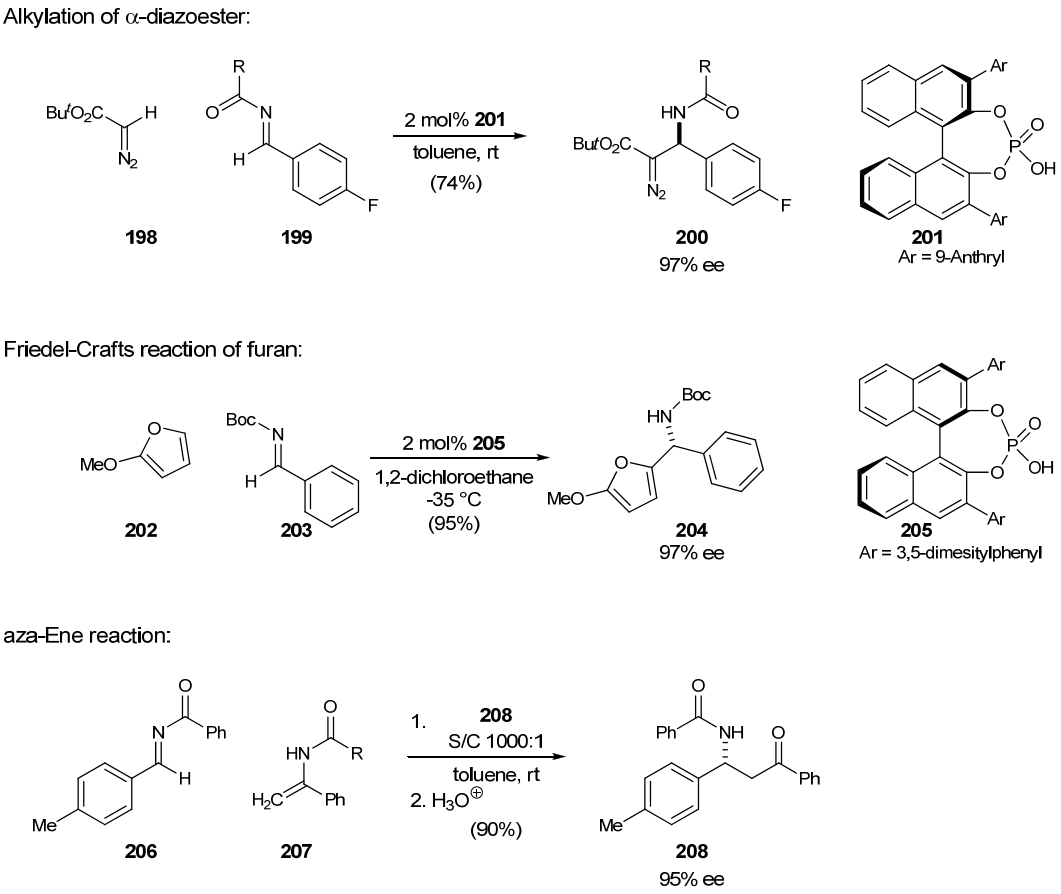
**Scheme 35**




Terada was also able to apply these phosphoric acid derived catalysts to various asymmetric transformations (Scheme 36).[82]

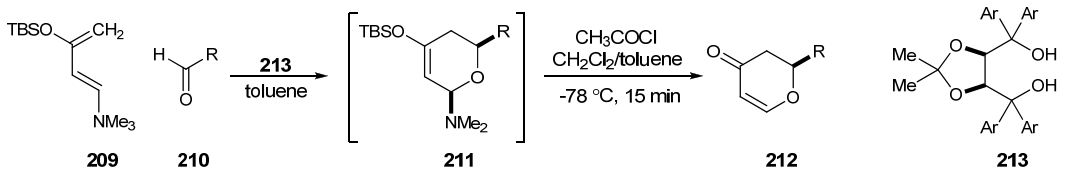
[82] (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (c) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2254.

**Scheme 36**




In 2003, Rawal and co-workers developed a class of chiral diols (TADDOL) which catalyzed hetero Diels-Alder reactions with excellent enantioselection (Scheme 37).[83] Rawal has extended the use of these TADDOL catalysts to Mukaiyama aldol reactions yielding products with good diastereo- and enantioselection.[84]

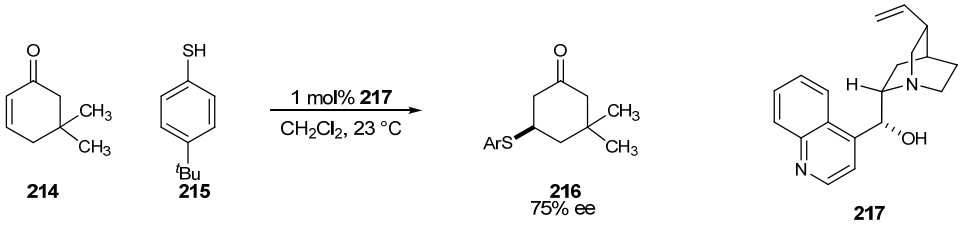
**Scheme 37**




[83] Huang, Y.; Unni, K.; Thadani, A. N.; Rawal, V. H. *Nature*, **2003**, *424*, 146.

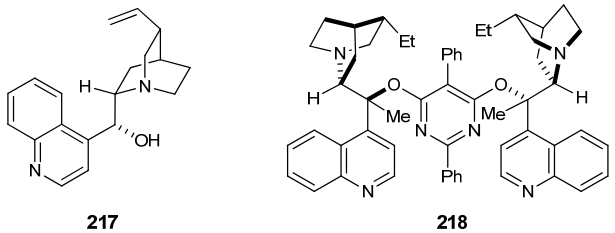
Cinchona alkaloids and their derivatives have also been established as effective Brønsted acid catalysts. In cases where a hydrogen bond donor group is not likely to be directly involved in stereoselection, a more appropriate term might be "hydrogen bond

**Scheme 38**




assisted" catalysis.[85,86] Pioneering work by Wynberg in 1981 established the efficacy of chinchona alkaloids with a free hydroxyl group in catalyzing enantioselective 1,2- and 1,4-additions to enones. The free hydroxyl group was indispensable for high enantioselection (Scheme 38). Further advancement of this class of catalysts was not made until much later when Deng published his work involving an unnatural cinchona alkaloid derivative for the same conjugate addition pioneered by Wynberg. It was reported that a free hydroxyl group was not necessary in this case and the bisalkaloid catalyst derived from the same enantiomer of the natural alkaloid provided opposite enantioselection. Hence, the mode of stereoinduction is different for these two catalysts.

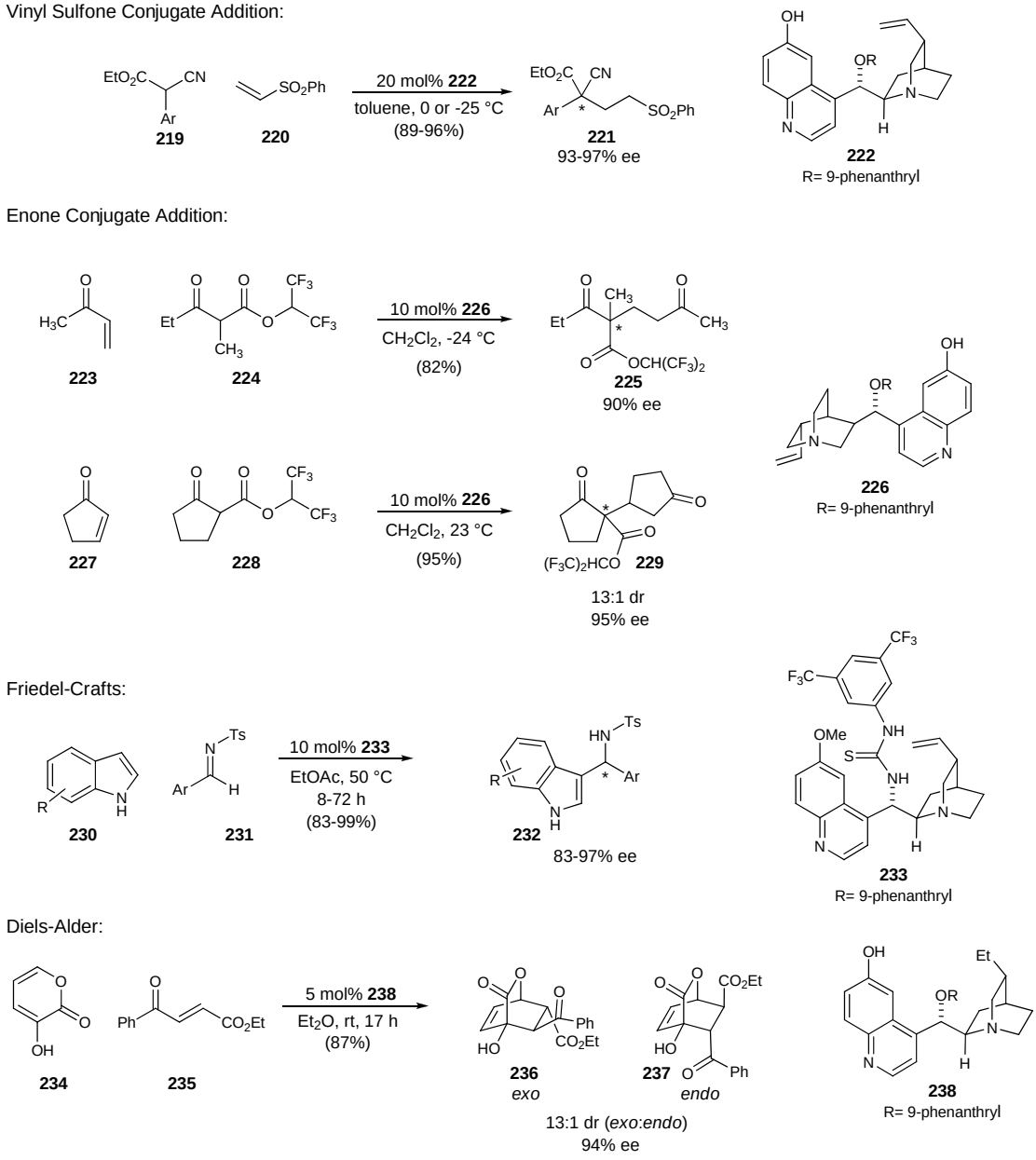
**Figure 10.** Hydrogen Bond Assisted Catalysis by Chinchona Alkaloid Derivatives




[84] (a) McGilvra, J. D.; Unni, A. K, Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130. (b) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5657.

Deng has demonstrated the use of these cinchona derived catalysts for many other enantioselective reactions such as conjugate additions to vinyl sulfones[85], enone

**Scheme 39**




[85] Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.

conjugate additions[86], the Friedel-Crafts reaction between imine and indoles[87], and Diels-Alder reaction between pyrones and α,β-unsaturated esters (Scheme 39).[88]

The following chapters will describe the design and development of a new class of Brønsted acid catalysts and their use in the enantioselective synthesis of diamines and diamino acids employing different variants of the aza-Henry reaction.

[86] Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 947.
[87] Wang, Y. Q; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.
[88] Wang, Y.; Li, H.; Wang, Y. Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364.

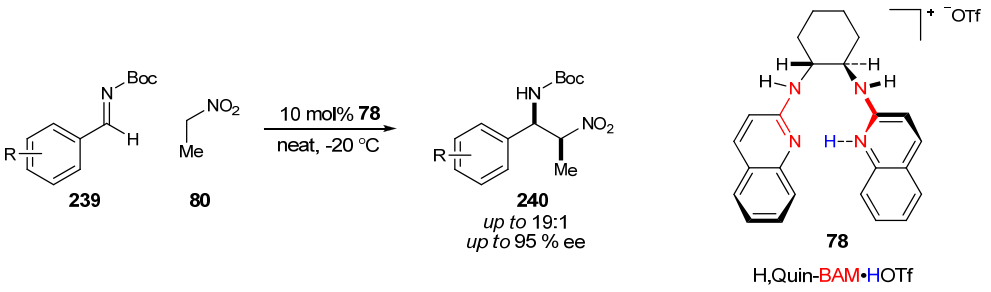
## *CHAPTER II*

# *CHIRAL PROTON CATALYZED ENANTIOSELECTIVE SILYL NITRONATE ADDITIONS TO AZOMETHINES: DEVELOPMENT OF A STEREOCHEMICAL MODEL FOR THE IONIC HYDROGEN BOND MEDIATED TRANSFER OF ASYMMETRY*

### *2.1 Chiral Proton Catalyzed Direct aza-Henry Reaction: Concepts and Previous Developments*

In 2004, the Johnston group reported the application of a chiral proton catalyst in performing a diastereo- and enantioselective aza-Henry reaction.[89] The bis(amidine) catalyst **78** was shown to be bifunctional in nature wherein it was responsible for activation of the nucleophile (deprotonation of nitroalkane) and the activation of the

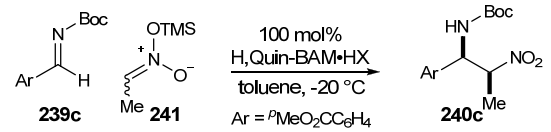
**Scheme 40**




electrophile (imine). That imine activation was operative followed from a series of experiments in which catalyst counterion was varied, with the most dissociated counterions ($SbF_6$, OTf) exhibiting the highest enantioselectivity (Table 1). It was also the first example of the use of polar-ionic hydrogen bonds in asymmetric catalysis. Scheme 41 illustrates the conceptual differences between polar-ionic and polar-covalent hydrogen bonding. As a design element, polar-ionic hydrogen bonds may offer greater

[89] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *65*, 212.

**Table 1.** Chiral Proton Catalyzed Additions of Silyl Nitronates to Imines: Effect of Ligand Counterion

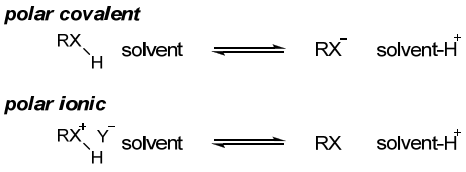



| entry | $X^-$ | dr[b] | %ee[b] | %yield |
|---|---|---|---|---|
| 1 | $CH_3CO_2$ | 10:1 | 71 | 34 |
| 2 | $CF_3CO_2$ | 10:1 | 73 | 43 |
| 3 | $TolSO_3$ | 12:1 | 79 | 43 |
| 4 | Cl | 8:1 | 33 | 30 |
| 5 | $BF_4$ | 18:1 | ***92*** | 64 |
| ***6*** | ***TfO*** | 17:1 | ***87*** | ***99*** |
| 7 | $PF_6$ | 9:1 | 57 | 64 |
| 8 | $SbF_6$ | 16:1 | 88 | 67 |

[a]All reactions were 0.25 M in substrate and proceeded to complete conversion. [b]Diastereomer ratios were measured by GC. Enantiomer ratios were measured using chiral stationary phase HPLC.

ability to activate electrophiles due to their charged nature. Additionally, they provide the flexibility of changing the counterion as a means to alter/improve stereoselection and modulate Lewis acidity.

**Scheme 41**




The determination of the $pK_a$ for BAM•HOTf complexes established that they did not possess enhanced basicity relative to their component functionality (as opposed to proton sponge) but their behavior as enantioselective catalysts indicates that the proton remains bound to the ligand throughout the reaction (sequestering of proton by an achiral base such as solvent would lead to a drop in enantioselection).[90]

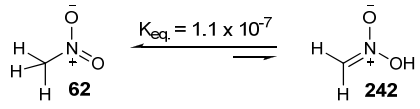
An understanding of proton coordination chemistry is the first step in the rational design of new enantioselective reactions based on inexpensive acid complexes, and might

[90] Hess, A. B.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**, *1*, 147.

ultimately reveal the extent to which peptide structural and stereochemical complexity is un/necessary during enzyme or antibody-catalyzed enantioselective chemical reactions. Towards this goal, we undertook an effort to generalize the reaction through systematic study of ligand structure on enantioselectivity, paying attention to particular variants that would provide insight into mechanism. We were motivated by the desire to uncover details that would be directly relevant in solving reactivity/selectivity problems encountered while developing a new reaction. Among the most pertinent questions was spatial relationship between reactants and catalyst during the carbon-carbon bond forming, enantioselective step.

The direct aza-Henry reaction in Scheme 40 proceeds without the addition of exogenous base which implies that H,Quin-BAM•HOTf was responsible for deprotonation of the pronucleophile to generate the nitronate. In the absence of any base, the nitroalkane is in equilibrium with its tautomer but this equilibrium lies overwhelmingly towards the nitroalkane ($K_{eq.}$ = 1.1x $10^{-7}$).[91] As a result, the concentration of the active nucleophile is too low (less than 0.1 equiv.) to afford any appreciable reactivity. A control experiment revealed that this was indeed the case and the uncatalyzed reaction did not provide any product over several days. It was also established that the free ligand afforded product with low enantioselection as does the addition of an exogenous base to experiments otherwise identical to Scheme 40.

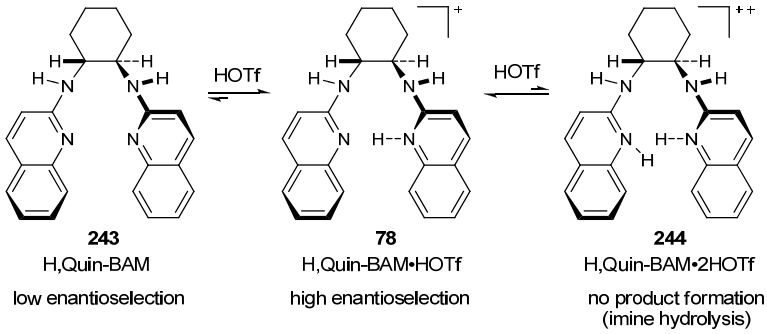
**Scheme 42**




[91] Turnbull, D.; Maron, S.H. *J. Am. Chem. Soc.* **1943**, *65*, 212.

The fact that the proton was indispensable for high enantioselection insinuates that the activation of the imine occurs by hydrogen bonding with the catalyst proton. The above data suggests that catalysis by H,Quin-BAM•HOTf is bifunctional[92] in nature and is made possible by the catalyst's ability to generate the active nucleophile by deprotonating the nitroalkane *and* activating the imine electrophile. A limited protonation state study revealed that H,Quin-BAM free base provided low enantioselection (~10% ee) while the monoprotonated salt afforded adducts with high enantioselection (88% ee). The application of the diprotonated salt resulted in the hydrolysis of the imine and no aza-Henry product was formed.

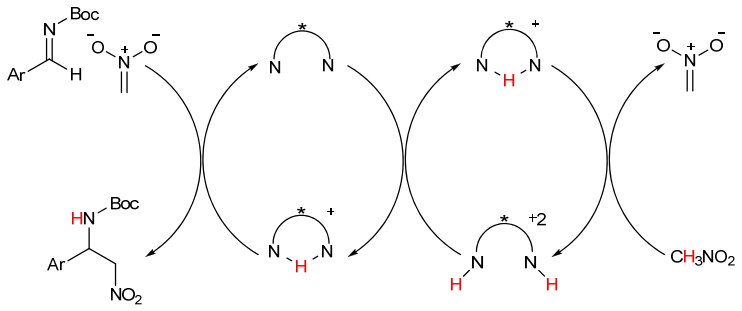
**Scheme 43**




The catalytic cycle shown below depicts the critical steps in the reaction (deprotonation of niroalkane and activation of imine) and also illustrates the possibility that a second molecule of the catalyst might participate as a base to activate (and deliver) the nitronate. In order to deconvolute these orthogonal catalyst roles, we considered first methods to investigate the nature of Lewis acid and imine activation. It leads us to the next task which is to ascertain the identity of the enantio-determining step.

[92] For examples from non-organocatalytic systems see: Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 1924. Ma, J. A.; Cahard, D.; *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 4566. France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.*, **2004**, *37*, 592. Gröger, H. *Chem. Eur. J.* **2001**, *7*, 5247.

**Figure 11.** Catalytic Cycle for the Chiral Proton Catalyzed Aza-Henry Reaction

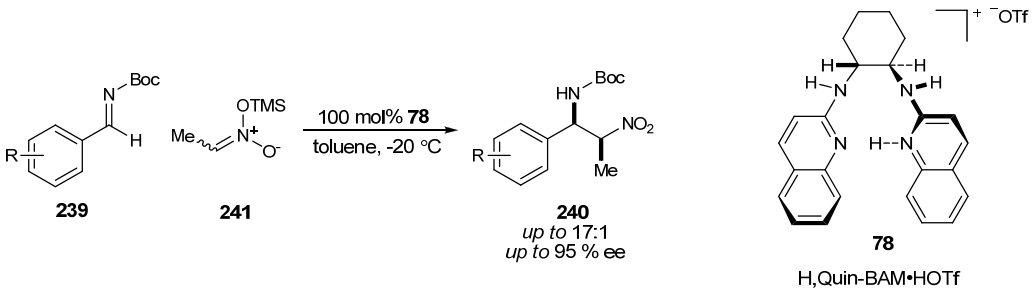



### *2.2 Design of Experiment to Elucidate Enantiosetermining Step: Silyl Nitronate Additions to N-Boc Imines*

Mechanistically, an enantioselective reaction between an electrophile and a nucleophile can be effected either by the intermediacy of a chiral electrophile, chiral nucleophile or both. The understanding of the origin of stereoselection is the first step to the application of this mode of catalysis to broader problems of interest. The bifunctional nature of BAM•HOTf complexes implicate the involvement of the chiral, non-racemic catalyst in two fundamental steps and in order to ascertain which of these steps is enantiodetermining, it was necessary to design an experiment which separates these two functions of the catalyst without changing the reaction dynamics to a large extent. To reduce the reaction to only a lewis acid activation phenomenon, a preformed nitronate could be used. Since deprotonation is no longer required, any enantioselection would be the result of the Brønsted acid activation of the imine. Analogous to the direct aza-Henry reaction reported by the Johnston group, it was discovered that H,Quin-BAM•HOTf also catalyzed the addition of preformed silyl nitronates to *N*-Boc imines (Scheme 44). It was contemplated that a comparative study between the nitroalkane nucleophile and the corresponding silyl nitronate could provide the basis for constructing a stereochemical model for this type of catalysis. If the addition of silyl nitronate (the indirect aza-Henry

reaction) provided similar levels of enantio- and distereoselection as the direct aza-Henry reaction, it would point to the possibility that a common aspect of the two reactions is activation of the imine and that it is also the enantiodetermining step in *both* of these reactions. The pursuit of a stereochemical model was fueled by a desire for the knowledge that would allow us to determine (and synthesize) more effective ligands as per the demands of the reaction being attempted.

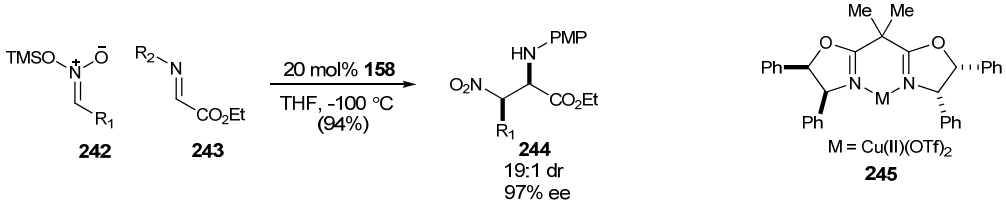
**Scheme 44**




### *2.3 Enantioselective Silyl Nitronate Additions in the Literature*

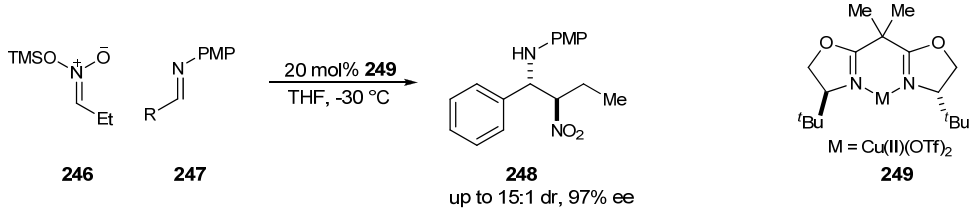
The first enantioselective addition of silyl nitronate to imino-esters was reported by Jørgensen in 2001. High enantio- and diastereoselectivities were realized by the use of Cu(II)-Box catalysts.

**Scheme 45**



The second and more general addition of silyl nitronates was accomplished by Anderson and co-workers who were able to use a wide variety of PMP protected imines to yield adducts with high dr and enantioselection. A commercially available Box-ligand was found to be most effective, with $Cu(OTf)_2$ as the best copper salt.

**Scheme 46**



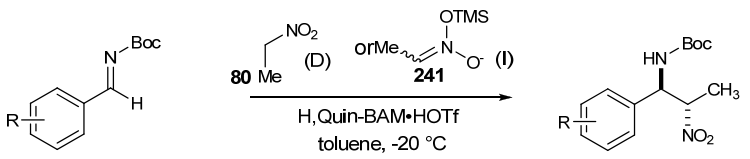

**246** **247** **248** **249**

up to 15:1 dr, 97% ee

### *2.4 Results and Discussion*

It was observed that the addition of silyl nitronates to imines is much faster than the addition of their nitroalkane counterparts. There was a significant background reaction which mandated the use of a full equivalent of the catalyst in order to obtain high enantioselection. As explained in section 2.1.1, in order to determine the enantiodetermining step, a comparative study was performed using the two nucleophiles and the same imine. Table 2 shows the results of this study.

**Table 2.** Comparison of Chiral Proton Catalyzed Direct and Indirect aza-Henry Reaction: Comparison of Substrates




239c 240c

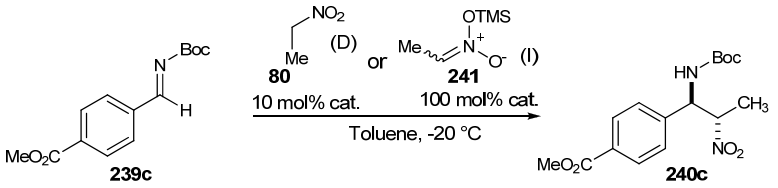
| entry | R | | catalyst (mol%) | D/I | dr[a] | %ee[b] | yield[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | $^{p}$Cl | **a** | 10 | D | 18:1 | 78 | 71 |
| 2 | $^{p}$Cl | **a** | 100 | D | 12:1 | 84 | 76 |
| 3 | $^{p}$Cl | **a** | 100 | I | 14:1 | 95 | 82 |
| 4 | H | **b** | 10 | D | 17:1 | 78 | 65 |
| 5 | H | **b** | 100 | I | 17:1 | 93 | 71 |
| 6 | $^{p}CO_2Me$ | **c** | 10 | D | 19:1 | 86 | 81 |
| 7 | $^{p}CO_2Me$ | **c** | 100 | I | 14:1 | 88 | 86 |

[a]Diastereomeric ratios determined by GC. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after chromatography.

Entries 1 and 3 indicate that the direct and indirect cases afford enantioselectivities within 15% of each other under slightly different reaction conditions (optimized for each case). Since the indirect aza-henry reaction has a significant background rate, one equivalent of the catalyst has to be employed in order to maintain high enantioselection. In an attempt to bridge the gap between reaction conditions, we performed the direct aza-Henry reaction with one equivalent of catalyst and discovered that the enantioselection increases thereby closing the gap with the silyl nitronate addition (entry 2). In order to establish the generality of this trend, we performed the comparison with two additional imines **239a** and **239b**. It was found that the trend extended to these imines as well affording products with similar diastereo- and enantioselection for the direct and indirect aza-Henry reactions. The close correlation in stereoselection between the direct and indirect aza-Henry reactions led us to hypothesize a common mode of stereoinduction/stereochemical model. These observations suggest that the enantiodetermining step is same in both these reactions. Furthermore, since there is no deprotonation involved when the silyl nitronate is used as the nucleophile, the enantiodetermining step is solely Lewis acid activation of

the imine by the catalyst. The following table illustrates that this trend also extends to catalysts other than H,Quin-BAM•HOTf. Although the enantioselection provided by H,$^{6}$Me-BAM•HOTf is lower than that afforded by H,Quin-BAM•HOTf, a similar trend is revealed in which the indirect aza-Henry reaction affords slightly higher enantioselection compared to the direct case (Table 3).

**Table 3.** Comparison of Direct and Indirect aza-Henry Reaction Catalyzed by Chiral Proton Catalysts

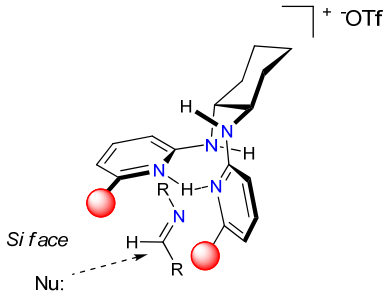



| entry | catalyst | D/I | dr[a] | %ee[b] | yield[c](%) |
|---|---|---|---|---|---|
| 1 | H,Quin-BAM•HOTf | D | 20:1 | 86 | 81 |
| 2 | H,Quin-BAM•HOTf | I | 14:1 | 88 | 86 |
| 3 | H,6-Me-BAM•HOTf | D | 13:1 | 52 | 74 |
| 4 | H,6-Me-BAM•HOTf | I | 12:1 | 70 | 77 |

[a]Diastereomeric ratios determined by GC. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after chromatography.

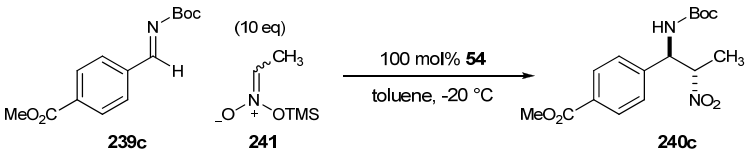
In a study designed to understand key structural elements important to enantioselection, it was initially hypothesized and later shown experimentally that the

**Figure 12.** Bidentate Proton Chelation and 6-Substitued Pyridines as Key Elements for Stereocontrol



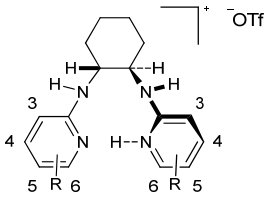
substitution at the 6-position of the pyridine ring is vital for obtaining azomethine facial selectivity (Table 4).

**Table 4.** Effect of Substitution on the 6-Position of the Pyridine ring



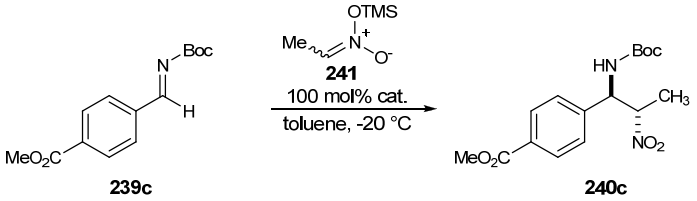

| entry | R | time (h) | % yield | dr[a] (*anti*:*syn*) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | [3]Me **a** | 88 | 85 | 3:1 | 1 |
| 2 | [5]Me **b** | 88 | 77 | 8:1 | 64 |
| 3 | [6]Me **c** | 163 | 56 | 12:1 | 70 |

[a]Isolated yields after chromatography. [b]Diastereomer ratios measured by GC. [c]Enantiomer ratios measured by HPLC using chiral stationary phases.



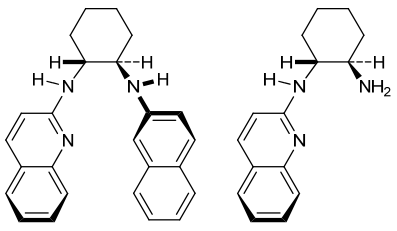

A simple pyridine ring afforded racemic product, as did the 3-methyl pyridine derivative. Enantioselection increased steadily going from a 5-Me pyridine to a 6-Me pyridine indicating that the 6-position was directly affecting the facial selectivity and that it was proximal to the "catalyst binding site". The importance of the bis(amidine) motif was established by evaluating structurally similar derivatives that lacked the second quinoline

**Table 5.** Importance of the Bis(Amidine) Scaffold in the Chiral Proton Catalyzed Indirect aza-Henry Reaction




| entry | catalyst | dr[a] | %ee[b] | yield[c](%) |
|---|---|---|---|---|
| 1 | **251**•HOTf | 5:1 | 3 | 76 |
| 2 | **252**•HOTf | 1.4:1 | 0 | 74 |

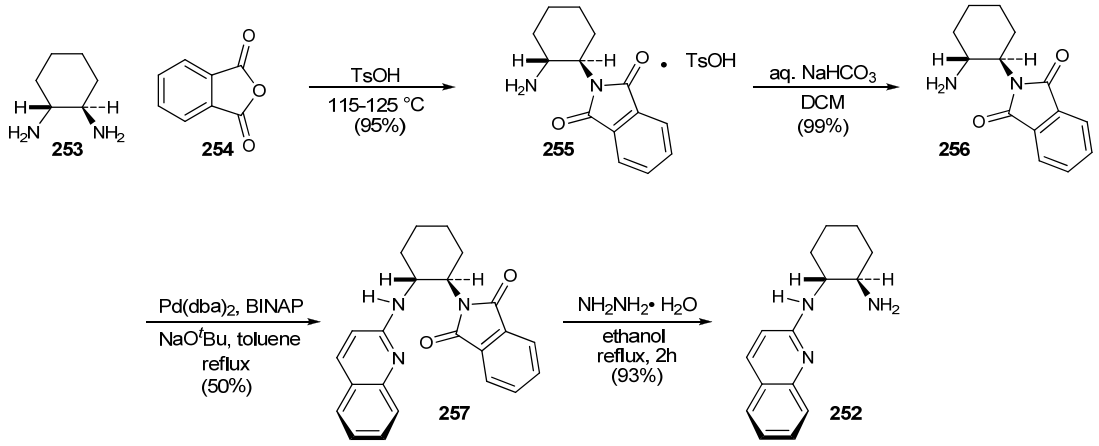
[a]Diastereomeric ratios determined by GC. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after chromatography.




H,Quin([2]Nap)-BAM
**251**
**252**

ring. The unsymmetrical quinoline-naphthalene catalyst **251** differs from H,Quin-BAM•HOTf only by a single nitrogen atom but was found to afford no enantioselection thereby highlighting that both quinoline rings are indispensable for obtaining high levels of stereoselection. The mono-quinoline derivative **252** was also found to be non-selective further highlighting the importance and effectiveness of the bis(amidine) scaffold. The synthesis of **252** was achieved as shown in Scheme 47. Mono protection of the enantiopure diamine **253** as the pthalimide was followed by the Buchwald-Hartwig amination with 2,4-dichloroquinoline leading to **257** which was deprotected to reveal the mono amidine **252**.

**Scheme 47**

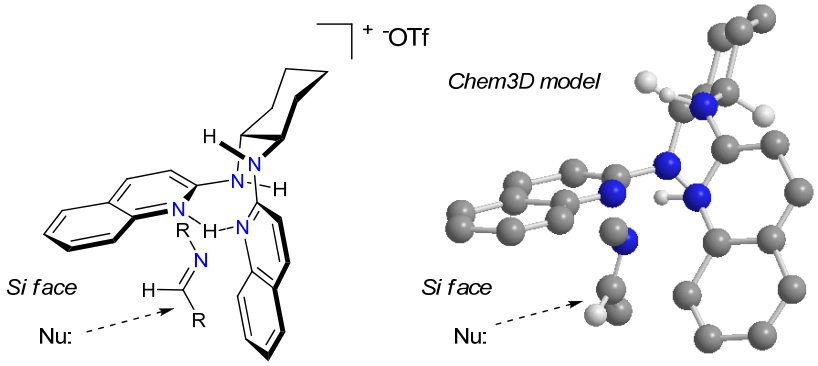



It was also discovered that only a 1:1 complex of ligand to HOTf was catalytically active and that the 1:2 complex resulted in the hydrolysis of the imine. This information coupled with the fact that the bis(amidine) scaffold was an essential element for stereoselection (Table 5) led to the development of a working stereochemical model for this reaction.

As shown in Figure 13, we postulate that the proton coordinates with the ligand in bidendate fashion. The binding of the imine to the catalytic proton renders the two faces differentiated by the quinoline rings. It can now be visualized how the substitutent on the

6-position might affect the stereochemical outcome due to its relative position with the electrophile.

**Figure 13** Proposed Catalyst Substrate Complex for the Enantioselective aza-Henry Reaction



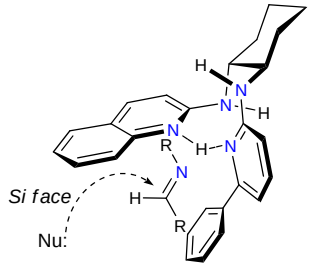

Appropriate substitution on the 6-position of the pyridine ring leads to the *Re* face being blocked, causing the nucleophile to attack primarily from the *Si* face, consistent with the observed selectivity. The model in Figure 13 does not represent a transition state but outlines the arrangement of atoms that lead to the observed stereochemistry in the product. We propose that as the imine approaches the catalyst proton, one of the quinoline rings drifts away thereby elongating its bond to the proton but still persisting in the vicinity and providing the requisite shielding of the *Re* face. Bidentate substrate co-ordination precludes the formation of the strongest possible H-bonding interaction (linear, 180°) but rather points to a donor-bifurcated hydrogen bonding system.[93]

It was hypothesized that if the substituent on the 6-position of the pyridine ring could be modified so as to provide even better blocking of the *Re* face, then potentially better enantioselectivities would result. This study was undertaken in an attempt to solve the problem of low generality of a related reaction (to be discussed in Section 2.2.1).

[93] The Weak Hydrogen Bond Desiraju, G. R.; Steiner, T. Oxford University Press. 1999.

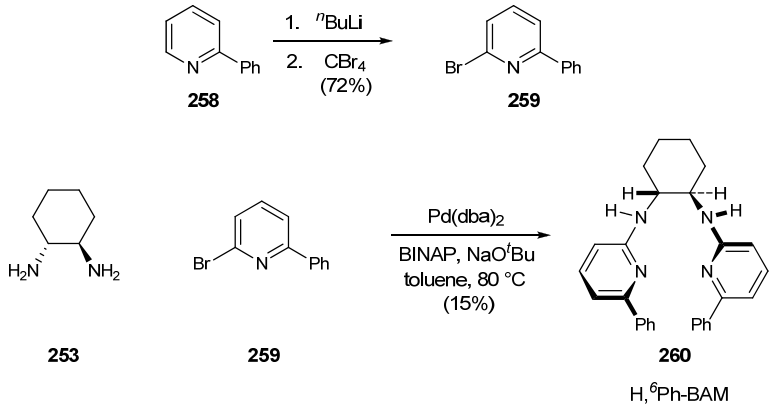
Among the first ideas was to introduce a phenyl ring in the 6 position. This was guided by the model proposed in Figure 13. It can be seen that in the proposed model, the carbocylic ring of the quinoline is the part that blocks the nucleophile. It was thought that if the substituent along the 6-position was a better blocking group, the enantioselection would increase. Introducing a phenyl group stems from the idea that it would render itself perpendicular to the pyridine ring thereby providing the full face of the (phenyl) ring as a blocking element (Figure 14).

**Figure 14.** Visualization of the Effect of a Phenyl Group at the 6-position



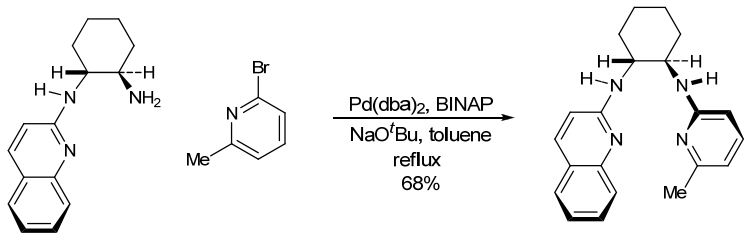

The requisite 2-bromo-6-phenyl pyridine was synthesized by the lithiation of 6-Ph pyridine followed by bromination with $CBr_4$ as shown in Scheme 48. Buchwald-Hartwig

**Scheme 48.** Synthesis of Ligand **172**



coupling of this pyridine with cyclohexyl diamine under the standard conditions afforded the desired catalyst. It was observed that the H,$^{6}$Ph-BAM•HOTf afforded no enantioselection in the aza-Henry reaction. This result was unexpected by comparison with H,$^{6}$Me-BAM•HOTf which afforded better enantioselection (70% ee) and was synthesized as shown in Scheme 49.

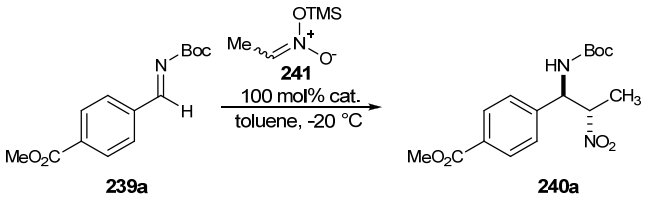
**Scheme 49**




**252** **261** **262**
H,Quin($^{6}$Me)-BAM

This comparison indicated that H,$^{6}$Ph-BAM•HOTf is missing a crucial element of stereocontrol. As discussed earlier, this catalyst had been structurally equipped with all that was essential to obtain enantioselection: substitution at the six- position, two pyridine rings for bidentate coordination to the proton, and 1 equivalent of TfOH.

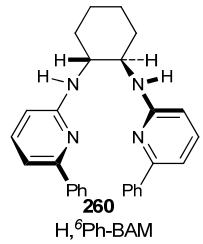
**Table 6.** Chiral Proton Catalyzed Indirect aza-Henry Reaction: Evaluation of Catalysts



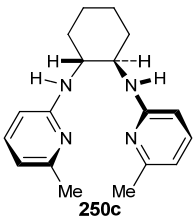

**239a** **240a**

| entry | catalyst | dr[a] | %ee[b] | yield[c](%) |
|---|---|---|---|---|
| 1 | **260**•HOTf | 1.4:1 | 1 | 69 |
| 2 | 1e•HOTf | 12:1 | 70 | 77 |

[a]Diastereomeric ratios determined by GC. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after chromatography.



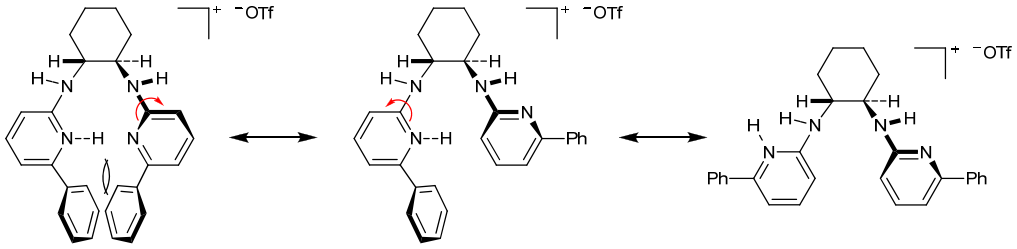

**260**
H,$^{6}$Ph-BAM




**250c**
H,$^{2}$Quin($^{6}$Me)-BAM

We ascribe the failure of H,$^{6}$Ph-BAM•HOTf to the repulsive interaction between the two phenyl rings which limits the ability of the ligand to achieve bidentate coordination to the proton. As a result, we think that the catalyst exists in a "swung out" conformation in solution and therefore is unable to provide enantioselection (Figure 15).

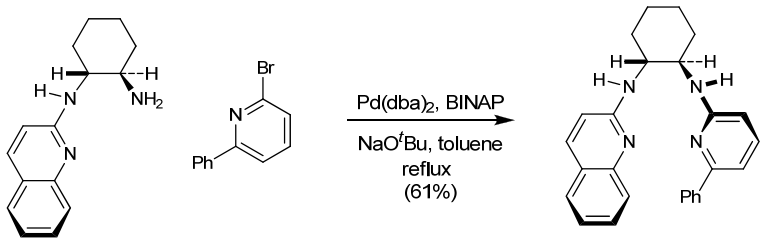
**Figure 15.** Possible Conformations of Catalyst **173**




**260** H,Quin($^{6}$Ph)-BAM **260a** H,Quin($^{6}$Ph)-BAM **260b**

Table 7 shows the results obtained for various new catalysts. These catalysts were

**Scheme 50**

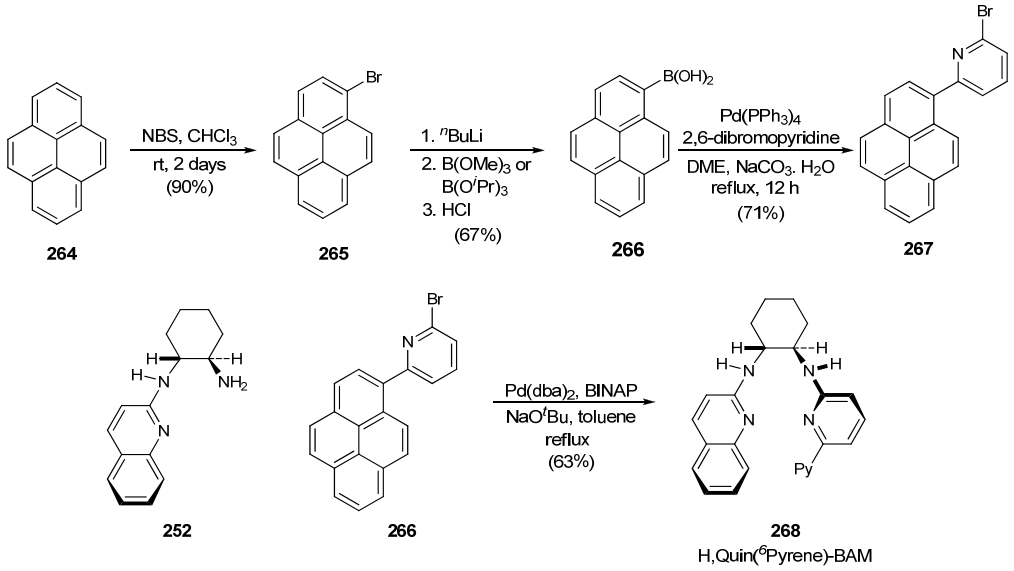



**252** **259** **263** H,Quin($^{6}$Ph)-BAM

inspired by the failure of H,$^{6}$Ph-BAM•HOTf and were designed so as to preserve the bidentate chelation to the proton. All the catalysts shown have a common theme of being different at the 6 position of the pyridine. In essence, the various substitutions on the 6-position were testing the amount of steric encumbrance that could be created in the catalyst's active site while preserving the desired conformation (as indicated by the enantioselection provided). Access to a wide range of catalysts with different steric

active-site capacity would be beneficial in applying this catalysis to substrates that have a different steric footprint. The unsymmetrical H,Quin($^{6}$Ph)-BAM was synthesized from the mono amidine **252** using Buchwald-Hartwig amination. In order to test the limit of

**Scheme 51.** Synthesis of Ligand **174**




**264** **265** **266** **267**

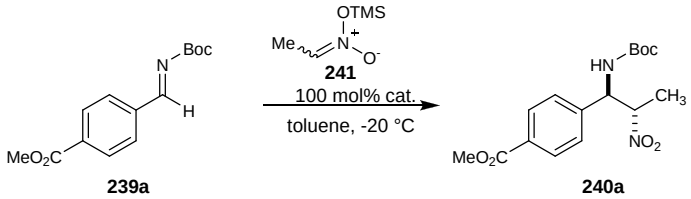
**252** **266** **268**

H,Quin($^{6}$Pyrene)-BAM

steric crowding that could be created in the catalyst pocket, the bulky pyrene derivative **268** was envisioned and synthesized as shown in Scheme 51.

Surprising results were obtained once again when the H,Quin($^{6}$Ph)-BAM•HOTf gave lower ee than the H,Quin($^{6}$Me)-BAM•HOTf. However, catalyst **268** with the large pyrenyl group in the 6-position afforded 87% ee which is close to H,Quin-BAM•HOTf. This suggests that the unsymmetrical catalyst **268** is able to maintain the bidentate chelation of the proton despite the presence of the bulky pyrene ring near the reaction site. Although we were not able to obtain a catalyst that performed better in the indirect aza-Henry reaction, this exercise provided us with alternate catalysts with different structures as was essential to solving an alternate problem as discussed in Chapter 3.

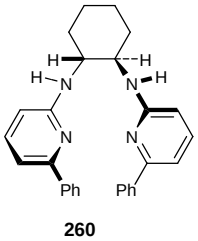
**Table 7.** Evaluation of Unsymmetrical Catalysts in the Chiral Proton Catalyzed Indirect aza-Henry Reaction




**239a** **240a**

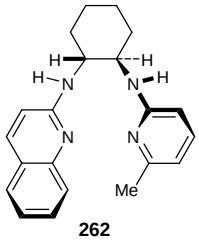
| entry | catalyst | dr[a] | %ee[b] | yield[c](%) |
|---|---|---|---|---|
| 1 | **173**•HOTf | 1.4:1 | 1 | 69 |
| 2 | **174**•HOTf | 6:1 | 84 | 72 |
| 3 | **175**•HOTf | 5:1 | 60 | 77 |
| 4 | **176**•HOTf | 8:1 | 87 | 71 |

[a]Diastereomeric ratios determined by GC. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after chromatography.



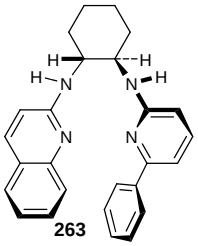

**260**

H,$^{6}$Ph-BAM



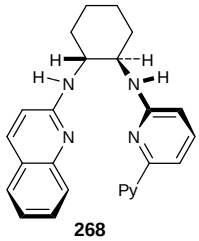

**262**

H,$^{2}$Quin($^{6}$Me)-BAM



**263**

H,Quin($^{6}$Ph)-BAM




**268**

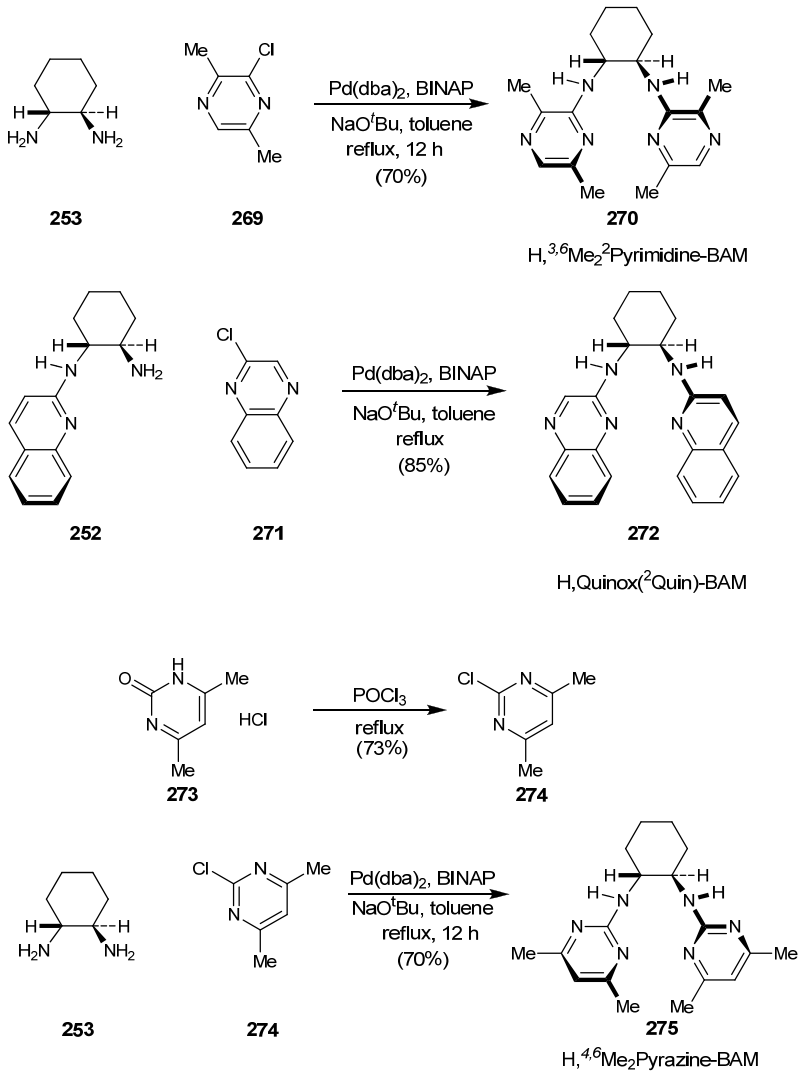
Py = pyrene

H,Quin($^{6}$Pyrene)-BAM

### *2.5 Design and Application of More Acidic Catalysts: Incorporation of Nitrogen Rich Heterocyclic Ring.*

Modifications to the ligand structure can be expected to impact a) catalyst Lewis acidity, b) basicity, and c) effectiveness in stereocontrol (both diastereo- and enantioselection). In order to obtain a wide variety of functional catalysts, we targeted the

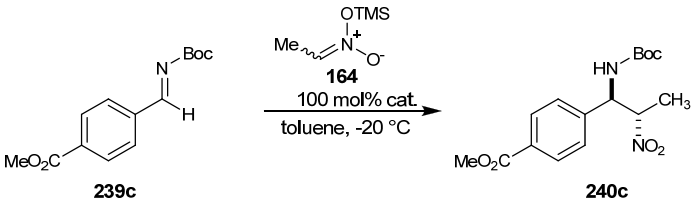
**Scheme 52.** Synthesis of Ligands **270**, **272**, and **2753**




synthesis of more acidic catalysts that could activate relatively inert functionalities such as the carbon-carbon double bond. It was thought that by incorporating a heterocyclic

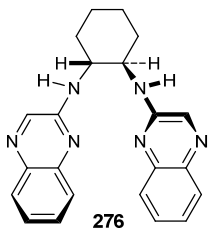
ring with two nitrogen atoms, we could access more acidic catalysts. The incorporation of an additional nitrogen atom into the aromatic ring will increase the number of basic sites in the molecule but at the same time, the higher electronegativity of nitrogen (compared to carbon) renders the aromatic ring π-electron deficient. We thought that a proton bound to such an electron deficient system would be more acidic. To test this hypothesis, several new ligands were synthesized as shown in Scheme 52.

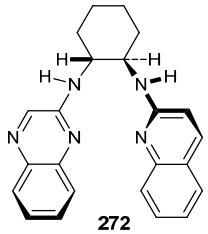
**Table 8.** Chiral Proton Catalyzed Indirect aza-Henry Reaction: Evaluation of Catalysts Featuring Nitrogen Rich Heteroaromatic Rings

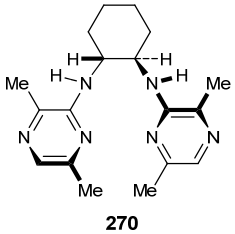



| entry | catalyst | dr | %ee | yield(%) |
|---|---|---|---|---|
| 1 | **276**•HOTf | 4:1 | 1 | 65 |
| 2 | **272**•HOTf | 3:1 | 10 | 69 |
| 3 | **270**•HOTf | 1.5:1 | -10, +15 | 80 |
| 4 | **274**•HOTf | 2:1 | 18 | 82 |

[a]Diastereomeric ratios determined by GC. [b]Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after chromatography.



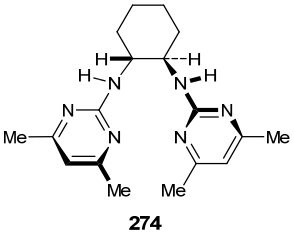
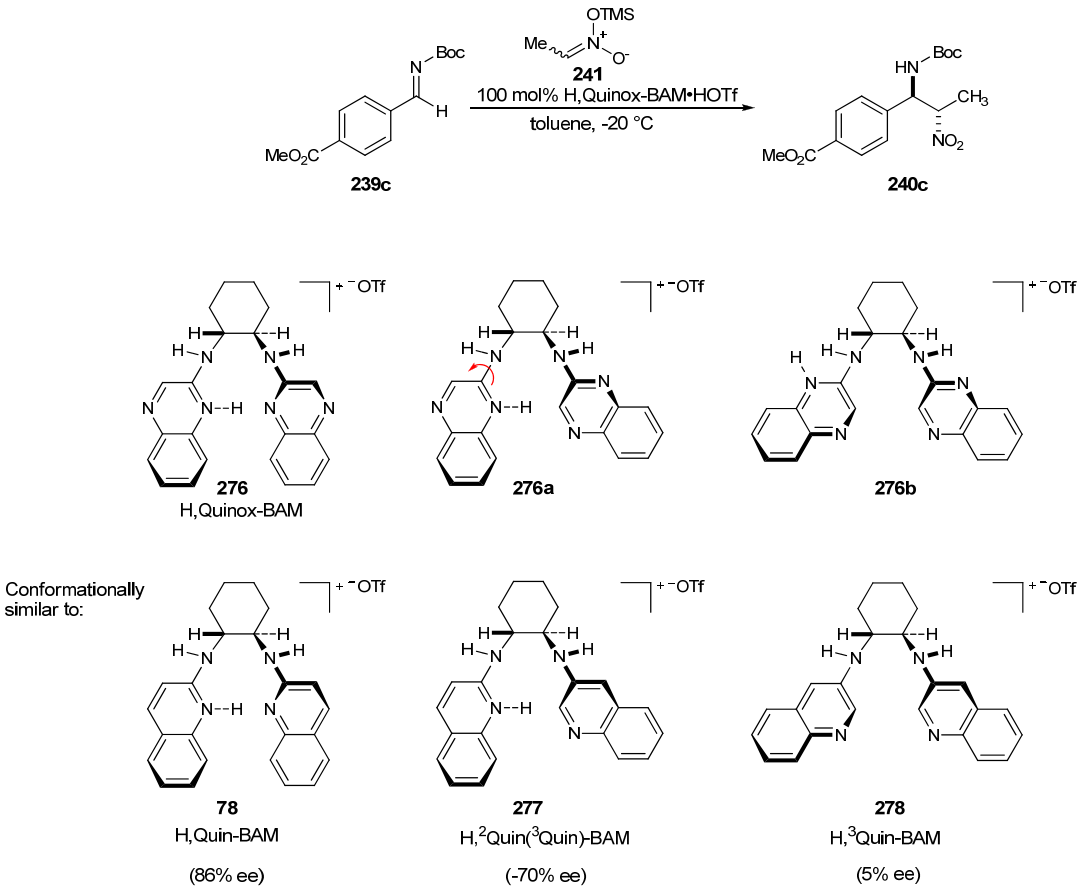




Table 8 outlines the the performance of these new catalysts. Among the first catalyst to be evaluated was H,Quinox-BAM•HOTf which afforded 1% ee. The racemic product could not be used to deduce any meaningful information about the effect of the extra nitrogen atom because we realized that this catalyst could attain conformations analogous to some other less effective catalysts (Figure 16). The enantioselectivities in parentheses

show the result obtained from the catalysts to which these conformations are being compared. Due to similar a complication in interpretation, no useful deduction could be drawn from the H,Quinox($^2$Quin)-BAM•HOTf result.

**Figure 16.** Possible Conformations of H,Quinox-BAM and Comparison to Structurally Related Catalysts




Ligand **270** was designed to minimize the possibility of rotation about the N-C bond thereby preventing access to conformations which could afford low enantioselection. The rationale this time was that rotation from the desired conformer would result in repulsive interactions between the methyl groups. However, low enantioselection was obtained and hence no conclusions could be drawn. The last idea was to synthesize ligand **275** which was symmetric about the N-C bond and hence a rotation would only lead to an identical

conformation. The low enantioselection obtained with this catalyst suggests that the activation of the imine occurs from modes other than the bidentate chelation of the proton. In summary, incorporation of an additional nitrogen in the aromatic ring leads to loss of enantioselection. At a minimum, it's potential involvement in proton coordination must be managed if such a modification is to be utilized.

In conclusion, the chiral proton catalyzed addition of silyl nitronates to *N*-Boc imines has been developed as a tool to uncover mechanistic details of the polar ionic hydrogen bond mediated transfer of asymmetry in the enantioselective aza-Henry reactions catalyzed by BAM•HOTf complexes. It was discovered that the direct and indirect aza-henry reactions afforded similar diastereo- and enantioselectivities indicating that these reactions proceed through the same enantio-determining step which is the activation of the imine. Also, systematic variation of the ligand structure revealed that the substitution at the 6-position of the pyridine is critical to high enantioselection. With this knowledge, we were able to construct a working stereochemical model for the chiral proton catalyzed aza-henry reaction.

## *CHAPTER III*

# *ENANTIOSELECTIVE BRØNSTED ACID CATALYZED ADDITIONS OF UNSUBSTITUED NITROACETIC ACID DERIVATIVES AS GLYCINE EQUIVALENTS: SYNTHESIS OF α,β-DIAMINO ACIDS*

### *3.1 Synthetic Approaches Towards Enantiopure α,β-Diamino Acids*

The enantioselective synthesis of α,β-diamino acids has attracted the interest of synthetic chemists due to their utility as versatile building blocks and as surrogates of natural amino acids for incorporation into peptides to modulate their conformational, biological, and chemical properties.[94,95,96,97,98] These simple but polyfunctional molecules represent a significant synthetic challenge owing to the presence of contiguous stereocenters in a flexible acyclic molecule. The difficulties are amplified when the sterically encumbered quaternary stereocenter(s) are generated. As mentioned briefly in Chapter 1, approaches towards α,β-diamino acids can be broadly classified into two categories: ones that create the carbon backbone and the others that introduce nitrogen atoms by starting with the requisite carbon backbone. This chapter will discuss approaches towards the synthesis of α-*un*substituted α,β-diamino acids and describe the development of a chiral proton catalyzed synthesis of this class of molecules.

#### *3.1.1 Construction of the Carbon Skeleton*

One of the most concise and straightforward methods in this category is the direct Mannich reaction between a prochiral nitrogen containing nucleophile and an imine. This

---

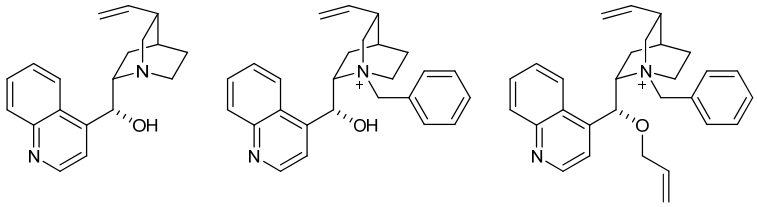
[94] Walsh, J. J.; Metzler, D. E.; Powell, D.; Jacobson, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 7136.
[95] Schirlin, D.; Gerhart, F.; Hornsperger, J. M.; Hamon, M.; Wagner, J.; Jung, M. J. *J. Med. Chem.* **1988**, *31,* 30.
[96] Sagan, S.; Karoyan, P.; Lequin, O.; Chassaing, G.; Lavielle, S. *Curr Med Chem* **2004**, *11*, 2799.
[97] Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.
[98] Kotti, S.; Timmons, C.; Li, G. G. *Chemical Biology & Drug Design* **2006**, *67*, 101.

reaction results in the formation of a Carbon-carbond and two stereocenters in a single step. Two complementary approaches in this class are 1) the direct Mannich reaction between glycine Schiff base and imines and 2) the direct aza-Henry reaction between appropriately substituted nitroalkanes and imines.

### *3.1.1.1 Mannich Reaction of Glycine Schiff Base Pronucleophiles with Imines*

The use of chiral phase transfer catalysis to effect alkylation of glycine Schiff bases was pioneered by O'Donnell and his work remains the inspiration behind much of the chemistry developed in this area. The addition products from this reaction could then be elaborated to the amino acid after hydrolysis and deprotection (Scheme 53).[99,100] The catalysts employed by O'Donnell were cinchonidine-derived phase-transfer catalysts of

**Scheme 53.** Glycine Schiff Base Alkylkation Strategy Pioneered by O'Donnell


**281** **282** **283**

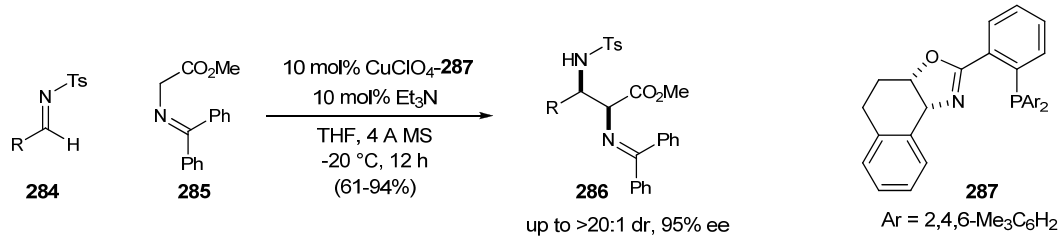
**cinchonidine**

type **282**. In 2003, the first example of a direct, catalytic asymmetric Mannich reaction between a glycinate and imine was reported by Jørgensen. A $CuClO_4$/phosphinooxazoline catalyst system was used to afford products with up to

[99] O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, 4625.
[100] O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775.

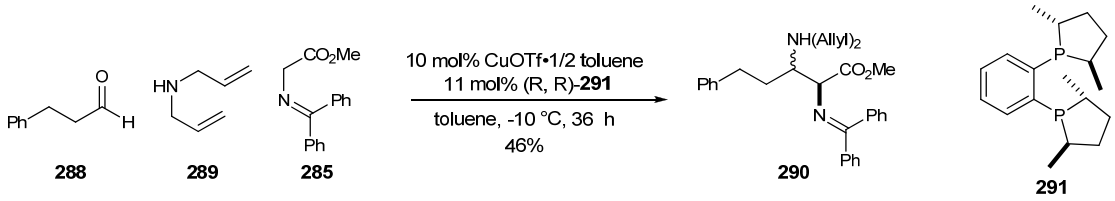
>20:1 dr and 97% ee. In general, aliphatic imines gave better *syn*-diastereoselectivity than aromatic imines. Glyoxyl imines fared worst with only 1.2:1 dr and 60% ee (Scheme 54).

**Scheme 54.**



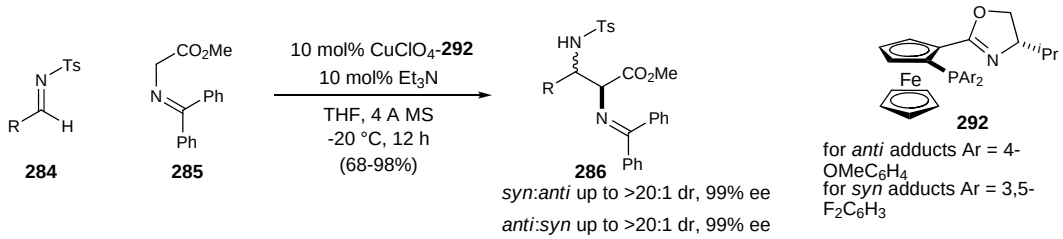

As shown in Scheme 55, Kobayashi's efforts into this area met with limited success when his attempt to perform a three component coupling using aldehyde, amine and Schiff base

**Scheme 55.**




afforded adducts with no diastereoselection and modest enantioselection. The modest yields rendered this protocol less attractive compared to addition to imines even though these starting materials are more stable than typical imines and the imine preparation is

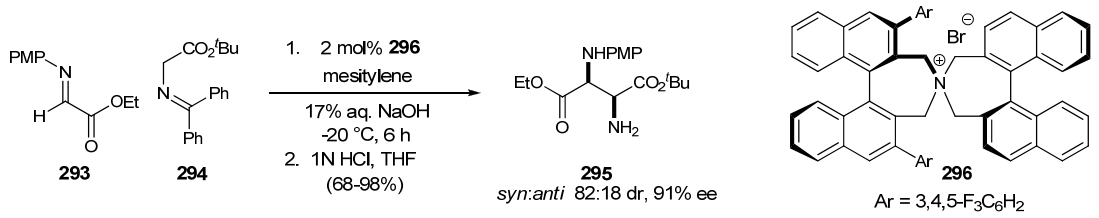
**Scheme 56.**



avoided.[101] The synthesis of *anti*- adducts via this chemistry remained elusive until Hou and co-workers reported a finding in which they discovered that tuning the electronics of the phosphine ligand has a significant effect on the diastereoselection of the reaction (Scheme 56).[102]

Phase transfer catalysis by a chiral, non-racemic quaternary ammonium bromide has been developed by Maruoka as a route towards α,β-diamino acids (Scheme 57). Adducts were obtained with good *syn*-diastereoselection and high ee. This method was suitable for glyoxyl imines and the resulting orthogonally protected esters enabled the conversion of one of the derivatives into a precursor of streptolidine lactam (a

**Scheme 57.**

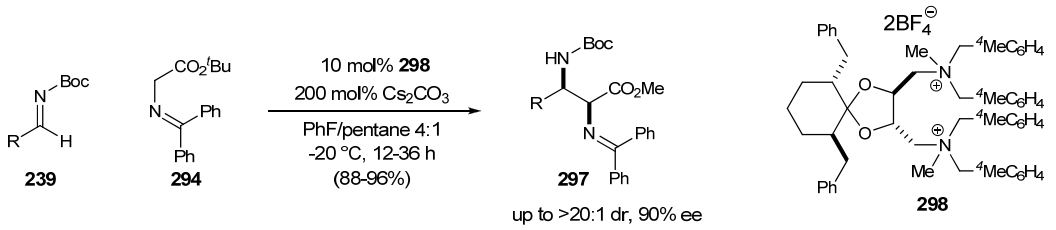



constitutent of streptothricin antibiotics).[103] After Maruoka's work, Shibasaki and co-workers reported a more general Mannich reaction performed under phase transfer conditions. They developed a tartarate derived two-center catalyst which afforded the Mannich adducts with high *syn* dr and modest to high enantioselection. In addition to

[101] Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533.
[102] Yan, X. X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X. L.; Yu, Y. D. *J. Am. Chem. Soc.* **2008**, *130*, 14362.
[103] Ooi, T.; Kameda, J.; Fujii, I.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397.

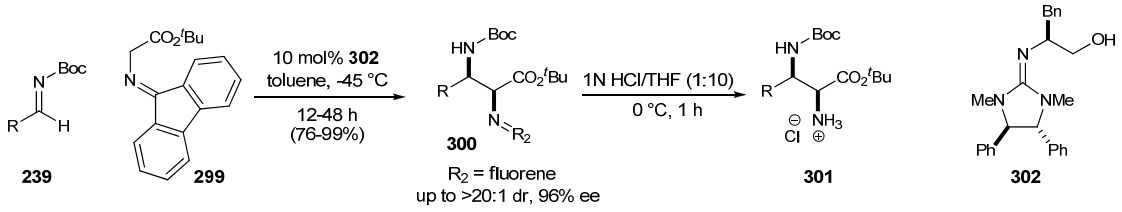
aromatic imines, enolizable aliphatic imines also showed good reactivity and stereoselection in this chemistry (Scheme 58).[104,105]

**Scheme 58.**




It was discovered by Kobayashi the fluorenone imine **299** derived from glycine ester exhibits better reactivity than the corresponding benzophenone imines (Scheme 59). Using a guanidine based catalyst, both aromatic and aliphatic imines provide adducts in high yields, excellent *syn*-diastereoselection, and high ee. The fluorenone motif is readily cleaved under mildly acidic conditions that do not affect the Boc group.[106]

**Scheme 59.**



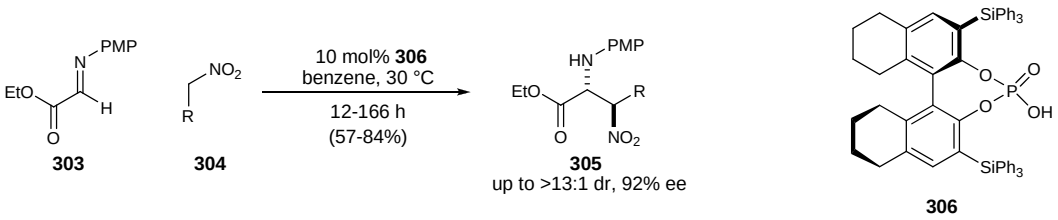

### *3.1.1.2 Mannich Reaction of Nitroalkane Pronucleophiles with Imines*

The use of α-unsubstituted nitroacetates in enantioselective Mannich reactions was first developed by our group and those results will be discussed in section 3.2. Since

[104] Okada, A.; Shibiguchi, T.; Oshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564.
[105] Shibiguchi, T.; Mihara, H.; Kuramochi, A.; Oshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794.
[106] Kobayashi, S.; Yazaki, R.; Seki, K.; Yamashita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 5613.

our work in 2007, other efforts in this area have been reported. Rueping and co-workers reported an enantioselective aza-Henry reaction of α-unsubstituted nitroalkanes with α-iminoesters.[107] The conceptual highlight of this report was the base-free conditions that could be employed (Scheme 60). The activation of the nitroalkane was achieved by octahydro-BINOL-phosphoric acid derivative. The adducts were formed with good *anti*-distereoselection and high enantioselection. The application of $^{4}$Me-phenylnitromethane as the nucleophile, however, provided products with low dr (2:1 *anti:syn*) but good ee (85%).

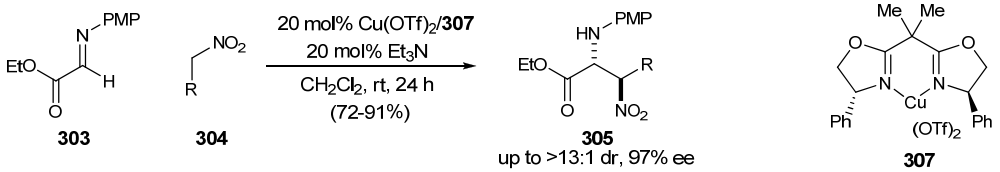
**Scheme 60.**




**303** **304** **305** up to >13:1 dr, 92% ee **306**

Jørgensen reported the Cu-BOX catalyzed aza-Henry reaction of nitroalkanes with α-iminoesters to generate β-nitro-α-amino esters with good *anti*-diastereoselection and good to high enantioselection.[108] This was among the first examples of direct, catalytic asymmetric aza-Henry reactions (Scheme 61).

**Scheme 61.**



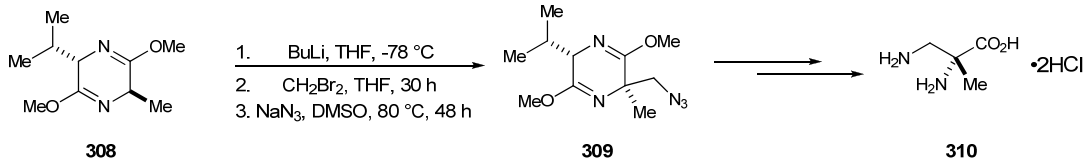

**303** **304** **305** up to >13:1 dr, 97% ee **307**

[107] Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.
[108] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992.

### *3.1.1.3 Nucleophilic Addition to Electrophiles Other than Imines*

The diastereoselective alkylation of enantiopure bislactam ethers has been studied by Mittendorf as a route to α,β-diamino acids. As shown in Scheme 62, the use of dibromomethane as the electrophile followed by the displacement of the bromide with

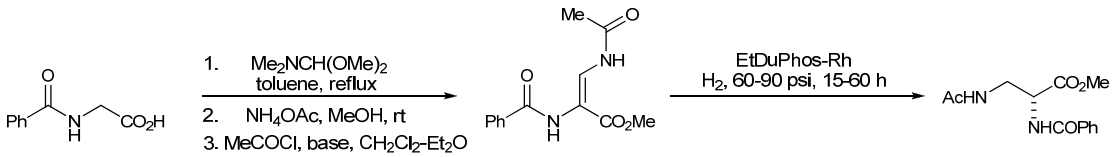
**Scheme 62.**




**308** **309** **310**

azide results in the bislactam ether azide derivative that can be elaborated into the corresponding diamino acid in 6 steps.[109] Amide acetals have also found use as electrophiles ultimately leading to the synthesis of α,β-diamino acids. Robinson and Lim reported the highly enantioselective synthesis of an α,β-diamino propionic acid derivative using this strategy. As shown in Scheme 63, condensation of hippuric acid with dimethyformamide dimethyl acetal, followed by the treatment with ammonium acetate resulted in the formation of the enamide which was subsequently acylated to produce the α,β-dehydro diamino acid. A highly enantioselective hydrogenation using Rh(I)-EtDuPhos provided the α,β-diamino esters in high yields and ee's.

**Scheme 63.**



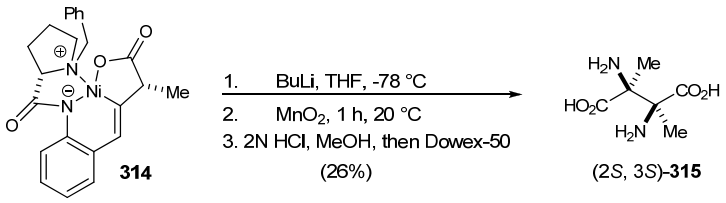

**311** **312** **313**
up to 99% yield
up to 99% ee

[109] Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939.

### *3.1.1.4 Dimerization Reactions of Glycinates*

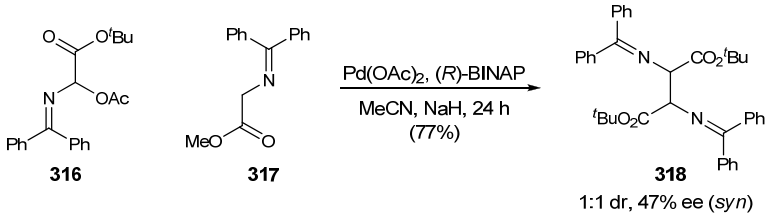
The oxidative dimerization of chiral, non-racemic Ni(II) complex derived from α-

**Scheme 64.**




imino alaninate[110] followed by acidic hydrolysis yielded the 2,3-diamino succinic acid derivative **315** (Scheme 64). The dimerization protocol is yet to succumb to enantioselective catalysis in an efficient manner. Efforts by Yudin to utilize a palladium mediated π-aza-allylic substitution using α-imino glycinates resulted in the formation of

**Scheme 65.**




the desired product in good yields but low diastereo- and enantioselection (Scheme 65).[111]

### *3.1.1.5 Ring Opening of Aziridines, Azetidones and Imidazolines*

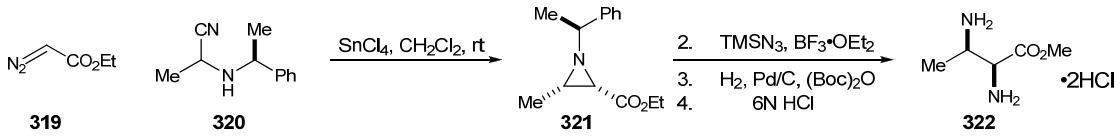
The synthesis of ring systems is enabled by a plethora of cycloaddition reactions which can be mediated by a Lewis acid, Brønsted acid, or light. The large variety of ring systems that can be created as intermediates for other chemical transformations are

[110] Belokon, Y. N.; Chernoglazova, N. I.; Batsanoc, A. S.; Garbalinskaya, N. S.; Bakhmutov, V. I.; Struchkov, Y. T.; Belikov. V. M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1987**, *36 part 2*, 779.
[111] Chen, Y.; Yudin, A. K. *Tetrahedron Lett.* **2003**, *44*, 4865.

responsible, in part, for the extensive study of cycloaddition reactions. One such cycloaddition is that of imines and alkyl diazoacetates to give aziridines which in principle could be opened by an amine nucleophile to generate a variety of diamine containing molecules. The application of this methodology to the synthesis of *vic*-diamines was discussed in Chapter 1. The present discussion aims to shed light on how these ring opening reactions have been applied to the synthesis of α,β-diamino acids.

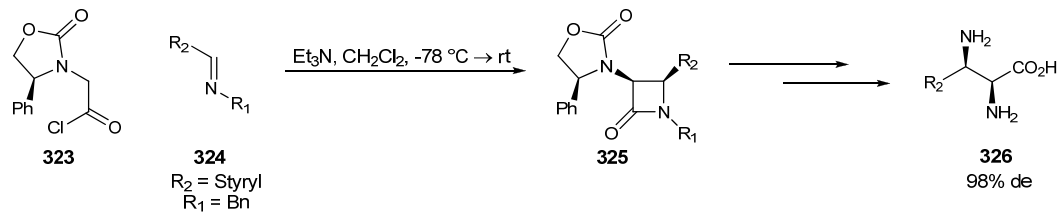
α-Amino nitriles have been applied as masked imines in the 2+1 cycloaddition with diazoacetates *enroute* to α,β-diamino acids. In an example by Yun and co-workers, a $SnCl_4$ mediated cycloaddition between ethyl diazoacetate and an α-amino nitrile led to

**Scheme 66.**




the formation of the *cis*-aziridine (albeit in low diastereoselectivity relative to the auxiliary) (Scheme 66). Ring opening with TMS-azide and further manipulations led to

**Scheme 67.**



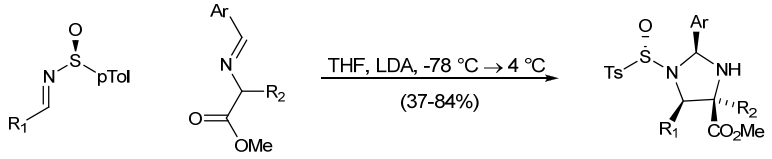

the synthesis of (2*S*, 3*R*)-diaminobutanoic acid.[112] A conceptually simpler method is the stereoselective construction of β-lactams and their subsequent deprotection. As shown in

[112] Lee, K. D.; Suh, J. M.; Park, J. H.; Ha, H. J.; Choi, H. G.; Park, C. S.; Chang, J. W.; Lee, W. K.; Lee, W. K.; Dong, Y.; Yun, H. *Tetrahedron* **2001**, *57*, 8267.

Scheme 67, the cycloaddition of an in situ formed ketene with an imine leads to the *cis*-3-amido-4-styryl-β-lactam. This compound can either be elaborated to the diamino acid directly or can be diastereoselectively alkylated at C-3 to eventually furnish α-substituted α,β-diamino acids.[113,114]

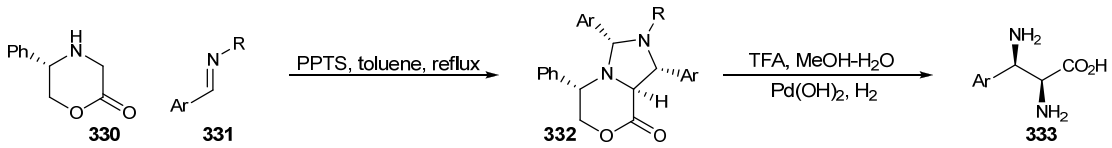
Structurally, imidazolidines and 2-carboxyimidazolines are cyclic versions of α,β-diamino acids. These can be synthesized using [3+2] cycloaddition utilizing imines and azomethine ylides. The use of chiral, non-racemic sulfinimines has been demonstrated in

**Scheme 68.**




effecting an asymmetric [3+2] cycloaddition. As shown in Scheme 68, enolates derived from α-alkyl-α-imino esters and LDA react with sulfinimines to furnish imidazolidines

**Scheme 69.**




with high endo selectivity and high diastereoselection.[115] Harwood has described the synthesis of enantiopure imidazolidines starting from (5*S*)-phenylmorpholin-2-one and generating the ylide in situ which then undergoes cycloaddition with imine.

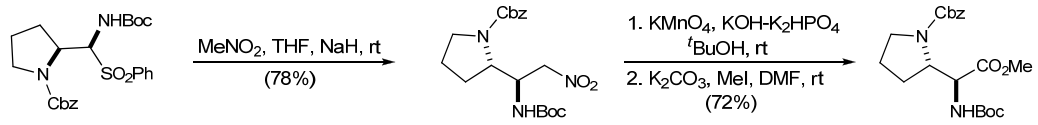
[113] Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.
[114] Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977.
[115] Viso, A.; Fernandez de la Pradilla, R.; Garcia, A.; Guerrer-Strachan, C.; Alonso, M.; Flores, A.; Martinez-Ripoll, M.; Fonseca, I.; Andre, I.; Rodriguez, A. *Chem. Eur. J.* **2003**, *9*, 2867.

Hydrogenolysis of the adducts revealed the underlying *syn*-α,β-diamino acid in high yields (Scheme 69).[116]

### *3.1.1.6 Nucleophilic Synthetic Equivalents of Carboxylates*

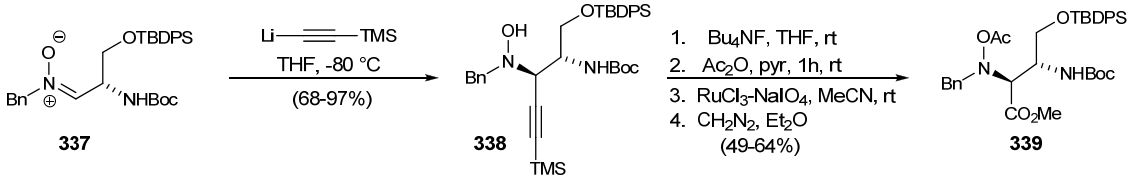
α-Amido sulfones have been used as an *N*-acyliminium equivalent in the addition of nitromethane as shown in the Scheme 70. The resulting nitro diamine was obtained in

**Scheme 70.**




9:1 dr and following a Nef reaction and esterification, the α,β-diamino acid was obtained (Scheme 70).[117] One of the well known surrogates for a carboxylate is an alkyne and this reactivity pattern of alkynes has been applied towards the synthesis of α,β-diamino acids. Merino and co-workers have shown that the addition of acetylides to nitrone (derived from L-serine) occurs with high diastereocontrol to afford the hydroxylamine. These products were then elaborated to the diamino acid by the removal of the TMS group, *O*-acylation, alkyne oxidation and esterification (Scheme 71).[118]

**Scheme 71.**

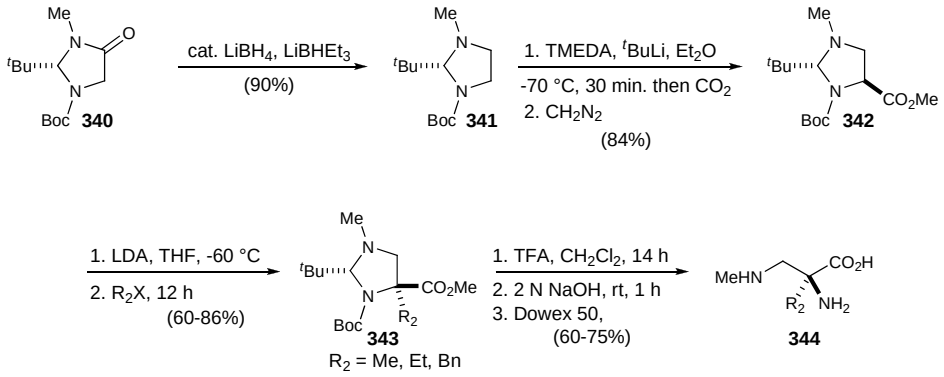



[116] Alker, D.; Harwood, L. M.; Williams, E. *Tetrahedron Lett.* **1998**, 39, 475.
[117] Foresti, E.; Palmeiri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.
[118] Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627.

### *3.1.1.7 Electrophilic Synthetic Equivalents of Carboxylates*

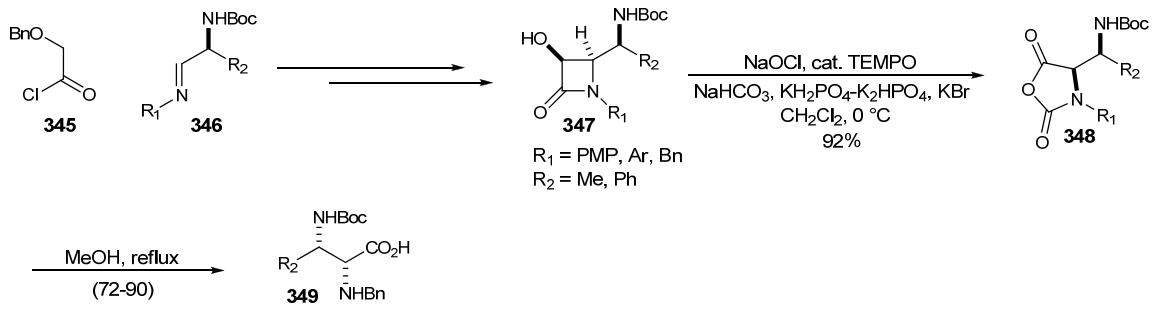
The use of electrophilic equivalents of carboxyl groups is less prevalent in the literature but there are some examples pertaining to their use in the synthesis of α,β-diamino acids. In a report by Seebach and co-workers, a glycine derived imidazolidinone was deoxygenated and then carboxylated with carbon dioxide with great diastereoselection (Scheme 72).[119]

**Scheme 72.**




The oxidation of β-lactams has been shown by Palomo to be a viable route towards α,β-diamino acids. The formation of β-lactams by a [2+2] ketene-imine cycloaddition and a subsequent oxidation using TEMPO results in the formation of *N*-carboxy anhydrides. No epimerization was observed in the oxidation step. The

**Scheme 73.**



esterification of the anhydrides by MeOH and trimethylsilyl chloride afforded the differentially protected amino acid in enantiomerically pure form (Scheme 73).[120,121,122]

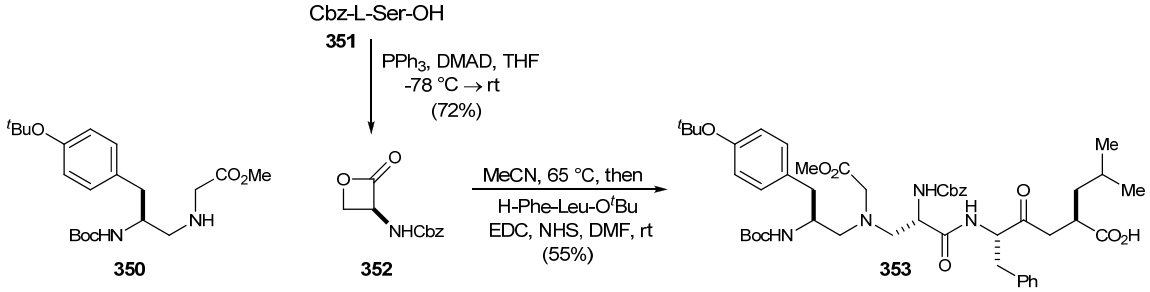
### *3.1.2 Introduction of Nitrogen Atoms Starting from the Requisite Carbon Skeleton*

Naturally occurring α-amino acids can be thought of as obvious starting materials for the synthesis of α,β-diamino acids by performing functional group manipulations of existing functionality. The advantages of this approach are that the enantiopure starting amino acids are commercially available and inexpensive. On the other hand, the disadvantage would be that access to the opposite enantiomer is not straightforward. This idea has been widely applied in the literature and there are various reports detailing numerous ways in which natural amino acids can be converted to α,β-diamino acids. Apart from this strategy, other methods also exist wherein the amine is incorporated via the diamination of an olefin or by electrophilic amination of enolates. This section will discuss examples from the literature which showcase some of the above ideas.

#### *3.1.2.1 The Use of Natural Amino Acids as Precursors*

α-Amino acids containing a β-hydroxyl group such as serine and threonine have been frequently employed as starting materials towards α,β-diamino acids by the

**Scheme 74.**

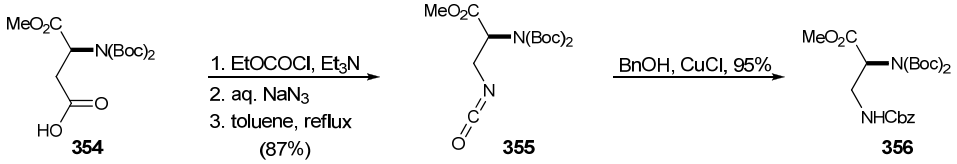



[120] Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M.; *J. Org. Chem.* **1994**, *59*, 3123.
[121] Palomo, C.; Ganboa, I.; Cuevas, C.; Boschetti, C.; Linden, A. *J. Org. Chem.* **1996**, *61*, 4400.
[122] Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Urchegui, R.; Linden, A. *Tetrahedron Lett.* **1997**, *38*, 4643.

conversion of the hydroxyl group into an amine. The Mitsunobu reaction has been the subject of intense investigation in this area although it requires the suitable protection of the acid and amine moieties to prevent undesired reactions such as β-elimination and aziridine formation.[123, 124]

As shown in Scheme 74, Vederas and co-workers have discovered that subjecting *N*-protected *L*-Serine to Mitsunobu conditions in the absence of an external nucleophile results in the formation of the β-lactone without epimerization. The lactone can be

**Scheme 75.**

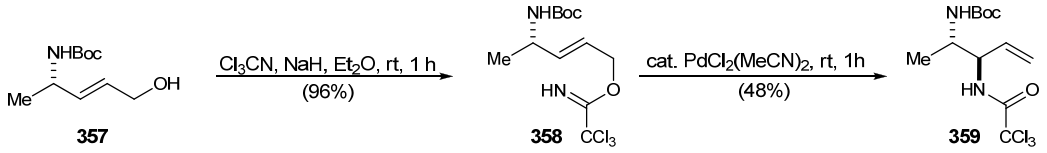



opened by an amine to afford the α,β-diamino acid moiety which can be elaborated further.[125,126] Apart from serine, aspartic acid has also been used as a precursor to α,β-diamino acids *via* a Curtius rearrangement (Scheme 75).[127, 128,129]

### *3.1.2.2 The Use of Enantiopure Allylic Alcohols and Amines*

The aza-Claisen rearrangement has been elegantly applied to the synthesis of

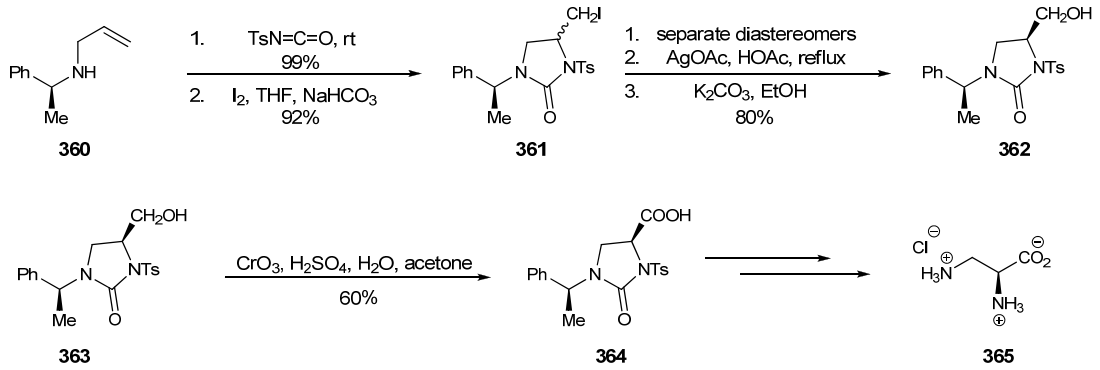
**Scheme 76.**




[123] Fabiano, E.; Golding, B. T.; Sadeghi, M. M.; *Synthesis* **1987**, 190.
[124] Golding, B. T.; Howes, C. J. *Chem. Res.* **1984**, 1.
[125] Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105.
[126] Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237.
[127] Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266.
[128] Lee, E. S.; Jurayj, J.; Cuahman, M. *Tetrahedron* **1994**, *50*, 9873.
[129] Zhang, L. H.; Kauffman, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918.

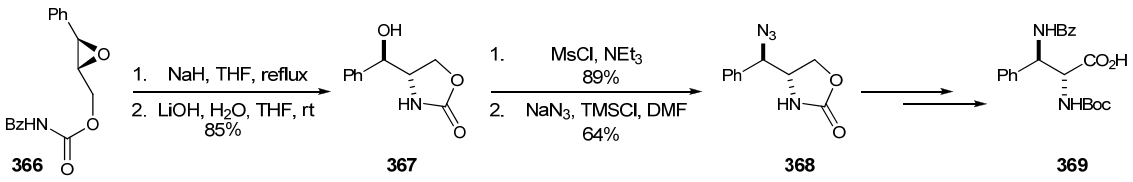
functionalized diamines that can be elaborated to the corresponding α,β-diamino acids (Scheme 76).[130] In a method developed by Cardillo, the enantiopure allylic amine **360** was converted into the tosyl urea **361** followed by an iodine mediated cyclization to give the iodo-imidazolidinones as a diastereomeric mixture. Separation of the diastereomers via column chromatography followed by transformation into hydroxymethyl imidazolidinone set the stage for an oxidation that would provide the corresponding diamino acid in protected form (Scheme 77).

**Scheme 77.**




In an example pertaining to the synthesis of a taxol side-chain analogue, Rossi employed the chiral, non-racemic epoxy carbamate **366** to synthesize the oxazolidinone **367**. Displacement of the alcohol as the mesylate with sodium azide afforded *syn*-**368** which was elaborated into the corresponding α,β-diamino acid in 5 steps (Scheme 78).

**Scheme 78.**

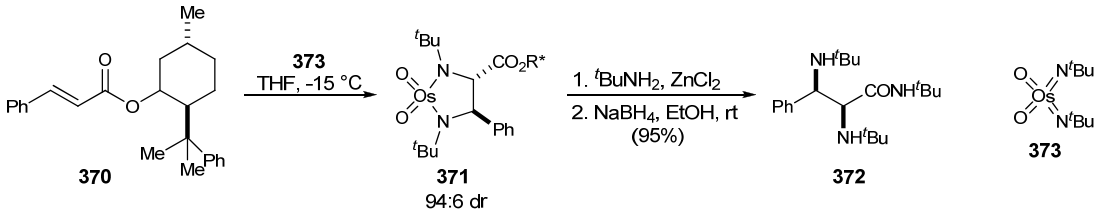



[130] Gonda, J.; Helland, A. C.; Ernst, B.; Bellus, D. *Synthesis* **1993**, 729.

### *3.1.2.3 Olefin Diamination*

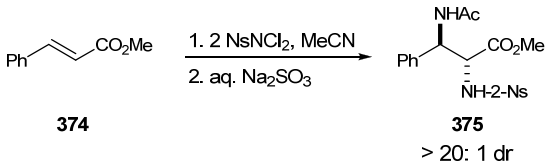
The enantioselective diamination of suitably substituted olefins is potentially a shorter route towards α,β-diamino acids. However, the direct asymmetric diamination of olefins is less studied compared to the analogous dihydroxylation reaction. Stoichiometric osmium mediated diamination of fumarates and cinnamates with the dimido complex **373** in the presence of $(DHQD)_2$-PHAL or $(DQD)_2$PHAL provide only racemic products. Incorporation of a chiral auxiliary, however, provides the diamine

**Scheme 79**




products with excellent distereoselectivity and good yields. [131,132] Li has reported the direct electrophillic amination of α,β-unsaturated esters using *N*,*N*-dichloro-2-nitrobenzenesulfonamide (2-$NsNCl_2$). This reaction provides the corresponding *anti*-α,β-diamino acids with high diastereoselection. An enantioselective version of this reaction has not yet been developed.[133]

**Scheme 80**

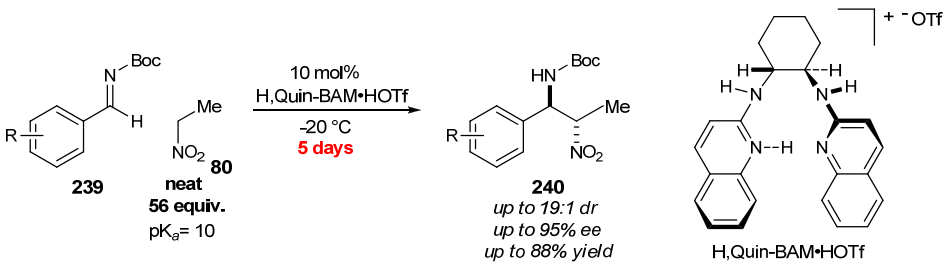



[131] Muniz, K.; Nieger, M. *Synlett* **2003**, 211.
[132] Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420.
[133] Li, G.; Kim, S. H.; Wei, H. X. *Tetrahedron Lett.* **2000**, 41, 8699.

### *3.2 Enantioselective Brønsted Acid Catalyzed Additions of Nitroacetic Acid Derivatives as Glycine Equivalents*

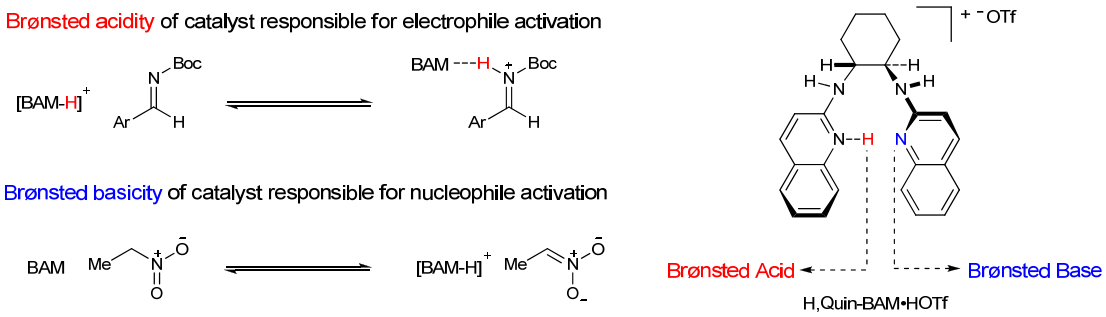
The chiral proton catalyzed aza-Henry reaction of nitroethane is summarized in scheme Scheme 81. While excellent diastereo- and enantioselection could be obtained, a

**Scheme 81.** Chiral Proton Catalyzed Nitroethane Additions to Imines




major limitation of these reactions was the long reaction times despite the use of excess nitroalkane (56 equiv., used as solvent). It was discovered that the BAM•HOTf catalysts were bifunctional in nature performing the two orthogonal roles of a Lewis acid (activation of the imine), *and* a Brønsted base (deprotonation of the nitroalkane). While

**Figure 17.** Bifunctionality of BAM•HOTf Catalysts

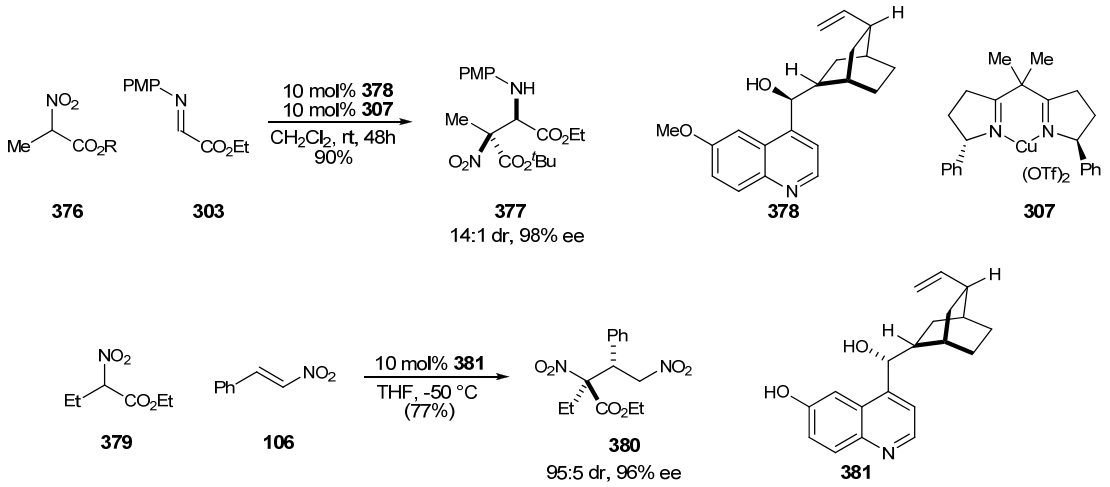



both of these modes are essential for a successful reaction, a comparison of the direct aza-Henry reaction to the indirect version (silyl nitronate additions) revealed that the primary mode of activation and stereoinduction in these reactions is the activation of the imine. Nonetheless, we hypothesized that nitroalkane acidity could be used to influence the rate

of this reaction since more facile deprotonation would result in a higher concentration of the active nucleophile. In principle, activated nitroalkanes with lower $pK_a$ than simple nitroalkanes would be expected to provide an increase in reactivity. Among readily available activated nitroalkanes, we decided to develop α-nitroacetates as suitable nucleophiles due to their potential application as amino acid equivalents.

The enantioselective synthesis of α-amino acids is an active area of asymmetric catalysis.[134] The use of chiral phase transfer catalysis to effect alkylation of glycine Schiff bases was pioneered by O'Donnell. The products could then be elaborated to the amino acid after hydrolysis and deprotection (Scheme 53).[135] The catalysts employed by O'Donnell were cinchonidine-derived phase-transfer catalysts. We were interested in developing a chiral proton catalyzed enantioselective addition of nitroacetic acid esters to imines as a method to generate α-amino acids. The products would also contain an orthogonally protected α,β-diamino acid motif. The use of nitroacetic acid derivatives as

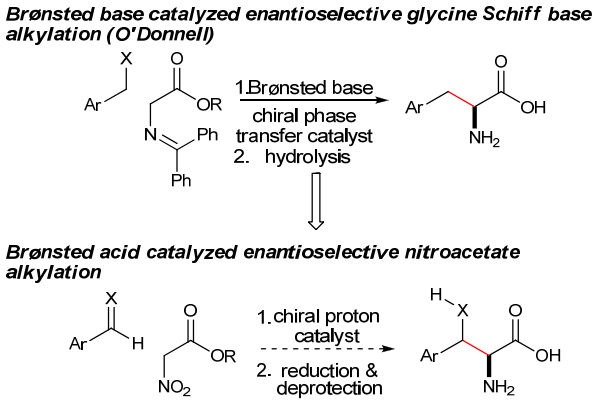
**Scheme 82.** Use of α-Nitrocetates in Enantioselective Transformations




[134] O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506.
[135] O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, 4625.

masked amino acids is well precedented[136] but their use in enantioselective transformations is limited to only two recent cases that produce non-epimerizable nitroacetate derivatives (Scheme 82).[137] Our strategy as an acid catalyzed complement to O'Donnell's Schiff base alkylation method is outlined in Scheme 83.

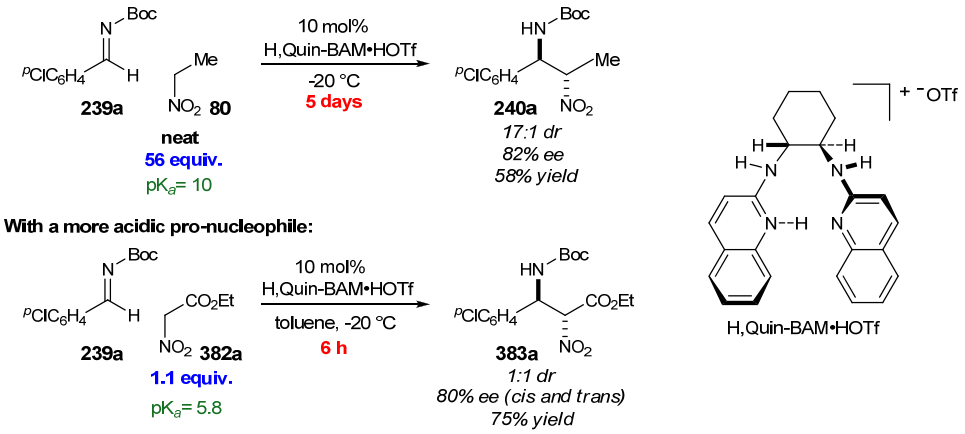
**Scheme 83.** Our Approach viz a viz O'Donneell's Approach




Preliminary experiments were performed with commercially available α-nitro ethyl acetate as the nucleophile. It was observed that the use of a single equivalent of the nucleophile and 10 mol% catalyst (H,Quin-BAM•HOTf) afforded the product in 80% ee. However, the diastereoselection was extremely poor (typically 1:1 to 2:1). Analysis of this result considering the three parameters of reactivity, distereoselection, and enantioselection indicated key differences as compared to the nitroalkane pronucleophiles. The direct aza-Henry reaction with nitroethane required the use of nucleophile as solvent and the reaction time was in the order of a few days. On the other

[136] (a) Shipchandler, M. T. *Synthesis* **1979**, 666. (b) Rosini, G.; Ballini, R. *Synthesis*, **1988**, 933. (c) Charette, A. B.; Wurz, R.P. ; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468. (d) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528.
[137] Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew Chem. Int. Ed.* **2005**, *44*, 105. (b) Knudsen, K. R.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.

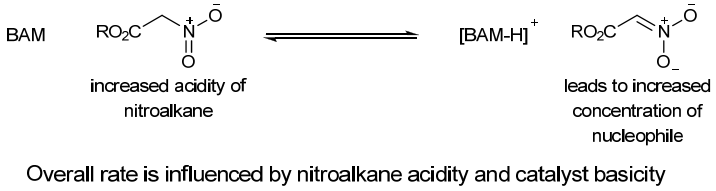
**Scheme 85.** Comparison of the Chiral Proton Catalyzed Additions of Nitroalkanes and Nitroacetates to Imines




hand, the reaction with ethyl nitroacetate was much faster and this can be attributed to the higher acidity of nitroacetates compared to nitroalkanes (Scheme 84).

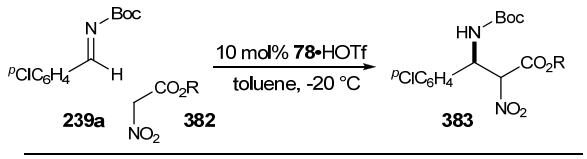
An underlying deduction from this phenomena is that the rate of the reaction is determined by the equilibrium governing the deprotonation of the pronucleophile by the catalyst, and hence, in order to increase the rate, either a more acidic nucleophile *or* a

**Scheme 84.** Principles for Obtaining Optimal Reactivity for Chiral Proton Catalyzed aza-Henry Reactions



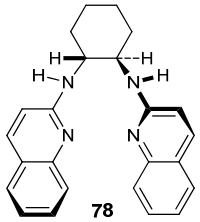

more basic catalyst needs to applied (Scheme 84). This concept was instrumental in solving low reactivity problem as described in Chapter 4. Enantioselection was expectedly similar to nitroalkanes and this is consistent with our stereochemical model which suggests that the primary mode of enantio-induction is through the activation of the imine by the catalyst. Hence, a slight change in the substitution of the nucleophile

**Table 9.** H,Quin-BAM•HOTf Catalyzed Addition of Nitroacetates to Imines: Initial Results




| entry | R | | dr[b] | %ee[b] *cis* | %ee[b] *trans* | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | Me | **b** | 1:1 | 82 | *nd* | 70 |
| 2 | Et | **a** | 1:1 | 80 | 80 | 75 |
| 3 | Bn | **c** | 1:1 | 71 | *nd* | 80 |
| 4 | $^t$Bu | **d** | 2:1 | 84 | 84 | 80 |

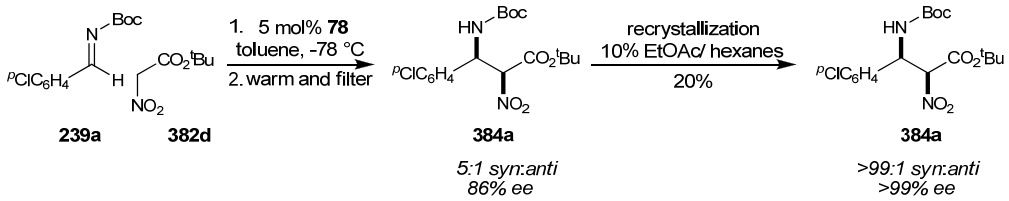
[a]All reactions were 0.3 M in substrate and proceeded to complete conversion. [b]Diastereomer and enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield.




would likely not affect the enantioselection to a large extent. The surprising part of this result was the low/non-existent diastereoselection as compared to nitroethane that afforded up to 19:1 dr. Since introduction of the ester group caused the dr to drop dramatically, it was hypothesized that the steric properties of the ester could be used to increase it. Limited success was achieved when a study performed by varying the ester groups revealed that *tert*-butyl nitroacetate afforded 84% ee and 2:1 dr (*syn:anti*) (Table 9). This nucleophile was chosen for further studies because of the ease with which the ester could be cleaved.

It was observed that if the reaction mixture was warmed after the reaction was complete, the diastereomeric ratio increased to about 4:1 (*syn:anti)*. It was soon

**Scheme 86.** *Syn* Selective Synthesis of Nitroacetate Adducts Using Recrystallization

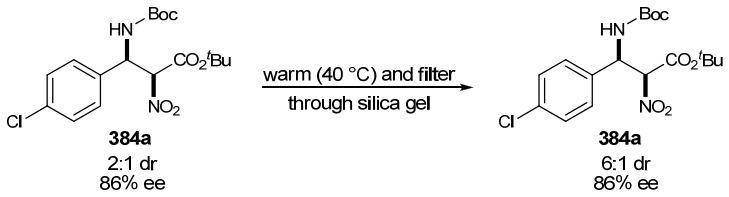



discovered that this ratio reflected the thermodynamic preference. Encouraged by this

observation, it was thought that recrystallization could be used as a means to obtain the product with high dr. As illustrated in Scheme 86, it was possible to get material with high optical purity but it turned out that the recrystallization was exceedingly difficult to reproduce. However, it was possible to obtain material consistently in 60-70% yield and 7:1 dr using the recrystallization process.

It was also observed that the high dr material epimerized over time to about a 4:1 mixture of diastereomers. It was clear at this point that the acidity of the nitroacetate was sufficient enough to cause tautomerization, causing the decrease in dr. We can rule out

**Scheme 87.** Epimerization of Nitroacetate Adducts

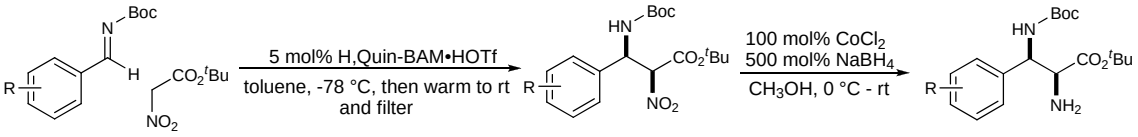



any retro-aza-Henry pathway for epimerization because the ee remained constant while the dr changed (Scheme 87). Additionally, the conservation of ee indicates that the benzylic carbon configuration is the same for both diastereomers. Using X-ray diffraction, it was determined that the major diastereomer (at equilibrium) was the *syn* diastereomer.[138]

Concurrent with the work to improve diastereoselection, an investigation was launched to assess the substrate scope of this reaction. As shown in Table 10, it was found that while some imines afforded products with high enantioselectivities, others gave uncharacteristically low enantioselection. The reduction protocol employed was a cobalt chloride mediated reduction by sodium borohydride. The enantiomeric excess of

[138] Pink, M; Shen, B.; Johnston, J. N. Unpublished results.

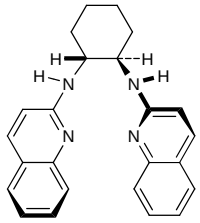
**Table 10.** H,Quin-BAM•HOTf Catalyzed Addition of Nitroacetates to Imines: Scope




**239** **382d** **384** **385**

| entry | R | | dr[b] | %ee[b] | yield(%)[c] |
|---|---|---|---|---|---|
| 1 | OAc | **d** | 3:1 | 85 | 74 |
| 2 | $^{p}CO_2Me$ | **c** | 2:1 | 85 | 82 |
| 3 | $^{p}Cl$ | **a** | 2:1 | 86 | 81 |
| 4 | $^{p}Me$ | **e** | 2:1 | 81 | 81 |
| 5 | Ar=2-naphthyl | **f** | 2:1 | 78 | 84 |
| 6 | $^{p}F$ | **g** | 2:1 | 67 | 79 |
| 7 | $^{o}CF_3$ | **h** | 2:1 | 70 | 80 |
| 8 | Ar=1-naphthyl | **i** | 2:1 | 62 | 83 |

[a]All reactions were 0.30 M in substrate and proceeded to complete conversion. [b]Diastereomer and enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after two step.

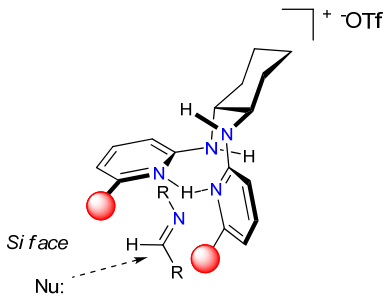


H,Quin-BAM

most of the adducts was determined at the amine stage. It had been established previously that the reduction process does not change the enantiomeric excess of the products.

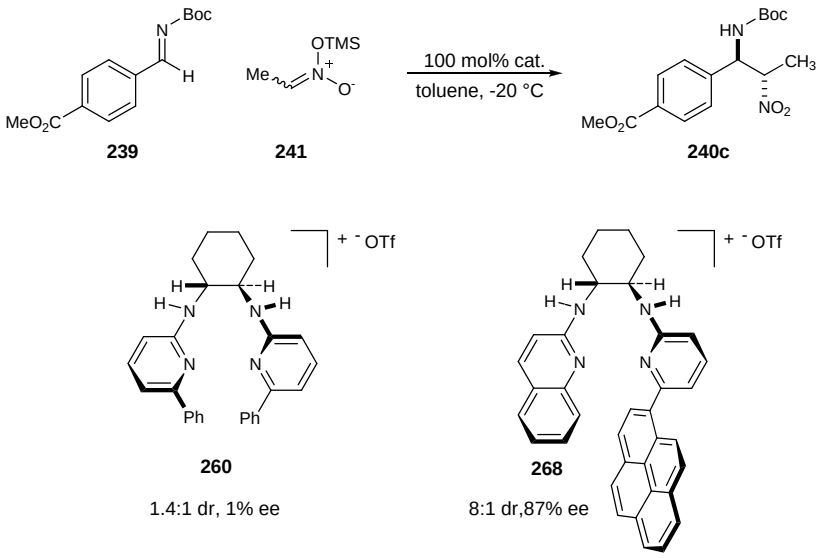
We hypothesized that a suitable change in catalyst structure might allow us to improve the diastereo- and enantioselection in these reactions. Guided by the stereochemical model for these reactions, it appeared that an improvement in facial selectivity could be achieved by incorporating a better shielding group on the six position of the pyridine rings. Catalyst modification studies with the indirect aza-Henry reaction indicated that substitution of bulky groups on the 6-position of both pyridine rings led to

**Figure 18**



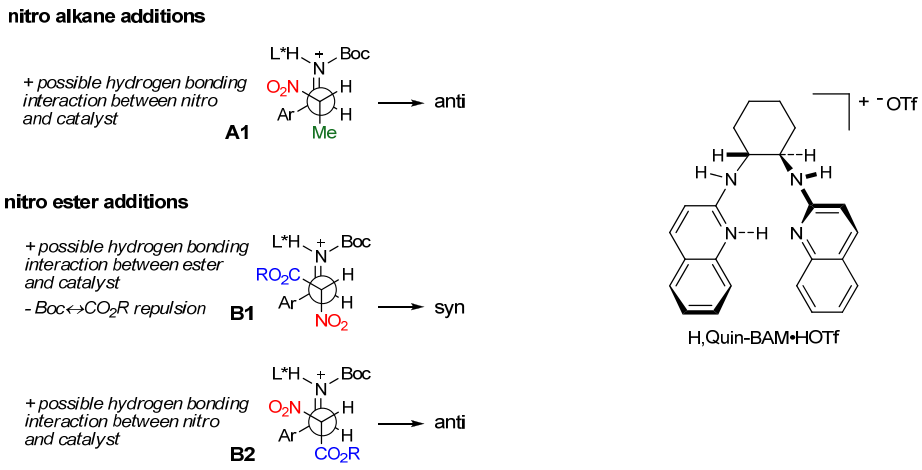
loss of enantioselection but the use bulky unsymmetrical catalysts maintained high enantioselection. We anticipated that the application of bulky unsymmetrical catalysts might afford the desired increase in enantioselection.

**Scheme 88**



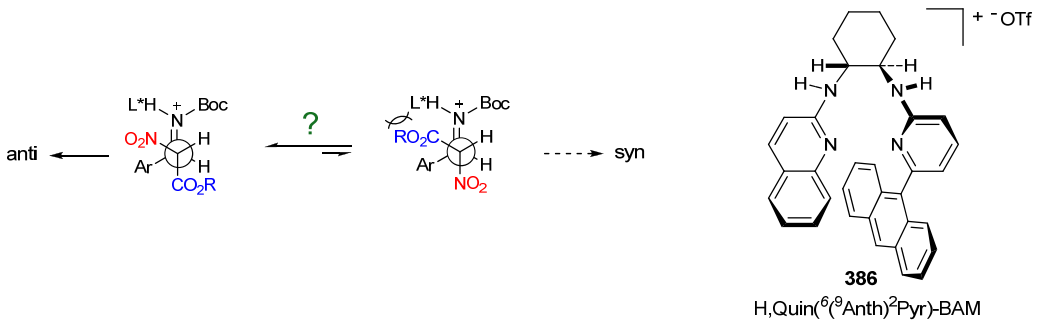

The production of nitroacetate adducts favoring the *syn*-diastereomer was in

**Figure 19**



contrast to the nitroalkane additions where the *anti*-adducts were favored. We hypothesized that this reversal in diastereoselection is a result of the competition between the ester and nitro groups for hydrogen bonding to the catalyst. Furthermore, we anticipated that catalyst control could be employed to influence this outcome. Specifically, we were interested in using bulky catalysts to disfavor the H-bonding interaction between the ester and catalyst which might result in the recovery of *anti*-diastereoselection.

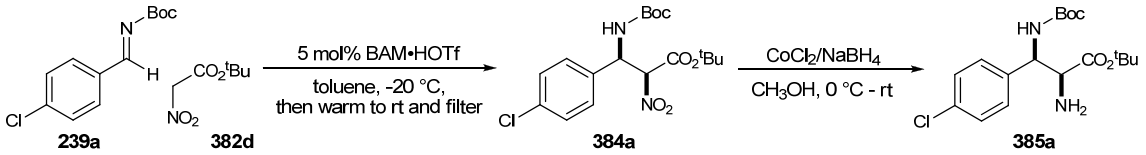
**Figure 20.** Hypothesis for Favoring the Formation of the *anti*-Diastereomer by Using Bulky Catalysts




The difficulty in solving these problems is accentuated by the fact that we must identify and develop a catalyst that incorporates all the structural features required in order to achieve high diastereo- and enantioselection. As mentioned above, our studies with the silyl nitronate additions suggested that unsymmetrical catalysts with hindered catalyst pockets might provide the requisite properties that we desire. In order to test our hypothesis, we evaluated a number of unsymmetrical BAM•HOTf catalysts for the addition of *tert*-butyl nitroacetate to imines. It was found that the catalyst with a 6-methyl group afforded modest enantioselection and low diastereoselection. Compared to H, Quin-BAM•HOTf , the enantioselection was diminished. Undaunted, we then proceeded to evaluate the 6-phenyl derivative **263** which also proved to be less effective than H,

Quin-BAM•HOTf. Gratifyingly, the application of catalysts with large aromatic substitutions at the 6-position (pyrene and anthracene) afforded the desired increase in enantioselection. Importantly, the catalyst loading could be lowered to 5 mol% without adversely affecting the stereochemical outcome.

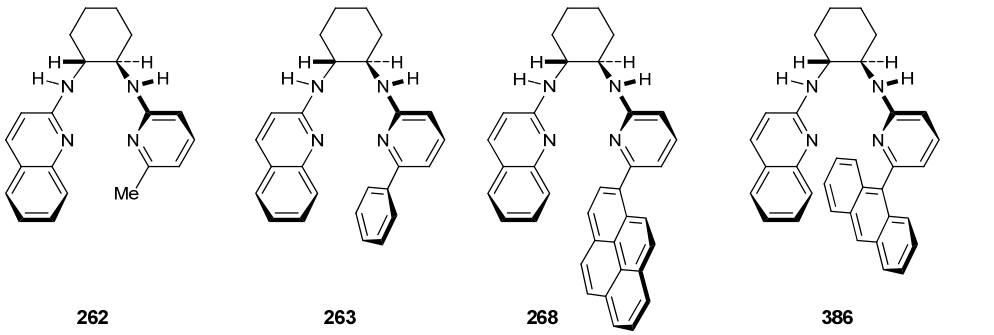
**Table 11.** Application of Unsymmetrical Catalysts to Increase Enantioselection




239a 382d 384a 385a

| entry | catalyst | %ee[b] |
|---|---|---|
| 1 | **262**•HOTf | 73 |
| 2 | **263**•HOTf | 54 |
| 3 | **268**•HOTf | 92 |
| 4 | **386**•HOTf | 93 |

[a]All reactions were 0.3 M in substrate and proceeded to complete conversion. [b]Diastereomer and enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield.



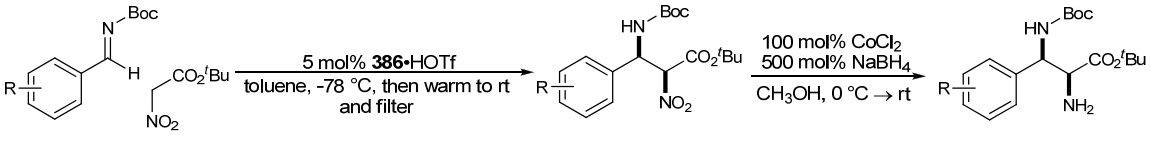

**262** **263** **268** **386**

H,$^{2}$Quin($^{6}$Me)-BAM H,Quin($^{6}$Ph)-BAM H,Quin($^{6}$($^{9}$Anth)$^{2}$Pyr)-BAM H,Quin($^{6}$($^{9}$Anth)$^{2}$Pyr)-BAM

Although we had designed catalyst **386** as a means to enhance *anti*-diastereoselection in addition to improving ee, we first decided to evaluate the scope of this increase in enantioselection across a range of imines. It was decided to use catalyst **386** for further studies (Table 11) and we were delighted to obtain (Table 12) improved enantioselection for a variety of imines. The new catalyst **386** provided high

enantioselection even for substrates that previously gave much lower enantioselection with H,Quin-BAM•HOTf.

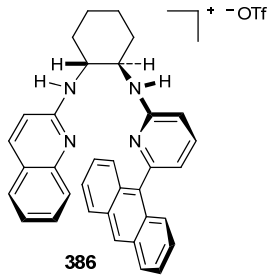
**Table 12.** Application of α-Nitroacetates as Glycine Equivalents using Chiral Proton Catalysis: Improved Scope and Enantioselection




239 382d 384 385

| entry | R | | dr[b] | %ee[b] | yield(%) |
|---|---|---|---|---|---|
| 1 | OAc | **d** | 3:1 | 99 | 74 |
| 2 | $^{p}CO_2Me$ | **c** | 2:1 | 95 | 83 |
| 3 | $^{p}Cl$ | **a** | 5:1 | 95 | 86 |
| 4 | $^{p}Me$ | **e** | 2:1 | 93 | 85 |
| 5 | Ar=2-naphthyl | **f** | 2:1 | 91 | 80 |
| 6 | $^{p}F$ | **g** | 4:1 | 93 | 85 |
| 7 | $^{o}CF_3$ | **h** | 2:1 | 80 | 80 |
| 8 | Ar=1-naphthyl | **i** | 2:1 | 83 | 71 |

[a]All reactions were 0.30 M in substrate and proceeded to complete conversion. [b]Diastereomer and enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield after two step.



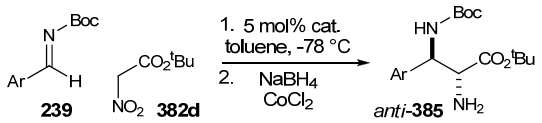

386

H,Quin($^{6}$,$^{9}$Anth)$^{2}$Pyr)-BAM

Although the issue of low substrate scope was resolved, the low dr remained a persistent problem (Table 12) although warming the reaction post-addition might epimerize any *anti*-adduct that might have been formed. It was contemplated that the catalyst might favor the kinetic diastereomer, and if epimerization could be avoided during isolation and reduction, product with high dr might be obtained. $^{1}$H NMR analysis of a reaction performed at -78 °C revealed that products were indeed being formed in high dr. Also identified was the fact that this was the *anti* diastereomer (by comparison of NMR data). However, attempts to purify this compound by chromatography (on silica gel) afforded only a 2:1 dr material now favoring the *syn* diastereomer. The epimerization was found to be accelerated by exposure to silica gel. However, it was evident that if the crude reaction mixture was allowed to sit at room temperature for extended periods of time, epimerization would occur. The sensitivity of the product to silica gel made it

difficult to separate it from the catalyst. Hence, it was decided that the reduction would be performed on the crude reaction mixture. To our delight, we observed that the dr was conserved after the reduction, and the amino esters could be obtained in good yields. Table 13 compares the results between the two catalysts.

**Table 13.** Comparison of Catalysts **78** and **386** for the Catalyzed Additions of *tert*-Butyl Nitroacetate to Imines

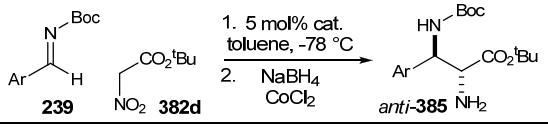



| entry | Ar | | catalyst | dr[b] (**5**) | dr[b] (**6**) | %ee[b] (**6**) | yield[c] |
|---|---|---|---|---|---|---|---|
| 1 | $^{p}$Cl | **a** | **78**•HOTf | 1:2 | 1:2 | 84 | 80 |
| 2 | $^{p}$Cl | **a** | **386**•HOTf | 5:1 | 5:1 | 95 | 88 |
| 3 | $^{p}$AcO | **d** | **78**•HOTf | 2.5:1 | 2.2:1 | 85 | 76 |
| 4 | $^{p}$AcO | **d** | **386**•HOTf | 11:1 | 11:1 | 89 | 74 |
| 5 | $^{2}$Np | **f** | **78**•HOTf | 4:1 | 4:1 | 78 | 69 |
| 6 | $^{2}$Np | **f** | **386**•HOTf | 12:1 | 11:1 | 91 | 80 |
| 7 | $^{p}$F | **g** | **78**•HOTf | - | 1:1 | 67 | 80 |
| 8 | $^{p}$F | **g** | **386**•HOTf | - | 7:1 | 93 | 81 |

[a]All reactions were 0.30 M in substrate and proceeded to complete conversion. [b]Diastereomer ratios were measured by $^{1}$H NMR (a reliable measurement was not possible for the addition product for entries 7-8). Enantiomer ratios were measured using chiral stationary phase HPLC. [c]Isolated yield (two steps).

It was found that reaction was very general and afforded *anti* α,β-diamino esters in good

**Table 14.** Chiral Proton Catalyzed Addition of α-Nitroesters to Azo-methines: Scope



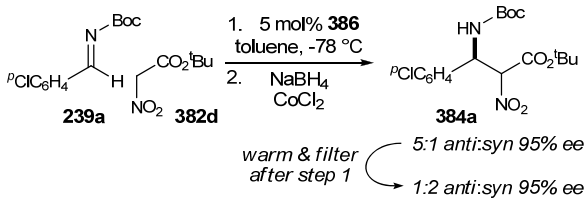

| entry | Ar | | catalyst | dr[b] (**5**) | dr[b] (**6**) | %ee[b] (**6**) | yield[c] |
|---|---|---|---|---|---|---|---|
| 1 | $^{p}$Cl | **a** | **386**•HOTf | 5:1 | 5:1 | 95 | 88 |
| 2 | $^{p}$AcO | **d** | " | 11:1 | 11:1 | 89 | 74 |
| 3 | $^{2}$Np | **f** | " | 12:1 | 11:1 | 91 | 80 |
| 4 | $^{p}$F | **g** | " | - | 7:1 | 93 | 81 |
| 5 | $^{p}$CF$_3$ | **j** | " | 7:1 | 7:1 | 88 | 83 |
| 6 | $^{p}$Me | **e** | " | 6:1 | 6:1 | 95 | 81 |
| 7 | $^{m}$PhO | **k** | " | 6:1 | 6:1 | 87 | 84 |
| 8 | $^{m}$Cl | **l** | " | 10:1 | 10:1[d] | 87 | 70 |
| 9 | $^{p}$MeO$_2$C | **c** | " | 8:1 | 8:1 | 95 | 84 |

[a]All reactions were 0.30 M in substrate and proceeded to complete conversion. [b]Diastereomer ratios were measured by $^{1}$H NMR (a reliable measurement was not possible for the addition product for entries 7-8). Enantiomer ratios were measured using chiral stationary phase HPLC. See Experimental Section for complete details. [c]Isolated yield (two steps). [d]Measured by GC.

yields for a wide variety of electronically diverse aldimines (Table 14).

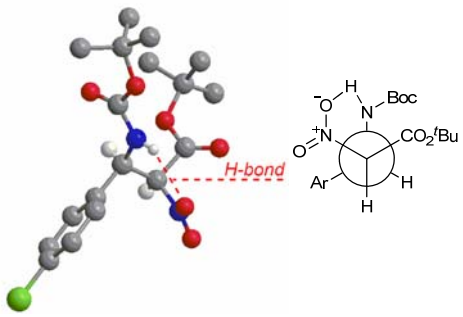
It was estabilished that the *anti* diastereoselection represents a kinetic selectivity by subjecting the product to conditions that favor epimerization. It was observed that a 5:1 (*anti*:*syn*) mixture resulted in a 1:2 (*anti*:*syn*) mixture after warming and filtering the

**Scheme 89.** Establishment of the *anti*-Diastereomer as the Kinetic Product




reaction mixture through silica gel (Scheme 89).[139] This post addition epimerization also highlights the fact that this catalyst can selectively deprotonate **382d** in a mixture of **382d** and **384**. Figure 21 shows the crystal structure of ***syn*-384a**. The H-bond between the carbamate N-H and nitro oxygen explains why the *syn* adduct might be favored thermodynamically.

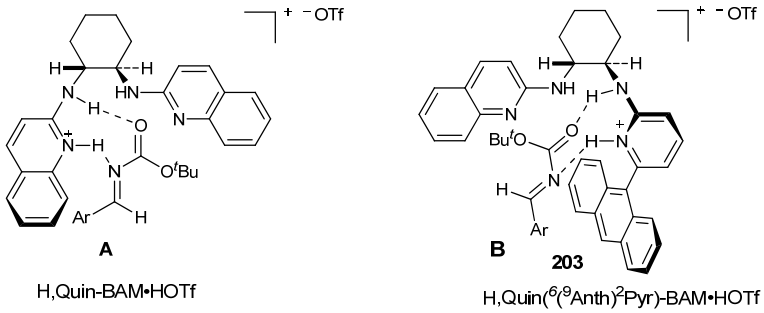
**Figure 21** Crystal Structure of ***syn*-384a**




[139] Note: Silica gel is not necessary for the epimerization but it accelerates the process.

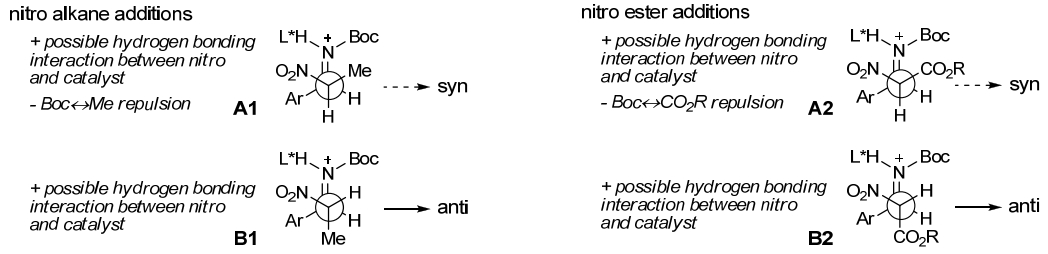
The stereochemical outcome of the nitroalkane and nitroacetate additions allow us to comment on the stereochemical model proposed in Chapter 1. The observation that the configuration of the imine derived carbon of the nitroacetate adducts and their nitroalkane counterparts are the same suggests similar orientation of the substrates by the catalyst. The unsymmetrical H,Quin$^{6}$($^{9}$(Anth)$^{2}$Pyr)BAM•HOTf has a significantly different structure than the symmetrical H,Quin-BAM•HOTf. The fact that these structural differences do not translate to a difference in the sense of enantioselection of the products lends itself as a support for our stereochemical model which proposes the bidentate chelation of the ligand to the proton. For example, were the catalyst were to bind simply as an amidinium ion, H,Quin-BAM•HOTf would offer equivalent binding sites, whereas H,Quin$^{6}$($^{9}$(Anth)$^{2}$Pyr)BAM•HOTf would offer competing recognition motifs (Figure 22).

**Figure 22.** Depiction of a Possible Scenario Alternate to the Proposed Stereochemical Model




The conservation of the kinetic, *anti*-diastereoselectivity in both these reactions

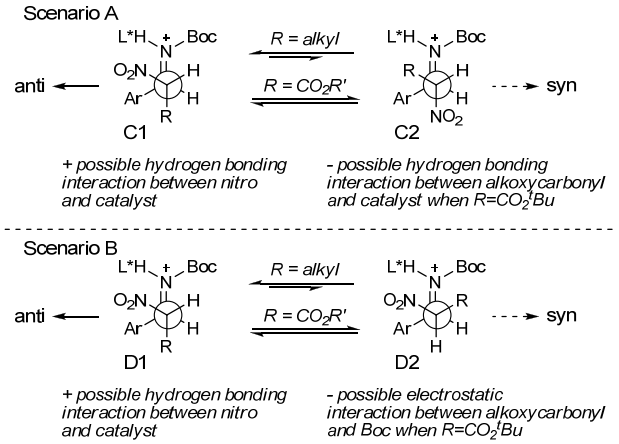
**Figure 23.** Newmann Projections for Nitroalkane and Nitroacetate Additions to Azomethines: Rationale for *anti*-Diastereoselectivity



(nitroalkane and nitroacetate additions) indicates that the catalyst plays an important role in determining diastereoselection. A rationale for the observed diastereoselectivity is presented in the Figure 23. The preference for the *anti*-diastereomer can be attributed to the possible hydrogen bonding interaction between the nitro group of the nucleophile and the imine bound catalyst. Additionally, the *syn* diastereomer might be disfavored by invoking repulsive interactions between the Boc group on the imine nitrogen and the alkyl (or ester) group on the nucleophile.

Although Figure 23 explains why the *anti*-diastereoselection is observed, it does not explain why there was no diastereoselectivity in nitroacetate additions when H,Quin-BAM•HOTf was used as the catalyst. Figure 24 illustrates two possible explanations for this observation. The first hypothesis was that the ester might compete with the nitro group to establish a hydrogen bonding interaction with the catalyst. This would allow an equilibrium between C1 and C2 leading to loss of diastereoselection. Since there is no

**Figure 24.** Two Scenarios Depicting Principal Assumptions for the Stereochemical Analysis of the Conserved (Kinetic) *anti*-Selectivity: Nitroalkane and Nitroester Additions




such possibility for nitroalkanes, C1 is the preferred conformer, leading to *anti* adducts. The second hypothesis uses the steric difference between the planar ester group and the

tetrahedral alkyl group. A smaller ester substituent would exist in equilibrium between D1 and D2 while D1 would be the preferred conformer for the alkyl group.

In conclusion, a diastereoselective and enantioselective synthesis of α, β-diamino esters was achieved in a single transformation utilizing chiral proton catalysis. In addition, the amine functionalities are now orthogonally protected providing opportunity for further chemoselective modifications. Comparison of the stereochemical outcome for the nitro esters and nitroalkane adducts allows us to understand the catalyst's role in diastereoselection and also lends support to our model for enantioselection.

## *CHAPTER IV*

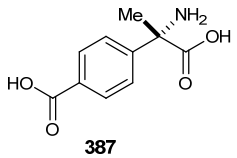
# *CHIRAL PROTON CATALYZED ENANTIOSELECTIVE ADDITIONS OF α-SUBSTITUTED NITROACETATES TO AZOMETHINES: SYNTHESIS OF α,α-DISUBSTITUTED α,β-DIAMINO ACID DERIVATIVES*

## *4.1 Synthetic Approaches Towards Enantiopure α,α-Disubstituted α,β-Diamino Acids*

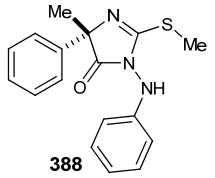
Non-proteinogenic α,α-disubstituted α-amino acids have attracted the attention of scientists in biochemistry and drug discovery due to their ability to modify the physical and chemical properties of peptides upon incorporation. α,α-disubstituted α-amino acid residues can impart helix-inducing properties when incorporated into peptides. This property is responsible for the membrane destabilization activity of peptaibols (a class of peptide broad-spectrum antibiotics).[140] These residues also enhance the resistance of constituent peptide towards chemical and enzymatic degradation.[141, 142]

Some α,α-disubstituted α-amino acids display interesting properties on their own accord, including enzyme inhibiton. α-Methyl-4-carboxyphenylglycine (MCPG) was the first compound discovered which displayed antagonist action at metabotopic glutamate

**Figure 25.**




**387**
MCPG



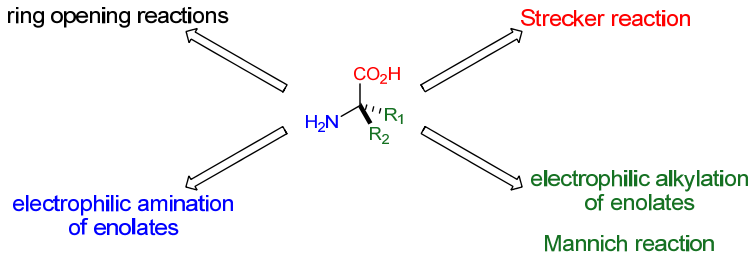

**388**
(*S*)-fenamidone

[140] Degenkolb, T.; Berg, A.; Gams, W.; Schlegel, B.; Grafe, U. *J. Pept. Sci.* **2003**, *9*, 666.
[141] Polinelli, S.; Broxterman, Q. B.; Schoemaker, H. E.; Boesten, W. H. J.; Crisma, M.; Valle, G.; Toniolo, C.; Kamphius, J. *Bioorg. Med. Chem. Lett.* **1992**, *5*, 453.
[142] O'Connor, S. J.; Liu, Z. *Synlett* **2003**, *14*, 2135.

receptors.[143] Another example is (*S*)-fenamidone which is a highly efficient fungicide.[144]

The synthesis of α,α-disubstituted α-amino acids has received considerable attention and it is still a much sought after transformation owing to the difficulty in the stereoselective creation of a fully substituted carbon center. Figure 26 shows the various approaches to these unnatural amino acids. Continuing with our interest in the synthesis

**Figure 26.** Approaches Towards α,α,-Disubstituted α-Amino Acids




of α,β-diamino acids, we decided to investigate if chiral proton catalysis would enable the synthesis of α-tetrasubstituted carbon centers in a stereoselective manner. The resulting α-substituted α,β-diamino acids would hence be a subset of the α,α-disubstituted amino acid family of compounds. Relevant syntheses of α-substituted α,β-diamino acids reported in the literature are discussed in the following sections.

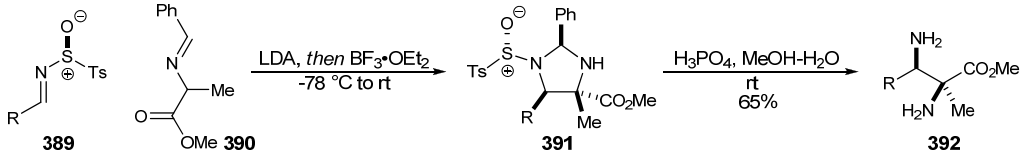
### *4.1.1 Approaches Employing Carbon-Carbon Bond Formation*

Diastereoselective enolate additions to enantiopure sulfinyl imines has been employed for the synthesis of α-tetrasubstituted α,β-diamino acids. Lithiated amino esters **390** react with sulfinimines **389** in the presence of $BF_3$•$OEt_2$ to afford 2-carbomethoxy-*N*-sulfinyl imidazolidines in a highly diastereoselective manner (Scheme 90). The application of standard aminal cleavage procedures can be used to reveal the α,β-diamino

[143] Schoep, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431.
[144] Genix, P.; Guesnet, J. L.; Lacroix, G. *Pflanzenschutz-Nachr. Bayer, Engl. Ed.* **2003**, *56*, 421.

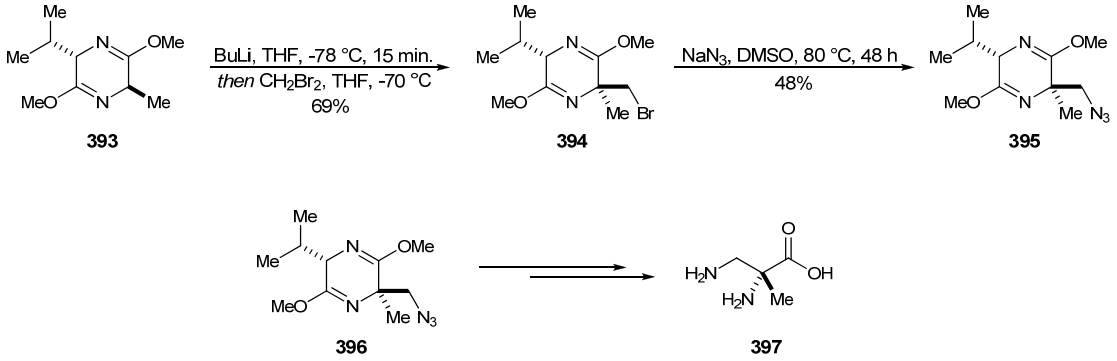
esters. The modulation of the aminal cleavage conditions allow either the deprotection or the preservation of the sulfinamide moiety. The use of a nucleophilic solvent (MeOH) deprotects the sulfonamide while the use of a non-nucleophilic solvent (THF) retains the protecting group. An interesting observation was that the use of racemic sulfinyl imine did not afford any diastereoselection.[145,146]

**Scheme 90.**




The alkylation of glycinates is a well studied method for the synthesis of amino acids and has also been applied towards the synthesis of α-substituted α,β-diamino acids.

**Scheme 91.**



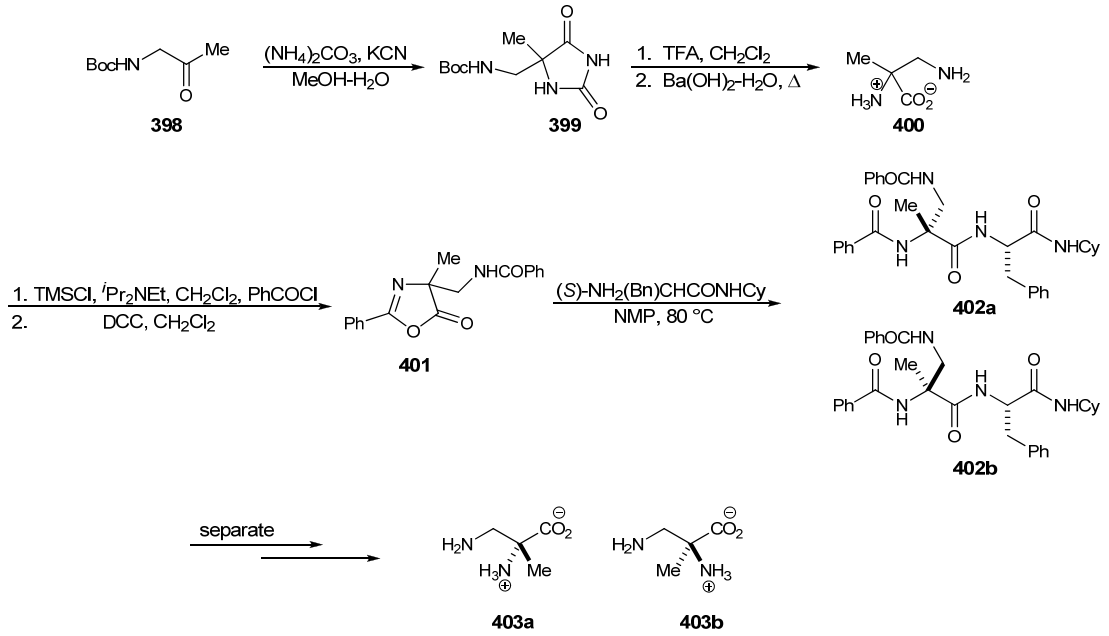

Mittendorf and co-workers have reported the diastereoselective alkylation of the bis-lactam ether **393** with dibromomethane followed by the substitution of the bromomethyl bislactam ether by sodium azide. The azide was subsequently reduced, and following a

[145] Viso, A.; Fernandez de la Pradilla, R.; Lopez-Rodrigues, M. L.; Garcia, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542.
[146] Viso, A.; Fernandez de la Pradilla, R.; Garcia, A.;Alonso, M.; Guerrero-Strachan, C.; Fonseca, I. *Synlett* **1999**, 1543.

six step sequence, enantiopure α-methyl-α,β-diamino acid was obtained as a hydrochloride salt (Scheme 91).[147]

The Bucherer-Bergs reaction has been applied by Obrecht as a tool to access enantiopure diamino acids although this method involves separation of a diastereomeric

**Scheme 92.**



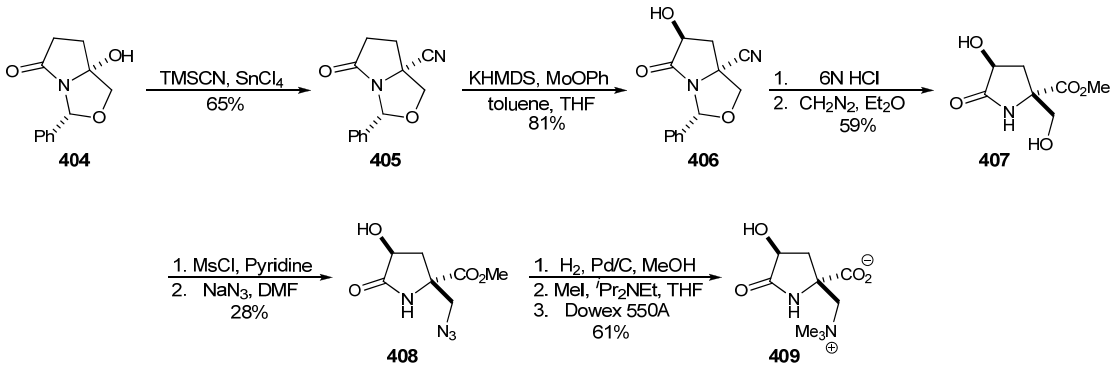

mixture and hence is not enantio- or diastereoselective. As shown in Scheme 92, the reaction of α-amido ketones with potassium cyanide in the presence of ammonium carbonate produces racemic hydantoins in good yields. After the cleavage of the carbamate and saponification, the racemic α-alkyl α,β-diamino acids were obtained. *N*-benzoylation and cyclization of the diamino acids provided the oxazolone **401**. Condensation with L-phenyl alanine cyclohexyl amide furnished diastereomeric peptides

[147] Hartwig, W.; Mottendorf, J. *Synthesis* **1991**, 939.

that were readily separated. Ultimately, peptide cleavage and removal of the benzamide protecting groups afforded both enantiomers of 2-amino-methyl alanine.[148]

The Strecker reaction has been employed for the total synthesis of (*S*)-dysibetaine which is a cyclic α-alkyl α,β-diamino acid. The requsite iminium ion for the addition of cyanide was generated from enantiopure bicyclic δ-lactam **404**. A diastereoselective addition of trimethylsilyl cyanide provided **405** which was further hydroxylated at C-4 in a highly diastereoselective fashion. Hydrogenolysis followed by acidic hydrolysis and esterification furnished the hydroxymethyl lactam **407**. Subsequent mesylation of the primary hydroxyl group was followed by substitution with azide. This set the stage for the reduction and deprotection steps ultimately leading to the synthesis of (2*S*, 4*S*)-dysibetaine (Scheme 93).[149]

**Scheme 93**

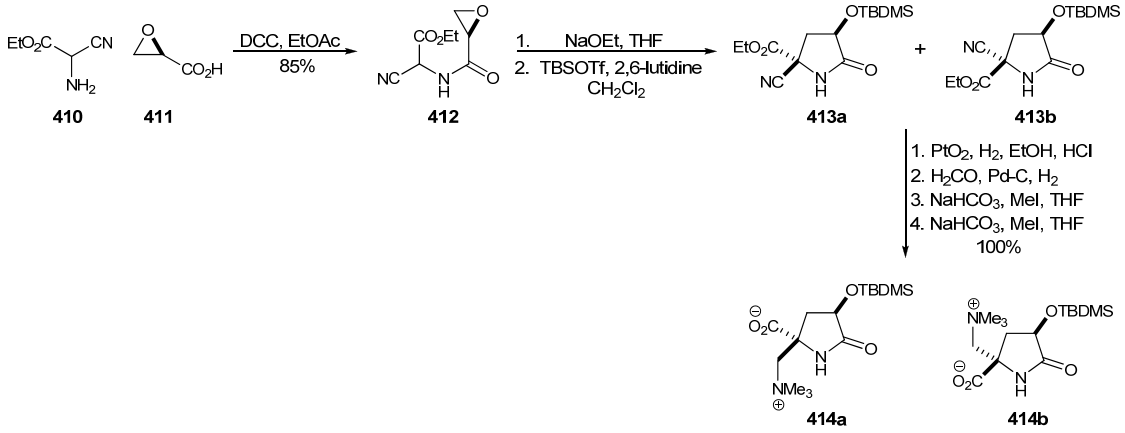



Snider has reported the total synthesis of two additional diastereomers of dysibetaine using oxirane ring opening as the key step. As shown in Scheme 94, the synthesis commences with the *N*-acylation of ethyl amino(cyano)acetate with enantiopure glycidic acid to afford the glycinamide **412**. On treatment with NaOEt, the glycinamide

[148] Obrecht, D.; Karajiannis, H.; Lehman, C.; Schonholzer, P.; Spielger, C.; Muller, K. *Helv. Chim. Acta* **1995**, *78*, 703.
[149] Langlois, N.; Le Nguyen, B. K. *J. Org. Chem.* **2004**, *69*, 7558.

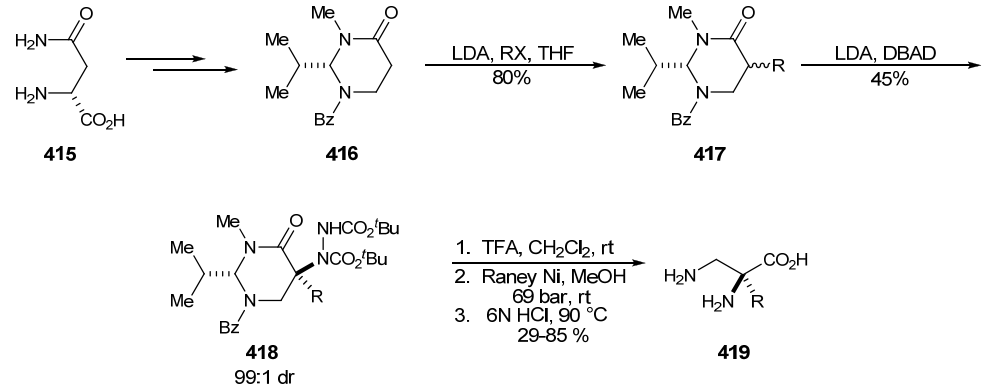
undergoes intramolecular alkylation to afford a diastereomeric mixture (45:55) of pyrrolidinones that were readily separated after silylation. Subsequent reduction of the cyano group followed by exhaustive methylation and saponification afforded the desired dysibetaines.[150]

**Scheme 94.**




One of the less explored methods is the introduction of substituents on a diamine backbone. An example pertinent to the synthesis of α-alkyl α,β-diamino acids was

**Scheme 95**



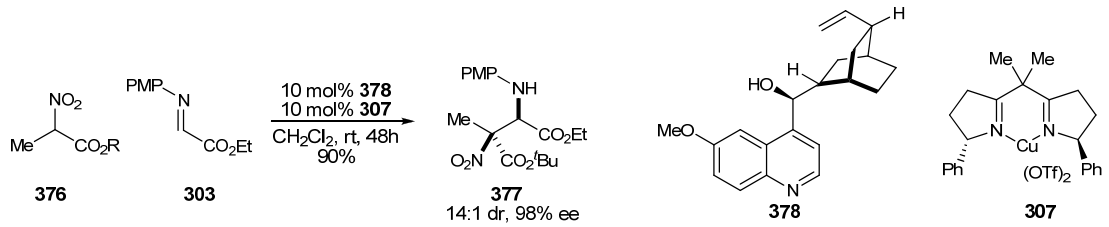

reported by Juaristi. The route relies on the optically pure pyrimidone which is available

[150] Snider, B. B.; Gu, Y. *Org. Lett.* **2001**, *3*, 1761.

from asparagine in 5 steps. This intermediate is subjected to alkylation using LDA and alkyl halides, although this proceeded with low diastereoselectivity. The following electrophilic amination with DBAD afforded **418** in a highly diastereoselective fashion. After an additional three steps accomplished the deprotection of various groups, the free diamino acid was obtained (Scheme 95).[151]

The aza-Henry reaction was first applied to the synthesis of precursors to these amino acids by Jorgensen who demonstrated that α-substituted nitroacetate **376** can be added to glyoxyl imine **303** in 14:1 dr and 98% ee. The catalysis was performed by a two-catalyst system wherein Cu(II)-BOX and cinchona alkaloid catalysts were used to activate the electrophile and nucleophile respectively. However, only one example was published and it was not established as a general method (Scheme 96).[152]

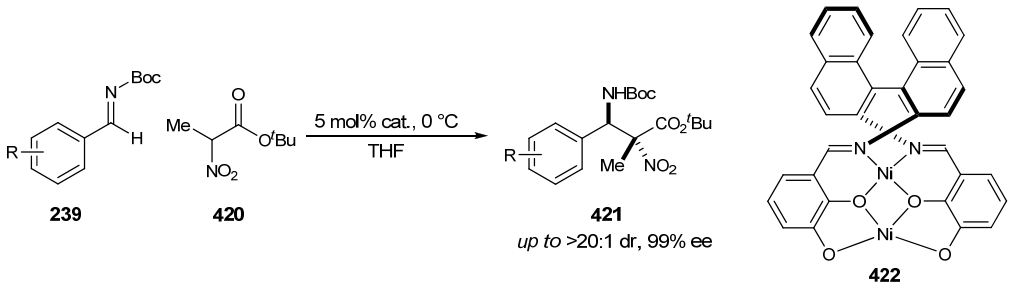
**Scheme 96**




Shortly before our work was published, Shibasaki reported a homodinuclear Ni(II)-Schiff base complex for the addition of α-substituted nitroacetates to *N*-Boc imines. The *anti*-adducts were obtained with high dr and excellent enantioselection. Three examples of enolizable alkyl imines were also found to undergo the reaction to produce products in

[151] Castellanos, E.; Reyes-Rangel, G.; Juaristi, E. *Helv. Chim. Acta.* **2004**, *87*, 1016.
[152] Knudsen, K. R.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.

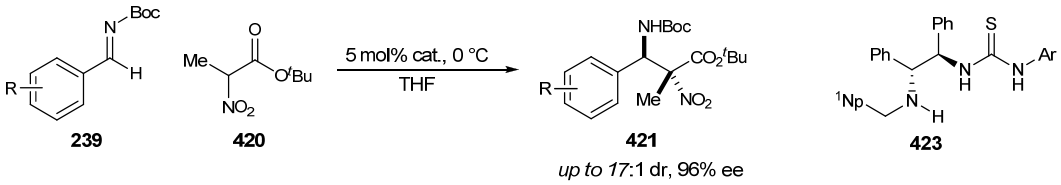
**Scheme 98**




high diastereo- and enantioselection although the yields were diminished compared to the aryl imines (Scheme 98).[153]

After our work was reported, Chen and co-workers reported the use of thiourea/secondary amine catalysts for the enantioselective addition of α-substituted nitroacetates to *N*-Boc imines. *syn*-Adducts were obtained in moderate to good dr and

**Scheme 97**

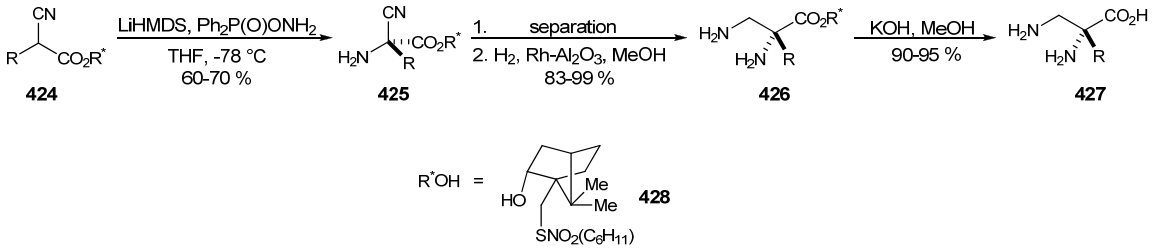



with high enantioselection. It was found that catalysts derived from 1,2-diphenylethylene diamine backbone were most efficient, and that a secondary amine moiety was critical in order to obtain high diastereo- and enantioselection (Scheme 97).[154]

[153] Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.
[154] Han, B.; Liu, Q-P.; Li, Rui.; Tian, X.; Xiong, X-F.; Deng, J-G.; Chen, Y-C. *Chem. Eur. J.* **2008**, *14*, 8094.

### *4.1.2 Approaches Employing Carbon-Nitrogen Bond Formation*

**Scheme 99.**



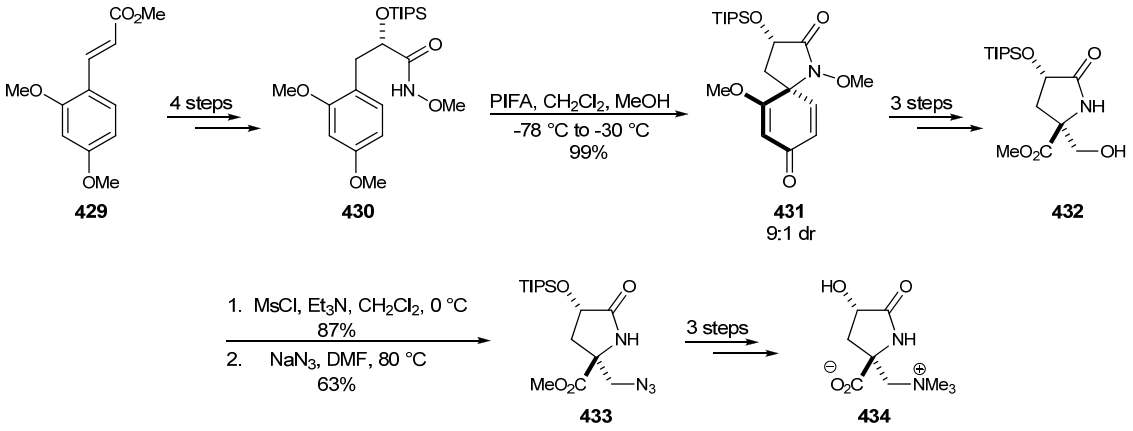

2-Cyano propanoates have been subjected to electrophilic amination in order to lead to α,β-diamino acids. Cativiela has reported that 2-alkyl and 2-benzyl-2-cyano propanoates containing a (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)-isobornyloxy group as a chiral auxiliary (R*) can be converted into 2-amino-2-cyano propanoates. The use of LHMDS and *O*-(diphenylphosphinyl)-hydroxylamine allows the amination to occur with moderate to good diastereoselectivity. Separation of diastereomers followed by hydrogenation reveals the diamino ester as a single diastereomer which leads to the enantiopure diamino acid upon hydrolysis with KOH/methanol (Scheme 99).[155]

The strategy of electrophilic amination has also been applied to the synthesis of (-)-dysibetaine. Wardrop's route to this target started from the α,β-unsaturated ester **429** which was converted to the enantiopure α-silyloxy methoxylamide **430** in 4 steps using Sharpless asymmetric dihydroxylation as the key step. PIFA was employed to promote the formation of the spirodienone **431** as an inseparable mixture of C-5 epimers. Following ozonolysis, reduction of the formyl group, and cleavage of the N-O bond, pyrrolidinone **432** was obtained. Conversion of the primary alcohol to a mesylate followed by displacement by azide set the stage for the end game which involved silyl

[155] Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2787.

deprotection, exhaustive methylation, and ester hydrolysis to afford the desired molecule (Scheme 100).[156]

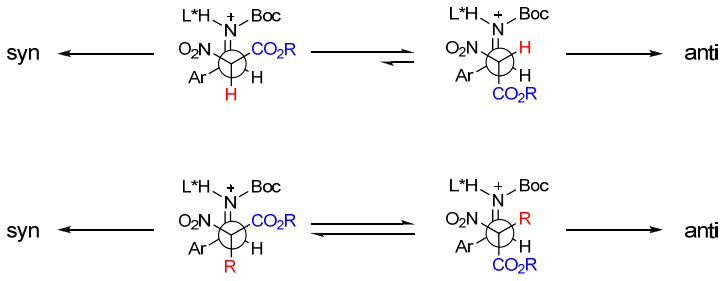
**Scheme 100.**




## *4.2 Strategic Considerations and Preliminary Results of Chiral Proton Catalyzed Synthesis of α-Substituted α,β-Diamino Acids*

The success of BAM•HOTf ligands in catalyzing the addition of α-unsubstituted nitroacetates indicates that the corresponding addition might be possible with the α-substituted derivatives although the use of more sterically hindered nucleophiles would

**Figure 27.** Hypothesis for the Expected Erosion of Diastereoselection in the Case of Substituted Nitroacetates as Compared to their *Un*substituted Analogues



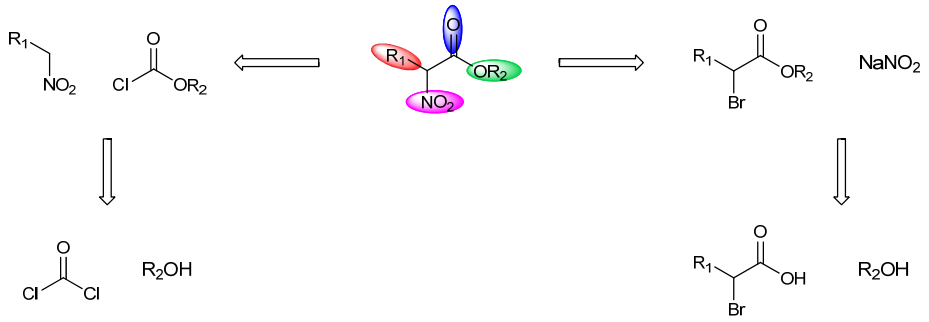

be expected to decrease reactivity. The substitution of a hydrogen atom with an alkyl group can also be expected to decrease diastereoselection (Figure 27) since the distinction

[156] Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230.

in the steric bulk of the groups being differentiated (ester and alkyl) would be diminished (compared to ester and H).

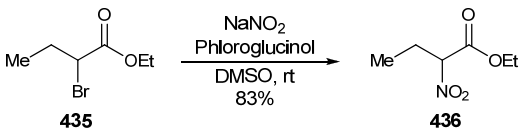
The synthesis of the requisite pronucleophiles can be envisioned in two ways: a

**Figure 28.** Complementary Approaches Towards the Synthesis of α-Alkyl Nitroesters




displacement reaction by nitrite anion on α-bromoesters or the use of nitronates as nucleophiles for an acylation reaction. The synthesis of nitroalkanes by the displacement of alkyl bromides and α-bromo esters has been extensively studied by Kornblum. This

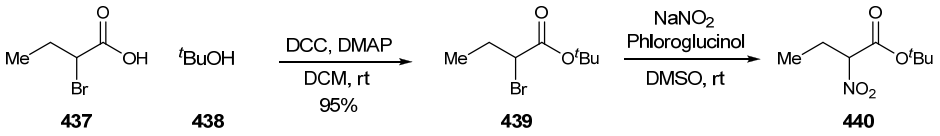
**Scheme 101.**




method is complicated by the ambident nature of the nitrite nucleophile which leads to *O*-alkylation products but this can be circumvented by the use of phloroglucinol as the alkyl-nitrite scavenger. Overall, this method offers the advantages of operational simplicity and cost-effectiveness. One limitation of Kornblum's method was that only α-bromo esters with an α-substituent underwent the displacement smoothly to produce the desired nitroacetate. In the absence of the α-substitutent (eg. ethyl bromoacetate), the

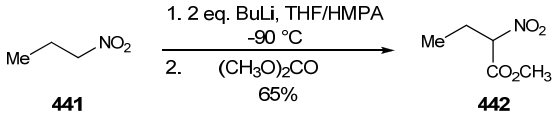
reaction only led to undesired compounds.[157] We synthesized *tert*-butyl-2-nitrobutanoate using this protocol as shown in Scheme 102.

**Scheme 102.** Synthesis of *tert*-butyl-2-Nitro butanoate Using Kornblum's Protocol



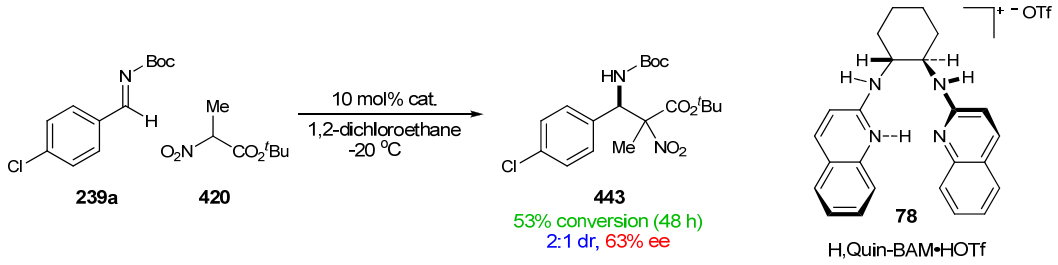

The complementary nitroalkane alkylation/acylation developed by Seebach and co-workers attempts to overcome *O*-alkylation by enhancing C-nucleophilicity. Seebach observed that the double deprotonation of nitroalkanes enhances the *C*-nucleophilicity of the nitronate (compared to *O*-nucleophilicity) resulting in C-alkylation selectively. The synthesis of different chloroformates, however, might require an additional step depending on the target molecule. While the exact $pK_a$ of the mono-deprotonated nitronate is unknown, Seebach estimates it to be around 33.[158,159]

**Scheme 104.** Seebach's Double Deprotonation Protocol for Acylation of Nitroalkanes




Mindful of the challenges that lay ahead, we first attempted to add α-methyl *tert*-butyl

**Scheme 103**



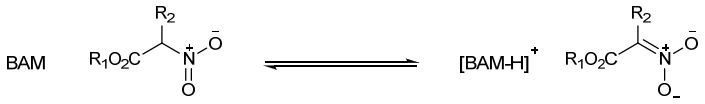

[157] Kornblum, N.; Blackwood, R. K.; Powers, J. W. *J. Am. Chem. Soc.* **1957**, *79*, 2507.
[158] Seebach, D.; Lehr, F. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 505.
[159] Seebach, D.; Henning, R.; Lehr, F.; Gonnermann, J. *Tetrahedron Lett.* **1977**, *13*, 1161.

nitroacetate using H,Quin-BAM•HOTf and the reaction did lead to product formation which was encouraging. However, the low reactivity, and stereoselection confirmed our hypothesis about the change in reactivity profile that an α-substitutent might bring about (Scheme 103).

### *4.3 Design and Application of an Electron Rich, More Basic Catalyst for Enhancement of Rate*

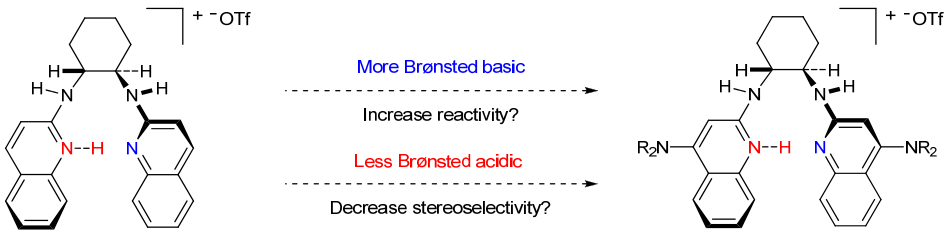
As discussed in Chapter 2, the rate enhancement afforded by BAM•HOTf complexes is a combined effect of two orthogonal modes of reactivity. The Brønsted

**Scheme 105.** Analysis of Factors Influencing the Rate of Chiral Proton Catalyzed Aza-Henry Reactions




acidic nature of these catalysts serves to activate the electrophile (imine) while their Brønsted basic property serves to deprotonate the pronucleophile prior to the addition. As depicted in Scheme 105, in order to increase the concentration of the active nucleophile, either the acidity of the pronucleophile needs to be enhanced or the basicity of the

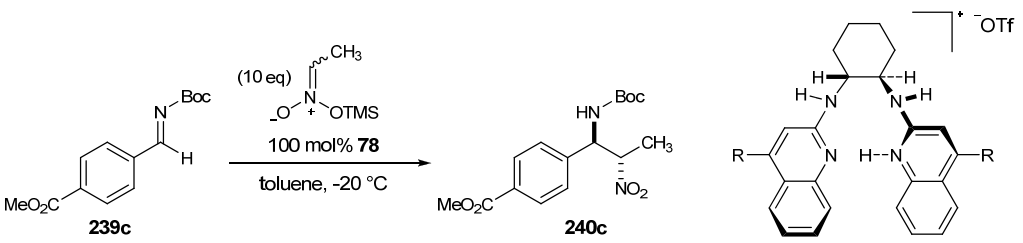
**Figure 29.** Projected Changes in Reaction Profile Effected by Electronic Modification of Catalysts



catalyst needs to be increased. Although convincing, this approach might be too simplistic to gauge the effect of a more basic catalyst because the silyl nitronate chemistry has shown that the Brønsted acidic nature of the catalyst is important for stereoselection. Hence, a balance in the acid-base properties of the catalyst is important to achieve high reactivity in conjunction with high stereoselection.

The design of a new catalyst must start by identifying the key features that we have determined to be indispensable for a successful reaction and the sites where a modification will enhance the property of interest without adversely affecting catalyst structure/function. In order to increase basicity, the incorporation of electron donating groups in the quinoline backbone is the simplest solution possible. To ascertain the best site where the new substitution should be introduced, we again take advantage of the catalyst screen from silyl nitronate additions which indicated that a methyl group on the 4-position of the quinoline (the lepidine ring) is almost identical to quinoline in terms of the reaction outcome (Figure 30). Hence, the steric nature of groups at the 4-position does

**Figure 30.** Similar Results from Quinoline and Lepidine Derived Catalysts Indicating the Sterically Benign Nature of a 4-Substitutent

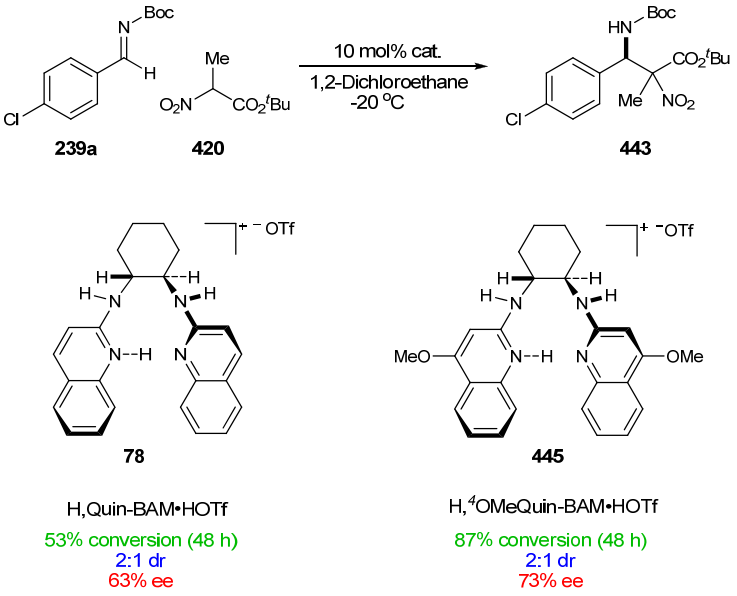



| entry | R | time (h) | % yield | dr[a] (*anti*:*syn*) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | H | 48 | 99 | 14:1 | 86 |
| 2 | Me | 68 | 74 | 16:1 | 85 |

[a]Isolated yields after chromatography. [b]Diastereomer ratios measured by GC. [c]Enantiomer ratios measured by HPLC using chiral stationary phases.

not influence stereoselection and this provides us the opportunity to maximize the electron donating potential of functionalities such as the alkoxy and amine groups. Gratifyingly, use of the bis-methoxy catalyst **445** provided a considerable increase in the conversion along with a moderate increase in enantioselection. The diastereoselection, however, remained poor. The success of an electron rich catalyst in increasing the rate of this reaction without causing a detrimental effect on stereoselection indicates that the Brønsted acid nature of the catalyst has been retained in an effective manner (Scheme 106).

**Scheme 106.** Increase in Reactivity Afforded by an Electron Rich Catalyst

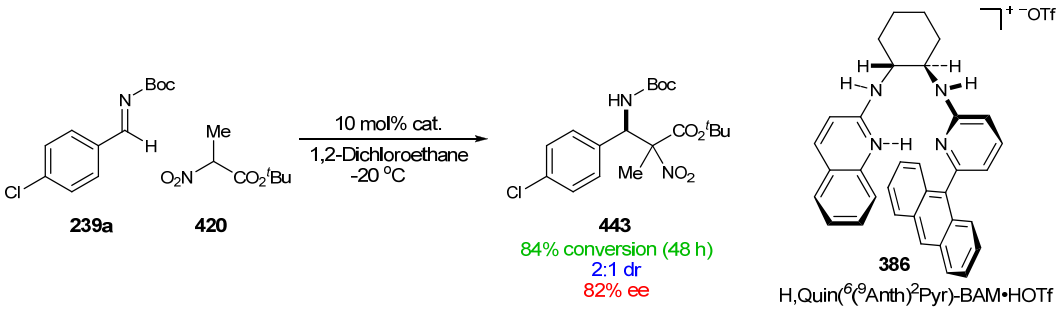



### *4.4 Amalgamation of Catalysts with Desired Reactivity and Selectivity Profiles: Design and Synthesis of Advanced BAM Ligands*

The increase in the rate of this reaction by employing a more basic catalyst was accompanied by some increase in enantioselection but the result was not optimal. From our experience with *unsubstituted* α-nitroacetates, unsymmetrical catalysts with a hindered substrate binding pocket provided higher enantioselection than symmetrical

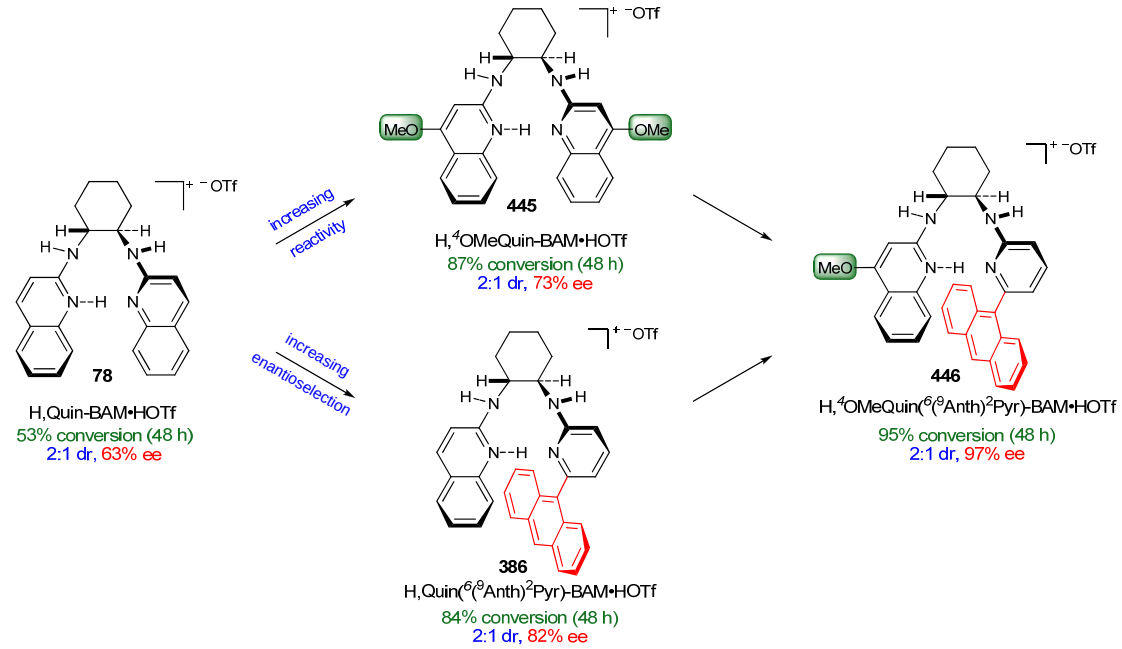
catalysts and hence attempts were made to test whether the same increase in enantioselection can be obtained in the case of α-substituted nitroacetates. To our delight, the unsymmetrical catalyst **386** afforded an increase in enantioselection (82% ee) while maintaining a good rate similar to that afforded by H,$^{4}$OMe-BAM•HOTf (Scheme 107).

**Scheme 107.** Improvement in Enantioselection by Employing the more Hindered, Unsymmetrical catalyst **386**



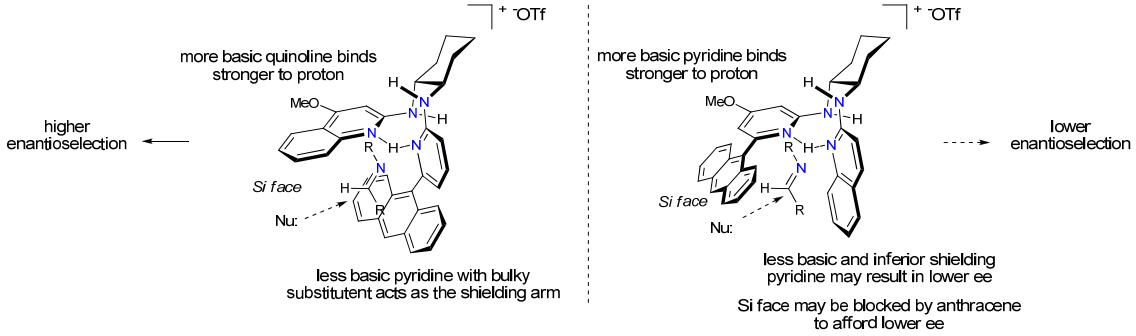

So far, it has been demonstrated that the problems of low reactivity and low enantioselection could be overcome by the use of two different catalysts which provide distinct advantages (compared to H,Quin-BAM•HOTf) owing to their unique structural and electronic properties. However, this constitutes only a proof of principle of the concepts that we have forwarded but is one step away from providing a reaction that is practical. In essence, the development of a new catalyst was required which combined the desired electronic and steric properties so as to provide optimal reactivity and enantioselection. The issue of low diastereoselection, however, remains a problem which we decided to tackle last in the development process. Figure 31 shows the algorithm used to rationally derive a new ligand structure that might hold the key to a successful reaction.

**Figure 31.** Algorithm for the Design of an Optimal Catalyst for the Chiral Proton Catalyzed Addition of α-Alkyl Nitroacetates to Imines




The unsymmetrical methoxy-anthracene catalyst preserved the essential structural elements that proved vital in our initial studies and was synthesized as shown in Scheme 108. Another derivative could be envisioned in which the methoxy substitution is on the

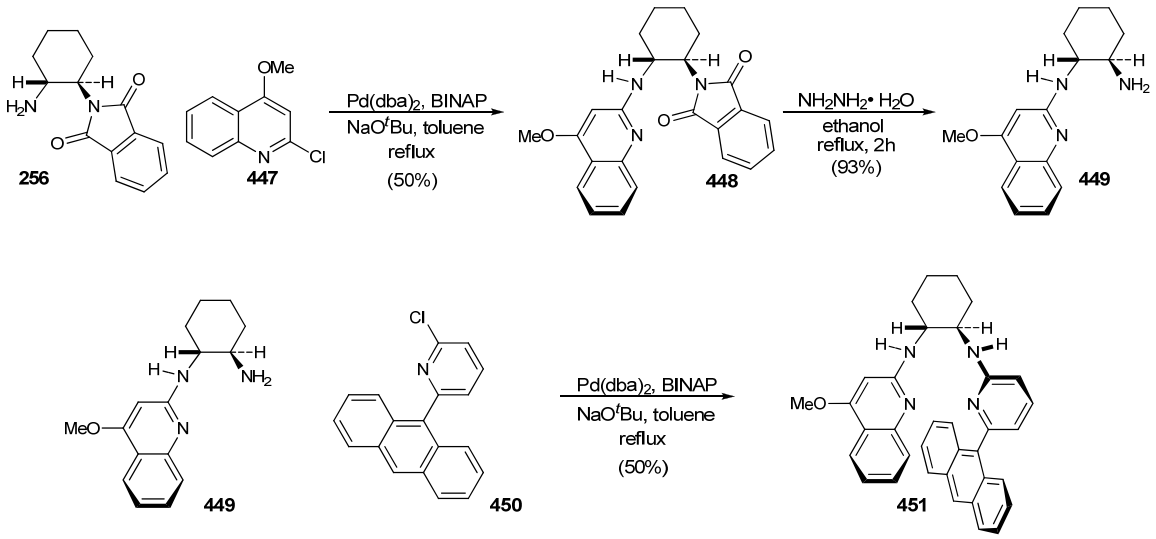
**Figure 32.** Comparison of Two Catalyst Candidates Incorporating the Desired Steric and Electronic Properties




pyridine ring with the anthracene moiety (Figure 32). Ligand **451** was chosen for initial studies for two reasons, the first being ease of synthesis and the second being to (presumably) place the proton closer to the quinoline ring (owing to its higher basicity) so

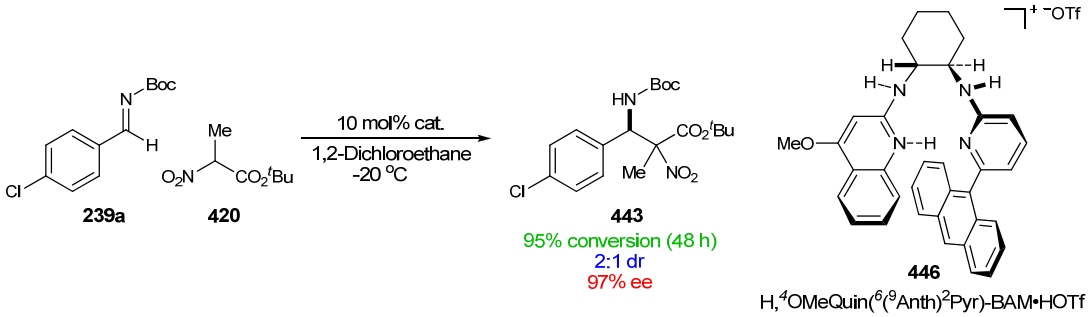
as to favor the transition state in which the anthracene acts as the blocking face thereby maximizing our chances of obtaining good enantioselection. Ligand **451** was synthesized as depicted in Scheme 108. The 2-chloro-4-methoxy quinoline was synthesized using a known protocol. Sequential Buchwald-Hartwig amination of the mono-protected cyclohexyl diamine provided the desired ligand.

**Scheme 108.** Synthesis of the Unsymmetrical Ligand **451**




We were delighted to discover that the new unsymmetrical catalyst provided optimal reactivity and excellent enantioselection as shown in Scheme 109.

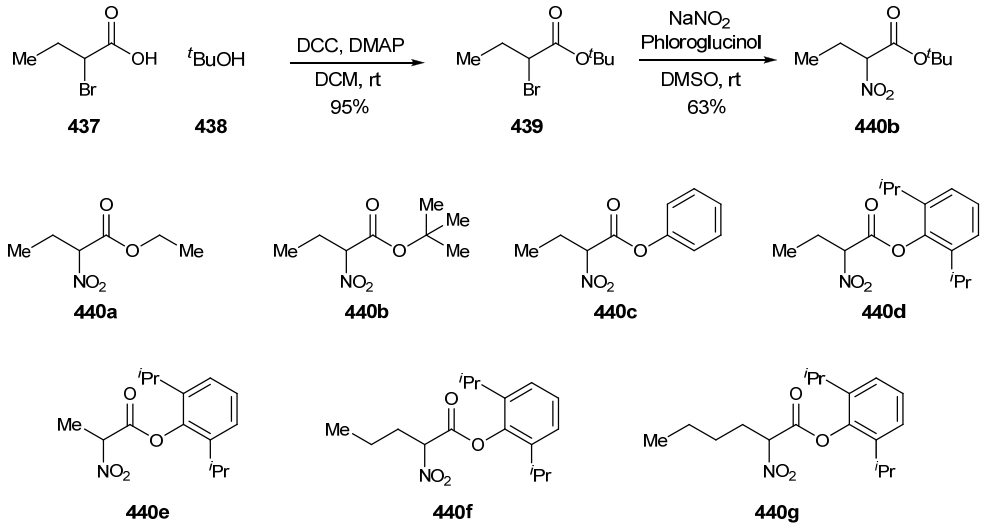
**Scheme 109.** Improvement in Reactivity and Enantioselection by Catalyst **446** Confirming Our Hypothesis



### *4.5 Impact of the Ester Group on Diastereoselection*

It was hypothesized that the steric nature of the ester group might be used to influence diastereoselection in combination with the hindered catalyst binding pocket.

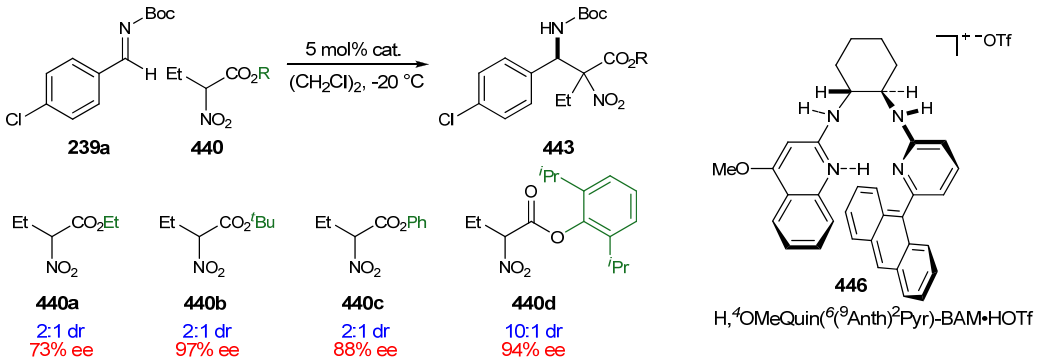
**Scheme 110.** Synthesis of Various α-Nitroesters Employing the Kornblum Protocol




This approach is complimentary to the solution developed for low diastereoselection in the case of α-*un*substituted nitroacetates where the ester was kept constant but the catalyst structure was modified. The synthesis of all the nitroesters was achieved using the Kornblum protocol as depicted in Scheme 110.

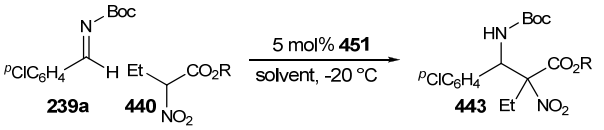
A screen of various nitroesters revealed that the use of a sterically bulky ester

**Scheme 111.** Modulation of Diastereoselection by Varying the Ester Moiety



(2,6-diisopropyl phenyl) afforded high diastereoselection. The change from an ethyl ester to *tert*-butyl ester provided a tremendous increase in enantioselection but the diastereoselection remained poor. The application of a phenyl ester was designed to shed light on any electronic effects that we might be able to exploit to our advantage. Finally, the use of 2,6-diisopropylphenyl ester afforded good diastereoselection (in addition to excellent enantioselection). A limited solvent screen revealed that the use of toluene as solvent afforded the highest diastereoselection. Table 15 summarizes these results. It was discovered that dichloromethane afforded higher reactivity but lower dr.

**Table 15.** Effect of Ester Groups and Solvent on the Addition of α-Substituted Nitroacetates to Imines




**239a** **440** **443**

| entry | R | | solvent | dr[b] | %ee[b] | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Et | **a** | $(CH_2Cl)_2$ | 2:1 | 73 | 92 |
| 2 | $^{t}$Bu | **b** | $(CH_2Cl)_2$ | 2:1 | 97 | 89 |
| 3 | Ph | **c** | $(CH_2Cl)_2$ | 2:1 | 88 | 81 |
| 4 | Ph | **c** | tol | 2:1 | 91 | 87 |
| 5 | 2,6-$^{i}$Pr$_2$C$_6$H$_3$ | **d** | $(CH_2Cl)_2$ | 10:1 | 94 | 84 |
| 6 | 2,6-$^{i}$Pr$_2$C$_6$H$_3$ | **d** | $CH_2Cl_2$ | 9:1 | 92 | 85 |
| 7[c] | 2,6-$^{i}$Pr$_2$C$_6$H$_3$ | **d** | $CH_2Cl_2$ | 11:1 | 93 | 88 |
| 8 | 2,6-$^{i}$Pr$_2$C$_6$H$_3$ | **d** | tol | 14:1 | 96 | 81 |

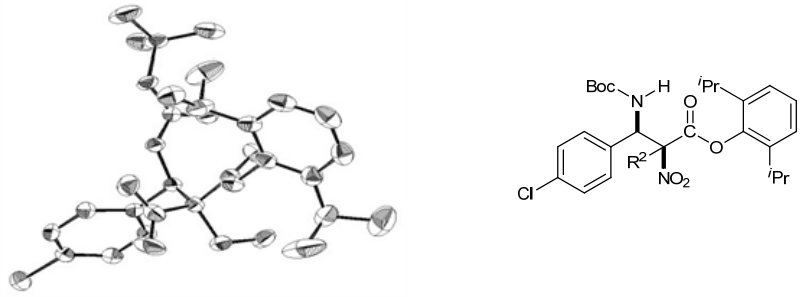
[a]All reactions are 0.3 M in imine and use 1.1 equivalents of the nitro ester. [b]Diastereomer ratios were measured using 1H NMR. Enantiomer ratios were measured using HPLC and a chiral stationary phase. [c]Reaction temperature was -78 °C.

### *4.6 Determination of Absolute and Relative Stereochemistry*

The absolute and relative stereochemistry of the aza-Henry adducts was determined by single crystal X-ray diffraction. The absolute stereochemistry at the benzylic carbon was the expected outcome based on previous chemistry reported by our group. Interestingly, the *syn*-diastereomer is favored in these additions, *opposite* to that

normally observed when using these catalysts with simple nitroalkanes or α-nitro *tert*-butyl esters (Figure 33).

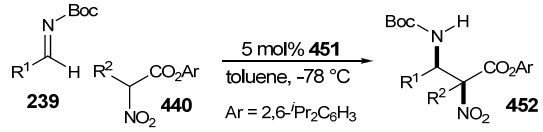
**Figure 33.** Determination of Absolute and Relative Stereochemistry of **443d** by X-ray Diffraction




## *4.7 Chiral Proton Catalyzed Additions of α-Substituted Nitroacetates to Azomethines: Reaction Scope*

These experiments determined conditions for an initial evaluation of scope

**Table 16.** Imine and Nitroalkane Scope for the Chiral Proton Catalyzed Additions of α-Nitroacetates to Azomethines



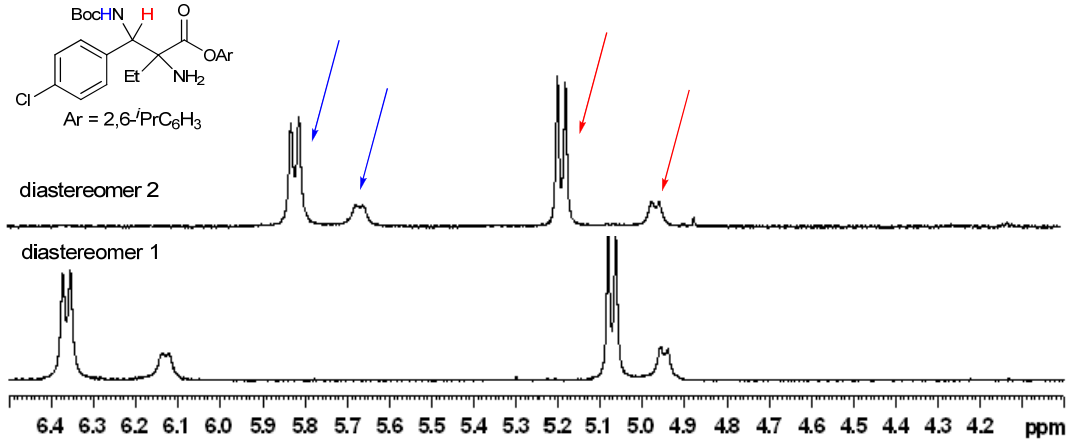

| entry | $R^1$ | $R^2$ | | dr[b] | %ee[b] | yield(%)[b] |
|---|---|---|---|---|---|---|
| 1 | $^{p}ClC_6H_4$ | Et (**6d**) | **443d** | >20:1 | 98 | 83 |
| 2 | $^{2}Np$ | Et | **452a** | >20:1 | 96 | 80 |
| 3 | $^{p}MeSC_6H_4$ | Et | **452b** | 13:1 | 98 | 81 |
| 4 | $^{p}PhSC_6H_4$ | Et | **452c** | 10:1 | 96 | 59 |
| 5[c] | $^{p}PhSC_6H_4$ | Et | **452c** | 8:1 | 96 | 83 |
| 6 | $^{p}MeC_6H_4$ | Et | **452e** | >20:1 | 97 | 61 |
| 7[c] | $^{p}MeC_6H_4$ | Et | **452e** | >20:1 | 96 | 80 |
| 8 | $^{p}MeOC_6H_4$ | Et | **452f** | 12:1 | 95 | 73 |
| 9 | $^{2}Furyl$ | Et | **452g** | 5:1 | 94 | 86 |
| 10 | $^{p}ClC_6H_4$ | Me (**6e**) | **452h** | 12:1 | 99 | 82 |
| 11 | $^{p}ClC_6H_4$ | $^{n}Pr$ (**6f**) | **452i** | 15:1 | 97 | 82 |
| 12[c] | $^{p}ClC_6H_4$ | $^{n}Bu$ (**6g**) | **452j** | 16:1 | 97 | 88 |

[a]All reactions are 1 M in imine and use 1.1 equivalents of the nitro ester unless otherwise noted. Conversions of 82% and 71% for entries 1-2, respectively, at 24 hours (approximated by 1H NMR). [b]Diastereomer ratios were measured using 1H NMR. Enantiomer ratios were measured using HPLC and a chiral stationary phase. Yields are for isolated, analytically pure product. [c]Reaction was 0.3 M in imine and was performed at -20 °C for entries 5, 12; -78 °C, 3.5 days reaction time for entry 7.

summarized in **Table 16**. Using α-nitro butanoate **440d** as a representative pronucleophile, a range of aromatic aldimines were used to target β-amino phenyl alanine derivatives **443d**/**452**. At the higher concentration and lower temperature used in this series, higher diastereoselection (20:1) and excellent enantioselection (98% ee) were observed for **443d/452** (83% yield) (**Table 16**, entry 1). A survey of additional electronically neutral (Table 16, entry 2) and rich aromatic aldimines (Table 16, entries 3-9) revealed generally high diastereoselection (8→20:1) and enantioselection (94-98% ee). In one case, a sluggish reaction at -78 °C (Table 16, entry 4) could be rectified by raising the reaction temperature to -20 °C, resulting in a slight drop in diastereoselection (10:1→8:1 dr, Table 16, entry 5). In another case (Table 16, entry 6), extension of the reaction time provided complete conversion and higher isolated yield (Table 16, entry 7). The lowest diastereoselection (5:1 dr) was observed for the furyl aldimine, but enantioselection remained high (94% ee, Table 16, entry 9). The catalyst tolerance to the nature of the α-alkyl group of the nitroester is also good. The behavior of chlorophenyl imine **239a** in the series **440e**, **440d**, **440f**, **440g** (**Table 16**, entries 10, 1, 11, 12) led to the derived α,β-diamino esters with generally high diastereoselection (12-20:1 dr), enantioselection (97-99% ee), and isolated yield (>82%). The reaction rate for the hexanoate **440g** was noticeably slower, but could be carried out at -20 °C (Table 16, entry 12) to deliver the desired product (16:1 dr, 97% ee) in good isolated yield (88%).

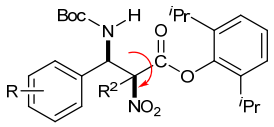
In order to demonstrate that the adducts from the nitroacetate additions can be conveniently transformed into the corresponding amino acids, a reduction protocol for the tertiary nitro group needed to be developed. It was found that the Zn/HCl conditions

**Figure 34.** Possible Rotamers Observed for the Amino Ester




successfully reduced the nitro group to an amine. However, as shown in **Figure 34**, additional peaks in the $^{1}H$ NMR were a cause for concern because they could not be separated from the amino esters. Reduction of a diastereomeric mixture of the adduct and careful chromatography revealed that both diastereomers could be separated but they both eluted with a different set of peaks (clearly seen for the –NH and benzylic –CH protons).

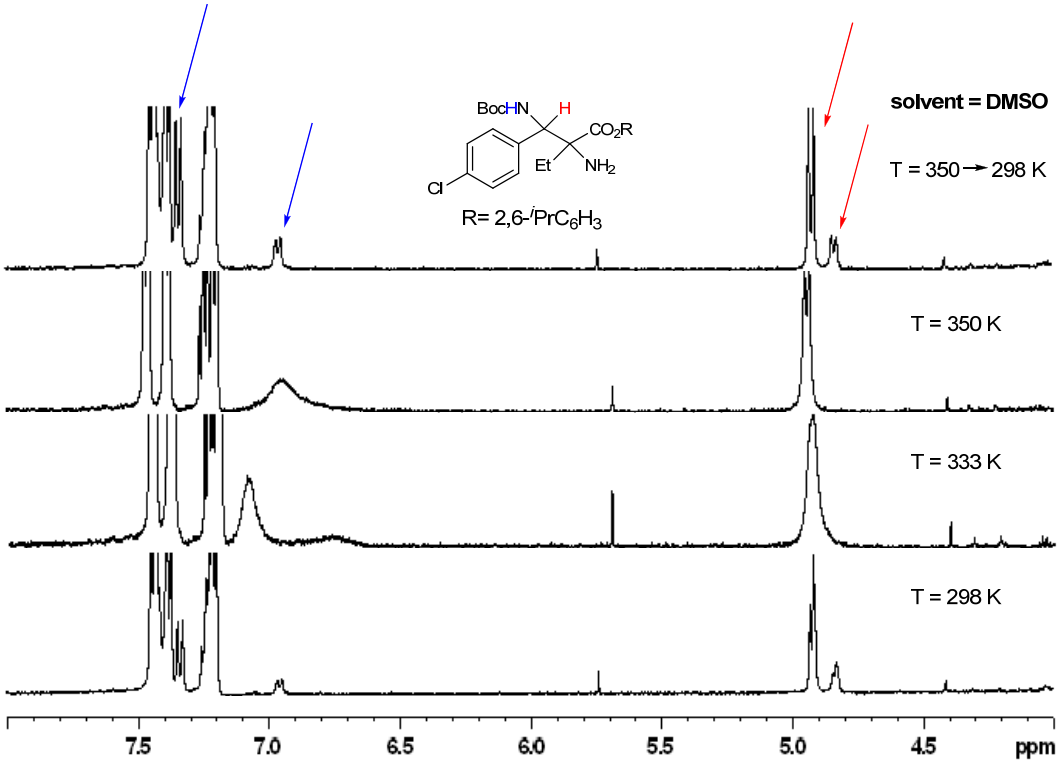
**Figure 35.** Most Likely Site of Hindered Rotation Caused by Bulky Ester Group




hindered rotation about the C–O bond

To determine whether the additional peaks were arising due to a rotamer (or an impurity), a variable temperature NMR experiment was performed where a sample of one diastereomer was heated from 299 K to 333 K and finally to 350 K. It was observed that the peaks converged at higher temperatures (and separated on subsequent cooling) confirming that these are not from any impurity but arise from restricted rotation about a sigma bond (Figure 36).

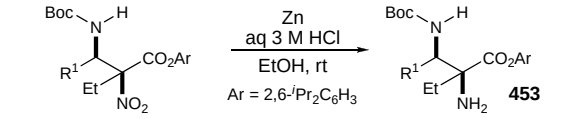
**Figure 36.** Variable Temperature NMR Experiment Indicating Restricted Rotation in the Amino Ester




The enantioenriched nitroester products could also be easily reduced to the protected *syn*-α,β-diamines by zinc reduction in aq HCl-EtOH at room temperature. The diastereo- and enantiomeric excess were unchanged in the diamine products. The

reduction could be achieved in a chemoselective fashion and was not complicated by deprotection of the Boc-carbamate (Scheme 112).

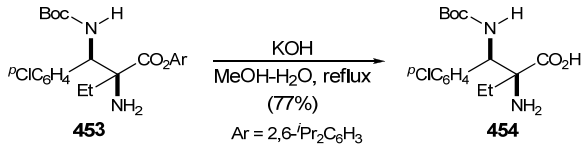
**Scheme 112.** Reduction of the Nitro Group to the Amine




**443d**, R = $^{p}$Cl (>20:1 dr, 96% ee) 83% yield, >20:1 dr, 97% ee
**452a**, R = $^{2}$Np (>20:1 dr, 96% ee) 88% yield, >20:1 dr, 97% ee

The saponification of the hindered ester moeity was expected to be challenging owing to the severely hindered nature of the ester. In an interesting report by Miyano[160], a comparative study of the hydrolytic cleavage of hindered esters revealed that 2,6-diisopropyl phenyl esters could be cleaved by hydroxide at high temperatures. Although amino ester **453** was more hindered than the reported examples, we were delighted to

**Scheme 113.** Saponification of theAmino Ester




observed that it could also be saponified to provide the free α-amino acid in 77% yield (Scheme 113).

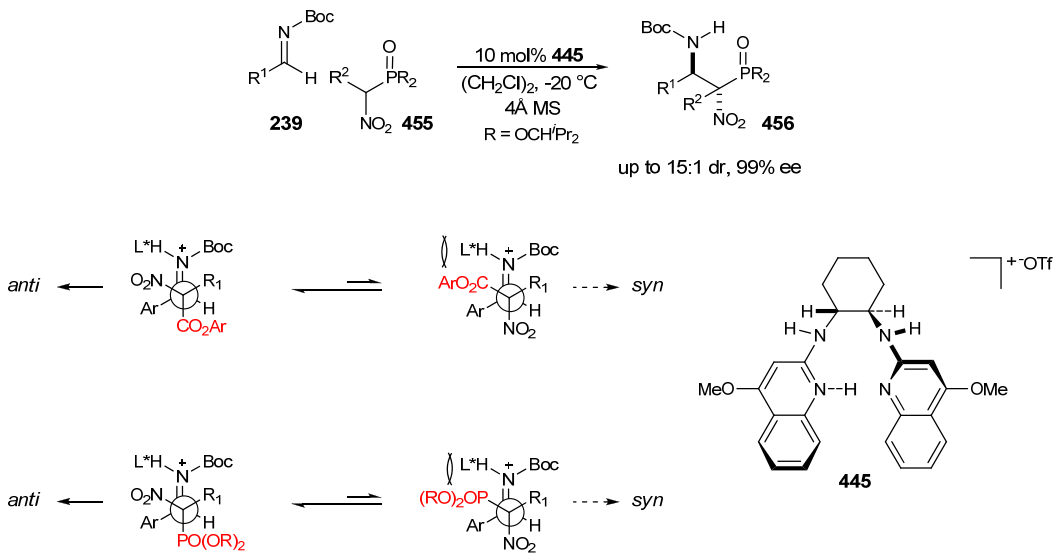
### *4.8 Catalyst Controlled Diastereo-Switching*

The production of the *syn*-diastereomer as the major product was somewhat unexpected since until this point, chiral proton catalyzed additions of nitroalkanes, unsubstituted nitroacetates, and nitrophosphonates afforded *anti*-adducts. While the

[160] Miyano, S.; Koike, N.; Hayashizaka, N.; Suzuki, T.; Hattori, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3034.

origin of *syn*-diastereoselection in the current case is not fully understood, some differences in the catalyst/nucleophile structure might be able to shed light on this outcome. The additions of α-substituted nitrophosphonates[161] provide the most similar example to α-substituted nitroacetates. In the case of nitrophosphonates, high anti-diastereoselection was achieved by using bulky nitrophosphonates with either H,Quin-BAM•HOTf or H,$^4$OMeQuin-BAM•HOTf. Figure 37 shows the rationale for the observed *anti*-selectivity is presented below along with an analogous hypothesis for nitroacetates.

**Figure 37.** Prediction of the Diastereoselective Outcome for Nitroacetate Additions Using Catalyst **445** Based on the Results Obtained with Nitrophosphonates

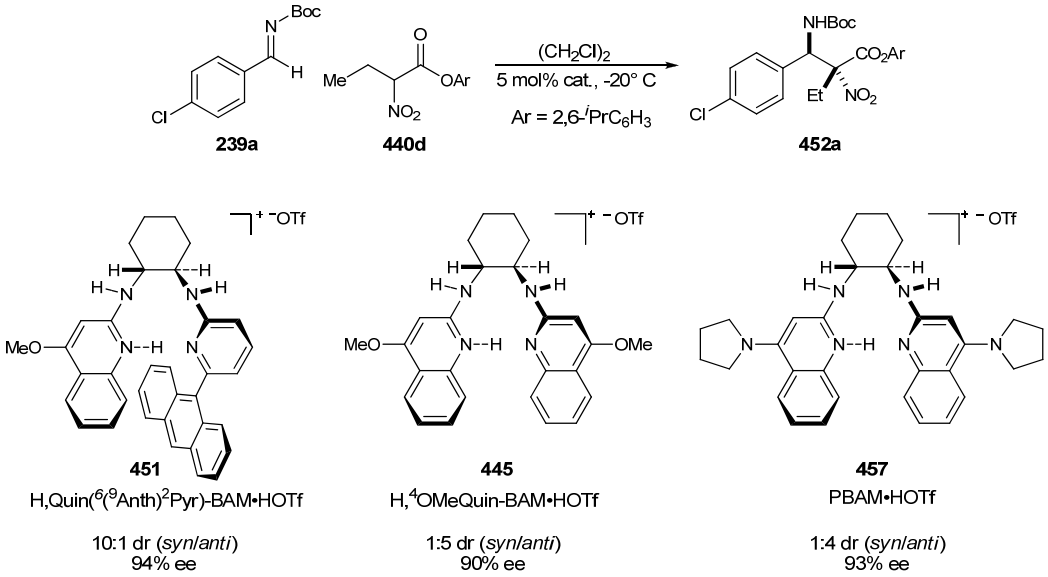



The important distinction between these reactions is the structure of the catalyst and the nature of the ester. It might be possible that the combination of a bulkier catalyst and an aromatic ester help to stabilize the hydrogen bonding of the ester to the catalyst proton (*or* destabilize the ester-H interaction) thereby promoting the formation of the *syn*-diastereomer. To evaluate for internal consistency, it was hypothesized that the use of

[161] Wilt, J. C.; Pink, M.; Johnston, J. N. *Chem. Commun.* **2008**, 4177.

H,$^{4}$OMeQuin-BAM•HOTf with 2,6-diisopropyl nitroacetates should afford the *anti*-

**Scheme 114.** Catalyst Controlled Diastereo-Divergence in the Chiral Proton Catalyzed Additions of α-Alkyl Nitroacetates to Imines

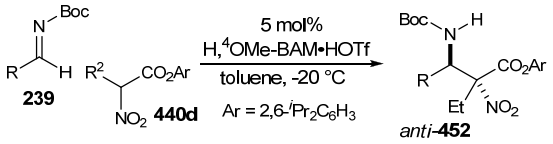



adducts. A catalyst comparison shown in Scheme 114 shows that the use of the less hindered catalyst does indeed lead to the *anti*- diastereomer as the major product although the selectivity is moderate. It was encouraging to observe that enantioselection remains high.

A survey of various imines revealed that the *anti*-adducts were obtained in moderate diastereoselection. In general, electron neutral and electron deficient imines performed better than electron rich in terms of diastereoselection. Enantioselection was uniformly high with most values being above 90%. It was also observed that diastereoselection decreased when the alkyl substitutent on the nitroacetate was changed from methyl/ethyl to $^{n}$butyl. Our model for diastereoselection indicates that this would be the expected outcome since the increase in the steric bulk of the substitutent would

decrease the differentiation between the ester and the alkyl group thereby diminishing the energy difference between the corresponding transition states (Figure 38).

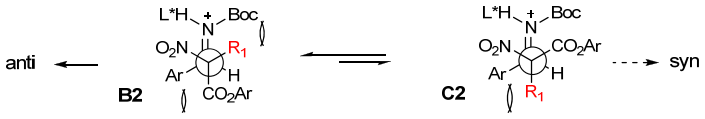
**Table 17.** Synthesis of *anti*-Adducts Employing catalyst **445**




| entry | R | $R^2$ | dr[b] | %ee[b] | conv. (%)[c] | yield(%) |
|---|---|---|---|---|---|---|
| 1 | $^{p}ClC_6H_4$ | Et | 10:1 | 92 | 95 | 83 |
| 2 | $^{p}CO_2MeC_6H_4$ | Et | 8:1 | 96 | 95 | 80 |
| 3 | $^{p}CF_3C_6H_4$ | Et | 7:1 | 85 | 77 | 70 |
| 4 | $^{p}FC_6H_4$ | Et | 8:1 | 96 | 91 | 79 |
| 5 | $^{p}SMeC_6H_4$ | Et | 6:1 | 91 | >95(60 h) | 84 |
| 6 | $^{p}OMe$ | Et | 4:1 | 86 | >95 | 84 |
| 7[c] | $C_4H_3S$ | Et | 4:1 | 85 | 52 | 71* |
| 8 | $^{p}Me$ | Et | 6:1 | 97 | -- | 82 |
| 9 | $^{p}Ph$ | Et | 8:1 | 92 | -- | 79 |
| 10 | $^{p}OAc$ | Et | 7.5:1 | 94 | 87 | 77 |
| 11 | $^{p}ClC_6H_4$ | Me | 10:1 | 92 | >95 | 86 |
| 12 | $^{p}ClC_6H_4$ | $^{n}Bu$ | 4.4:1 | 90 | 69 | 80* |

[a]All reactions are 1 M in imine and use 1.1 equivalents of the nitro ester unless otherwise noted. [b]Diastereomer ratios were measured using 1H NMR. Enantiomer ratios were measured using HPLC and a chiral stationary phase. Yields are for isolated, analytically pure product.[c]Reaction time was 3 days.

**Figure 38.** Erosion of Diastereoselection Due to Increasing Steric Bulk of α-Substitutent ($R_1$)




In summary, a direct synthesis of α-substituted *syn*-α,β-diamino acid derivatives of phenyl alanine has been developed. This required the development of catalyzed additions of substituted α-nitroesters, providing α-nitro-β-amino esters with high diastereo- and enantioselection. Key to this development is the finding that methoxy substitution in the catalyst leads to a more active bifunctional system, and hindered aryl esters **440d-g** work synergistically with the catalyst to provide high diastereoselection;

achiral catalysis (DMAP) of the same addition proceeds with low diastereoselection (<2:1 dr). The diamine functionality is readily unmasked as in Scheme 113.

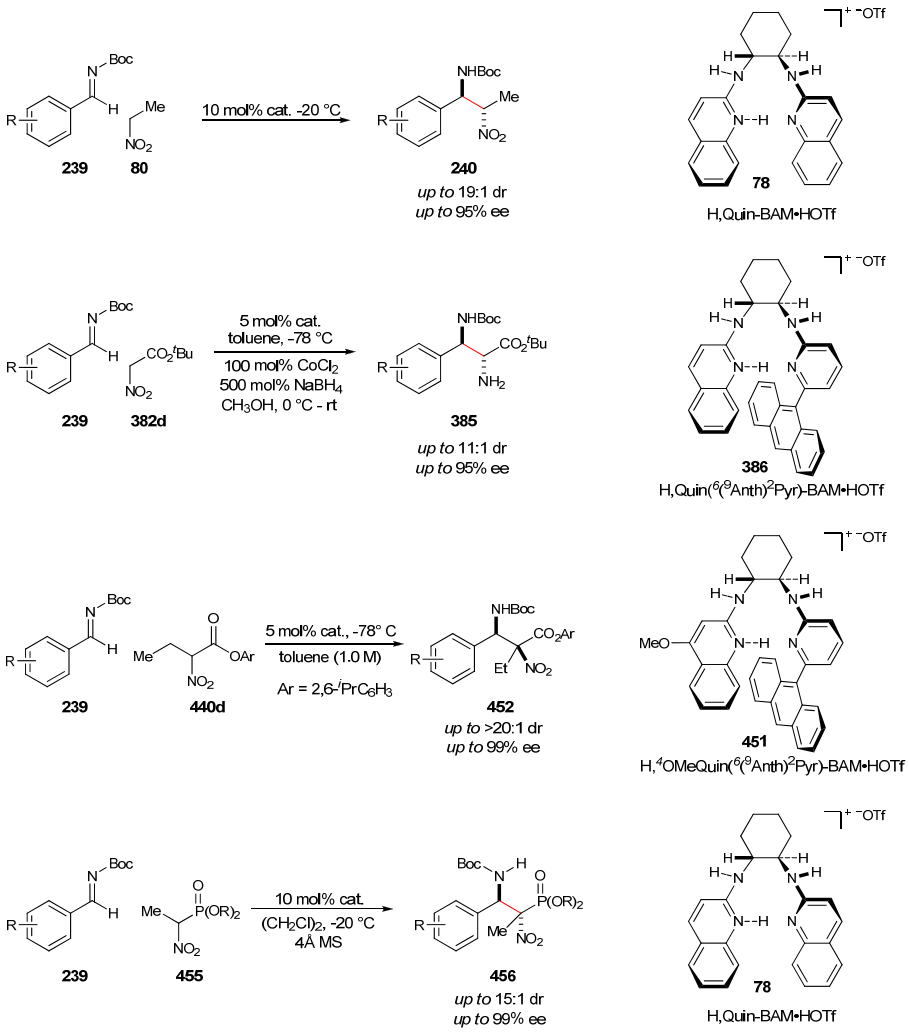
## *CHAPTER V*

# *DEVELOPMENT OF ENOLIZABLE ALKYL IMINES AS VIABLE SUBSTRATES FOR THE CHIRAL PROTON CATALYZED AZA-HENRY REACTION: APPLICATION OF PHENYL NITROMETHANE AND BROMONITROMETHANE AS PRECURSORS TO PHENETHYLAMINES AND α-AMINO AMIDES*

### *5.1 Scope, Limitations, and New Avenues in Chiral Proton Catalysis*

The chiral proton catalyzed aza-Henry reaction has been shown so far to be a general method for the synthesis of a variety of functionalized diamines. The advantages

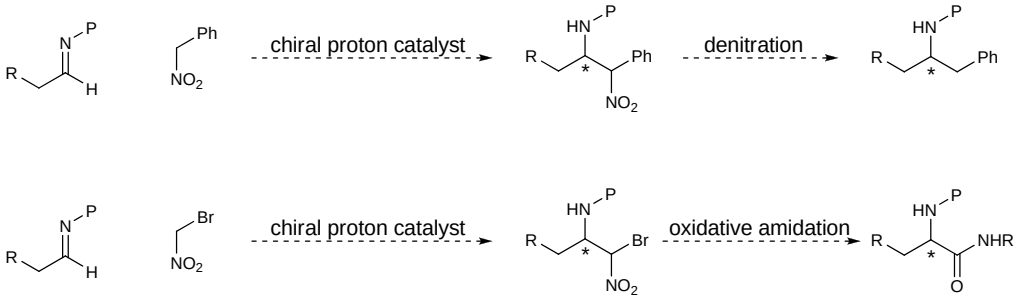
**Scheme 115.** Chiral Proton Catalyzed aza-Henry Reactions



of this approach include the brevity and the generation of orthogonally protected diamines allowing further chemoselective transformations (Scheme 115).[162] With the goal of further broadening the genrality, a critical examination revealed a reliance on aryl imines in order for a successful reaction to occur. The application of enolizable alkyl imines to this transformation would open avenues towards the synthesis of a larger family of these valuable compounds in an enantioselective manner. The use of alkyl imines, however, is complicated by their propensity to isomerize to the corresponding enamine thereby destroying the azomethine functionality. Our goal was to develop enolizable alkyl imines as suitable electrophiles for chiral proton catalyzed aza-Henry reactions.

The selection of suitable nucleophiles was guided by our interest in developing routes to diverse amines and amino acid derivatives in an enantioselective fashion with brevity. We envisioned the use of two relatively less frequently employed nucleophiles phenyl nitromethane and bromonitromethane as precursors to novel amines. As shown in

**Scheme 116.** Potential Application of the aza-Henry Adducts




Scheme 116, phenyl nitromethane adducts would afford phenethyl amines upon denitration of the adducts. The bromonitromethane adducts could be converted to novel α-amino amides by employing a reaction developed in our research group. Synthetically,

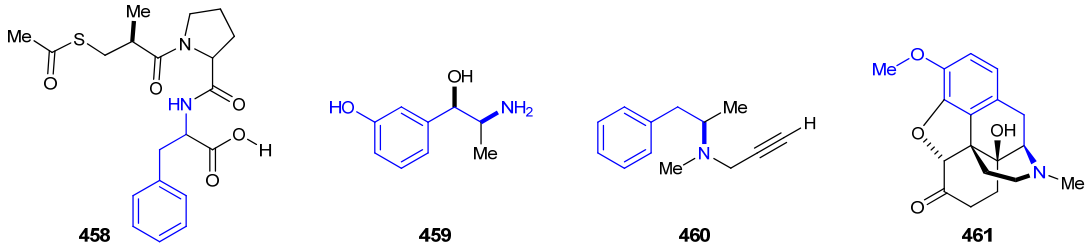
[162] Wilt, J. C.; Pink, M.; Johnston, J. N. *Chem. Commun.* **2008**, 4177.

we would be employing bromo nitromethane as a nucleophilic carboxylate equivalent in the aza-Henry reaction.[163]

### *5.2 Phenethyl Amines: Significance and Synthetic Approaches*

Homobenzylic amines are common pharmacophores found in pharmaceutically active compounds such as Cetapril® (antihypertensive), Aramine® (antihypotensive), Dofetilide® (antiarrythmic), Edepril® (antiparkinsons), Foradil® (bronchpdilator),

**Figure 39.** Enantiopure Phenethyl Amines Currently Prescribed as Drugs




OxyContin (analgesic). The structures of these molecules are shown in Figure 39. Amphetamine is also a well known drug that contains a homobenzyllic amine group but it is administered in racemic form. Despite immense utility, the synthesis of enantiopure homobenzylic amines remains a challenge.

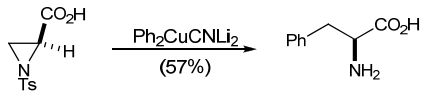
The ring opening of aziridines offers a convergent way for the construction of the homobenzylic amine moiety.[164,165] This reaction, however, has some challenges associated with it such as the requirement of a suitable activating/protecting group on the aziridine which allows facile ring opening but can be easily removed later. Electron withdrawing groups such as *N*-Boc, *N*-Cbz, and *N*-tosyl are in principle good candidates

[163] Shen, B.; Makley, D. M.; Johnston, J. N. *Unpublished Results*
[164] McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347.
[165] Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

but easily removable groups such as the *N*-Boc have rarely been employed due to poor reactivity and occurance of side-reactions which include the attack of nucleophiles on the carbamate carbonyl.[166,167,168]

The most frequently employed activating group is the *N*-tosyl due to its favorable reactivity profile. It was shown by Young that the enantiopure aziridine-2-carboxylic acid **462** could be opened by organocuprates in a regioselective manner affording the

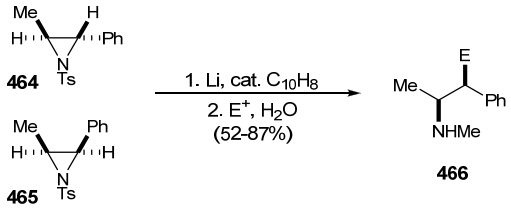
**Scheme 117.**




**462** **463**

enantiopure homobenzylic amino acid **463**.[169] In comparison to the use of aziridine-2-carboxylates, the use of a free carboxylic acid affords better regioselectivity (side-reaction with the ester do not pose a problem when employing organocuprates as nucleophiles). Reductive opening of phenyl substituted aziridines at the benzylic carbon

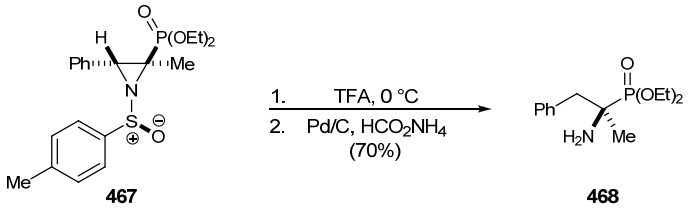
**Scheme 118.**




has been achieved using lithium in naphthalene. Activation of nitrogen using electron withdrawing groups was not necessary in this case. As shown in Scheme 118, the C-3

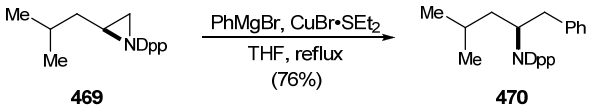
[166] Travins, J. M., Wtzkorn, F. A. *Tetrahedron Lett.* **1998**, *39*, 9389.
[167] Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761.
[168] Cantril, A. A.; Osborn, H. M.; Sweeney, J. *Tetrahedron Lett.* **1998**, *54*, 2181.
[169] Church, N. J.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 151.

**Scheme 119.**




aziridine stereocenter was preserved but the benzylic center underwent inversion. The stereochemistry at the benzylic carbon indicates the thermodynamic preference since both (2*S*,3*S*) and (2*R*,3*S*) aziridines (**464**, **465**) afforded the same product.[170] A similar strategy was applied to the synthesis of α-amino phosphonates by McCoull. As shown in Scheme 119, the *trans*-substituted *N*-sulfinyl aziridine **467** was deprotected and then hydrogenolyzed as the free aziridine to afford the first asymmetric synthesis of (*R*)-α-methylphosphophenylalanine. Sweeney and co-workers have reported the ring opening of *N*-Dpp (diphenylphosphoryl) imines by organocuprates in refluxing THF to yield the corresponding phenethylamines in good yields. At the temperature that this reaction was successful, the decomposition of orgnaocuprates has been reported in the literature. The exact identity of the reacting species was not established in this case (Scheme 120).[171]

**Scheme 120.**

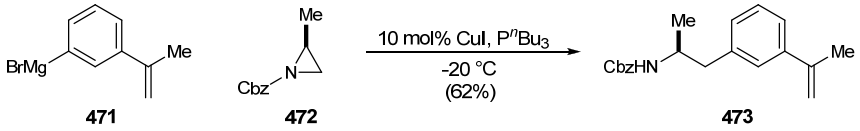



Efficient ring openings of aziridines by functionalized aryl cuprate reagents has been achieved by Achmatowicz where *N*-Cbz imines could be employed without any

[170] Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210.
[171] Cantril, A. A.; Osborn, H. M.; Sweeney, J. *Tetrahedron* **1998**, *54*, 2181.

significant side reactions. The ring opening was regioselective preferring the least substituted carbon of the aziridine (Scheme 121).[172]

**Scheme 121**

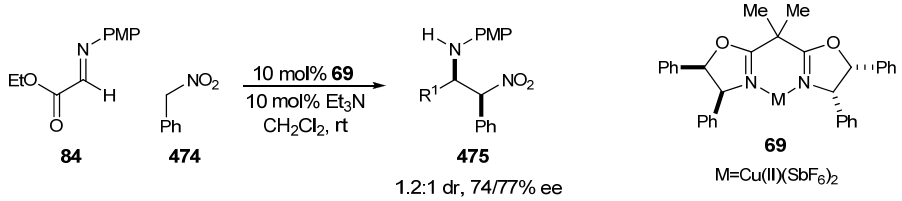



**471** **472** **473**

### *5.3 Application of Phenyl Nitromethane and Bromo Nitromethane in the Literature*

The use of phenyl nitromethane in aza-Henry reactions is rare but has been studied by Jørgensen who demonstrated their use in enantioselective aza-Henry reactions with glyoxyl imines. As depicted in Scheme 122, the adducts were formed with poor diastereoselection and moderate enantioselection which was in stark contrast to other nitroalkanes which afforded good dr and excellent enantioselection.

**Scheme 122**




**84** **474** **475**

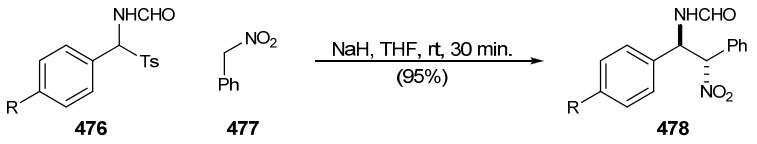
1.2:1 dr, 74/77% ee

**69**

M=Cu(II)(SbF$_6$)$_2$

Petrini and co-workers have shown that α-formamidoaryl sulfones could be

**Scheme 123**




**476** **477** **478**

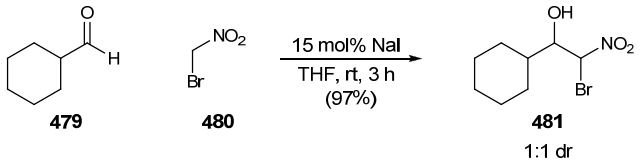
19:1 dr

[172] Ackmatowicz, M.; Chan, J.; Wheeler, P.; Liu, L.; Faul, M. M. *Tetrahedron Letters* **2007**, *48*, 4825.

converted to the corresponding imines *in situ* followed by the subsequent addition of a nitroalkane. Phenylnitromethane could also be employed in this reaction and the product was isolated in good yield and with excellent diastereoselection. This report did not describe the use of phenyl nitromethane in an enantioselective reaction (Scheme 123).[173]

The use of bromo nitromethane in Henry reactions has been reported by Concellón who reported a samarium diiodide mediated synthesis of 1-bromo-1-nitro-2-

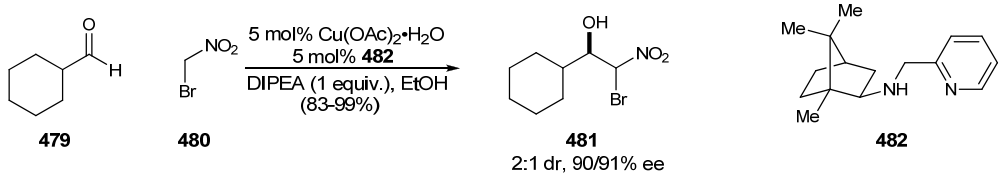
**Scheme 124**




**479** **480** **481**
1:1 dr

alkanols. This method was further simplified by employing sodium iodide as catalyst

**Scheme 125**

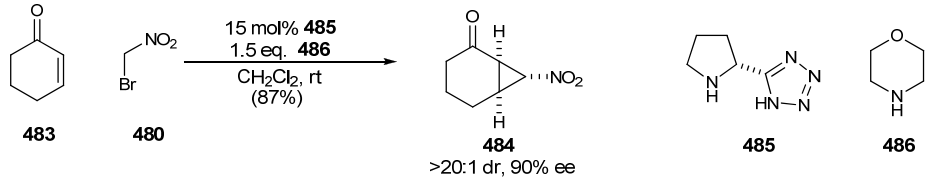



**479** **480** **481** **482**
2:1 dr, 90/91% ee

which is easier to use and inexpensive compared to samarium iodide (Scheme 124).[174,175] Pedro has developed an enantioselective version of the nitro-aldol reaction with bromo nitromethane. Treatment of a variety of aldehydes (aromatic, heteroaromatic, aliphatic) led to the formation of adducts with high yields and enantioselection. Although the

[173] Petrini, M.; Torregiani, E. *Tetrahedron Lett.* **2006**, *47*, 3501.
[174] Clark, N. G.; Croshaw, B.; Leggetter, B. E.; Spooner, D. F. *J. Med.Chem.* **1974**, *17*, 977.
[175] Concellon, J. M.; Rodriguez-Solla, H.; Concellon, C.; Garcia-Granda, S.; Diaz, M. R. *Org. Lett.* **2006**, *8*, 5979.

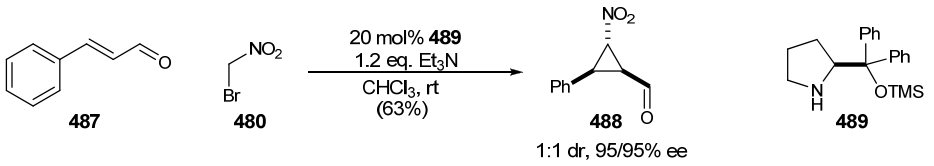
**Scheme 126**




diastereoselection was low in all cases, the ee for each diastereomer was high (Scheme 125).

α-Bromo nitromethane has also been used for enantioselective nitrocyclopropanation reactions. Ley has employed a pyrrolidinyl tetrazole catalyst for the nitrocyclopropanation of enones. It was observed that cyclic enones afforded better diastereo- and enantioselection than acyclic ones (Scheme 126).[176] Cordova has extened this nitrocyclopropanation reaction to α,β-unsaturated aldehydes using a prolinol derived catalyst. The nitrocyclopropanes were obtained in poor dr but high enantioselection (Scheme 127).[177]

**Scheme 127**

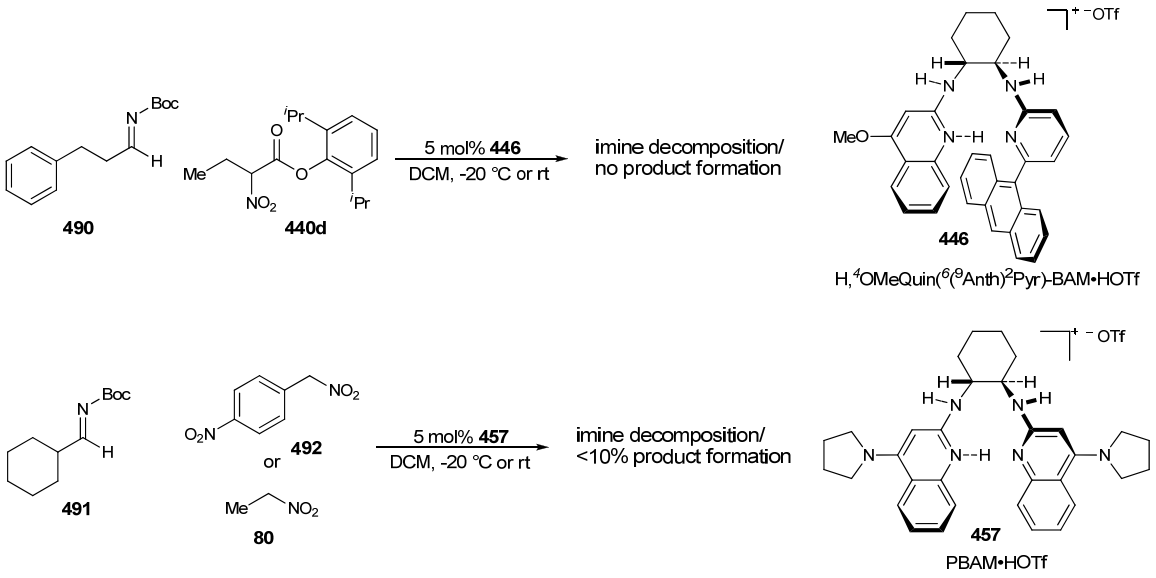



### *5.4 Enolizable Alkyl Imines in Chiral Proton Catalysis: Preliminary Findings and Phenyl Nitromethane Additions*

It has been well established that the most effective imine protecting group for chiral proton catalyzed aza-Henry reaction is the *N*-Boc due to its ability to engage in two point binding to the ligand-bound proton. Hence, alkyl *N*-Boc imines were our first

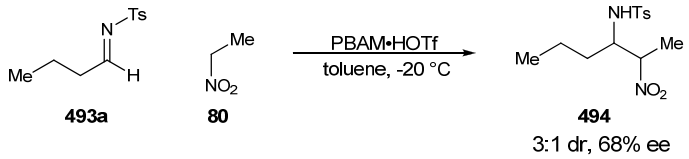
[176] Wascholowski, V.; Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Synthesis* **2008**, *8*, 1269.
[177] Vesely, J.; Zhao, G.; Bartoszewicz, A.; Armando Córdova *Tetrahedron Lett.* **2008**, *49*, 4209.

**Scheme 128.** Instability of Alkyl *N*-Boc Imines Towards Chiral Proton Catalysts



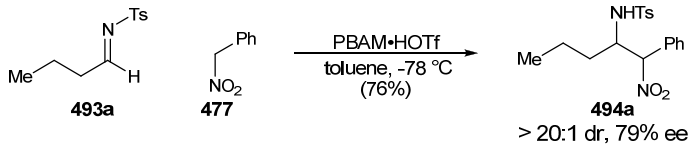

choice in attempting to extend this chemistry to enolizable imines. The synthesis of alkyl *N*-Boc imines is known in the literature but their use as electrophiles is scarcely reported because of complications arising due to their tautomerization to the corresponding enamine. Our attempts to perform aza-Henry reactions with either nitroalkanes or nitroacetates (Scheme 128) resulted in extensive decomposition and trace product formation if any. Since imine stability is influenced by the protecting group, it was decided to investigate whether the reactivity of suitably protected imines could be modulated in order to obtain the desired product. Another imine protecting group that has been utilized frequently in addition reactions is the *N*-tosyl group. Early attempts to employ these imines in the direct aza-Henry reaction catalyzed by PBAM•HOTf revealed that these are suitable substrates in terms of reactivity but provide poor diastereoselection and only moderate enantioselection (Scheme 129). This representative example utilized nitroethane as the nucleophile.

**Scheme 129.** Alkyl Tosyl Imines as Suitable Substrates for Chiral Proton Catalyzed Reactions




The application of phenyl nitromethane as the pronucleophile results in a faster reaction allowing us to perform it at lower temperature. This increased reactivity is due to the enhanced acidity of phenyl nitromethane compared to nitroethane. The adducts were formed with excellent diastereoselection but modest enantioselection as shown in Scheme 130. It was hypothesized that the steric nature of the tosyl group could be used to alter the

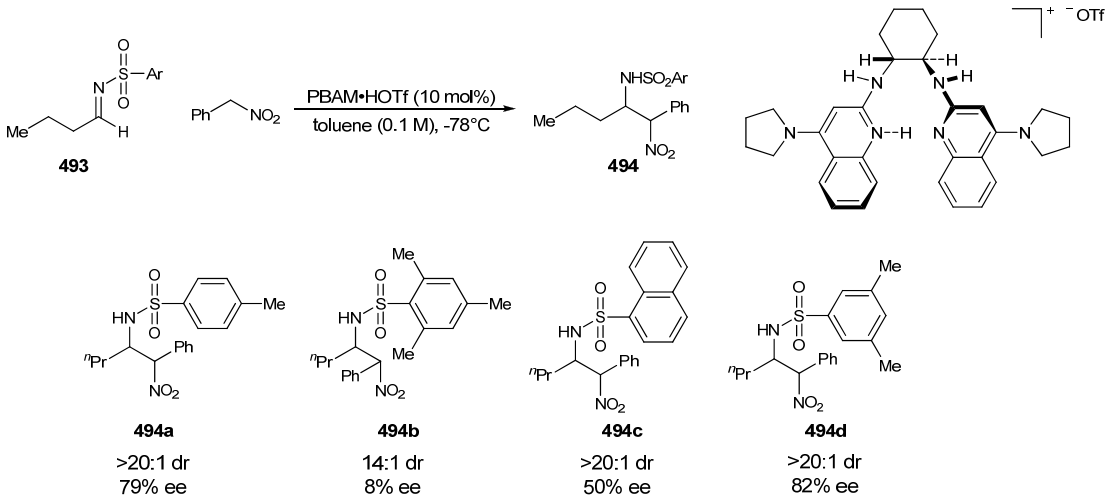
**Scheme 130.** PBAM•HOTf Catalyzed Addition of Phenyl Nitromethane to Alkyl *N*-Tosyl Imine




binding of the imine to the catalyst thereby effecting an increase in enantioselection. It was discovered that *ortho* substitutions (eg. 2,4,6-trimethyl sulfonyl) in the phenyl ring resulted in a dramatic decrease in enantioselection (Scheme 132). Interestingly, the 1-naphthylsulfonyl group can be considered as a phenyl ring in which only one *ortho* substitution is present and it provides enantioselection which lies between that provided by the tosyl group (no *ortho* substitution) and the 2,4,6-trimethyl sulfonyl group (two *ortho* substitutions). A marginal increase was obtained by the use of the 3,5-dimethyl sulfonyl group but the increase was not significant and hence alternative solutions were pursued. It seems reasonable to attribute the loss of stereoselection to distortion of the

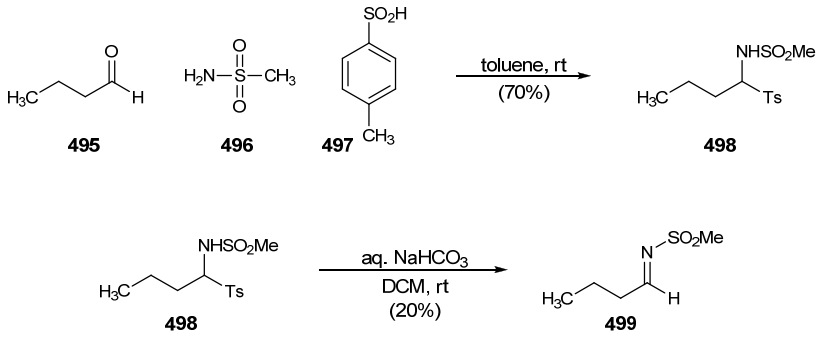
optimal binding arrangement of the imine caused by the *ortho*-substutitions (Scheme 132).

**Scheme 132.** Effect of the Steric Profile of the Sulfonyl Protecting Group on Stereoselection

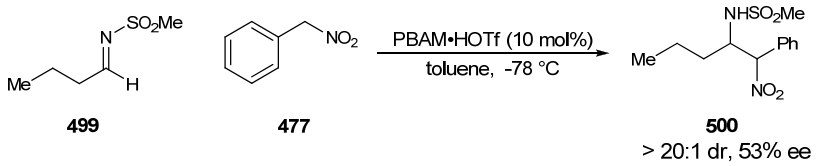



Along similar lines, it was hypothesized that a smaller sulfonyl group might be the right size so as to preserve optimal catalyst-substrate binding and subsequently lead to higher enantioselection. The methyl sulfonyl group is an ideal candidate for testing this hypothesis and hence was synthesized as shown in Scheme 131. The elimination of the α-amido sulfone was extremely facile and coupled with the instability of the imine to the

**Scheme 131.** Synthesis of the Methylsulfonyl Protected Alkyl Imine



**Scheme 133.**



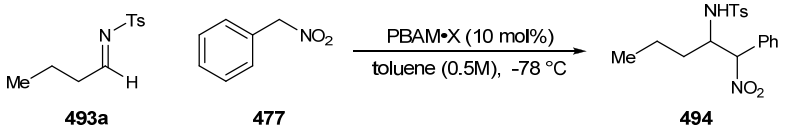

**499** **477** **500**

> 20:1 dr, 53% ee

reaction conditions, it was difficult to obtain high yields in this reaction. Unfortunately, this imine afforded diminished enantioselection indicating that methyl sulfonyl group may not be suitable for obtaining high stereoselection due to its steric and/or electronic differences compared to the phenyl sulfonyl moiety (Scheme 133).

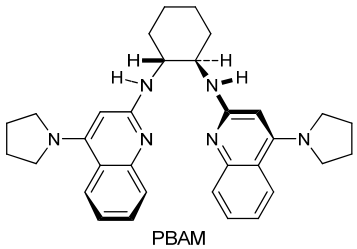
Counterion effects have been shown to cause changes in the reaction profile and hence we performed a counterion screen as depicted in Table 18. It was observed that the PBAM free base performed relatively poorly affording 67% ee and 7:1 dr. Triflimide and bis(triflyl)methane performed similarly to triflate affording 82% and 79% ee respectively. Camphorsulfonic acid, fluorosulfonic acid, and phenyl sulfinic acid afforded lowest dr and ee among the acids tested. The use of camphorsulfonic acid might lead to

**Table 18.** Counter-ion Effects in the Chiral Proton Catalyzed Additions of Phenyl Nitromethane




**493a** **477** **494**

| entry | X | dr | %ee | %yield |
|---|---|---|---|---|
| 1 | none | 7:1 | 67 | 31 |
| 2 | TfOH | >20:1 | 79 | 85 |
| 3 | $HNTf_2$ | >20:1 | 82 | 80 |
| 4 | $CH_2Tf_2$ | >20:1 | 79 | 79 |
| 5 | CSA | 7:1 | 65 | 35 |
| 6 | $FSO_3H$ | 9:1 | 68 | 55 |
| 7 | $C_4F_9SO_3H$ | >20:1 | 80 | 65 |
| 8 | $PhSO_2H$ | 6:1 | 65 | 41 |



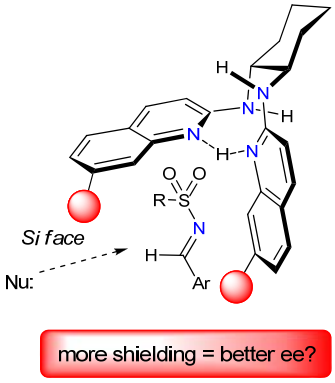

PBAM

[a]All reactions are 0.5 M in imine and use 1.5 equivalents of the nitroalkane unless otherwise noted. [b]Diastereomer ratios were measured using 1H NMR. Enantiomer ratios were measured using HPLC and a chiral stationary phase. Yields are for isolated product.

complications arising from either a matched or mismatched scenario but this possibility was not further studied. Nonafluorosulfonic acid performed similarly to triflate affording excellent diastereoselection (>20:1) and moderate ee (80%). The marginal increase in enantioselection obtained with triflimide was encouraging but overall, changes to the counterions failed to provide the increase in enantioselection we desired.

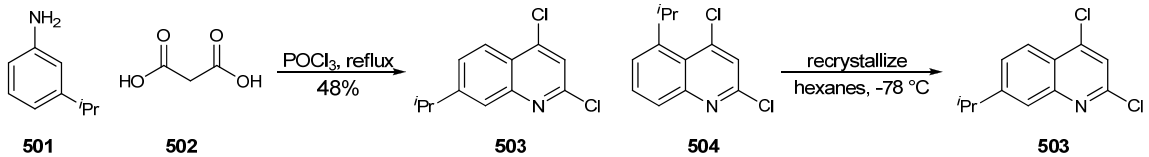
The enantioselection for phenyl nitromethane addition proved to be insensitive to subtle changes to the nature of the catalyst (counter-ions) but was responsive to changes in the structure of the imine, although we were not able to use that to our advantage. Since the reaction provides good enantioselection, it can be assumed that it fulfills

**Figure 40.** Hypothesis for Increasing Enantioselection by Incorporating 7-Substituted Quinolines in BAM Catalysts




requirements posed by our proposed stereochemical model but the facial discrimination needs further improvement. In order to achieve that, it was decided to design new

**Scheme 134.** Synthesis of 7-Isopropyl-2,4-dichloroquinoline

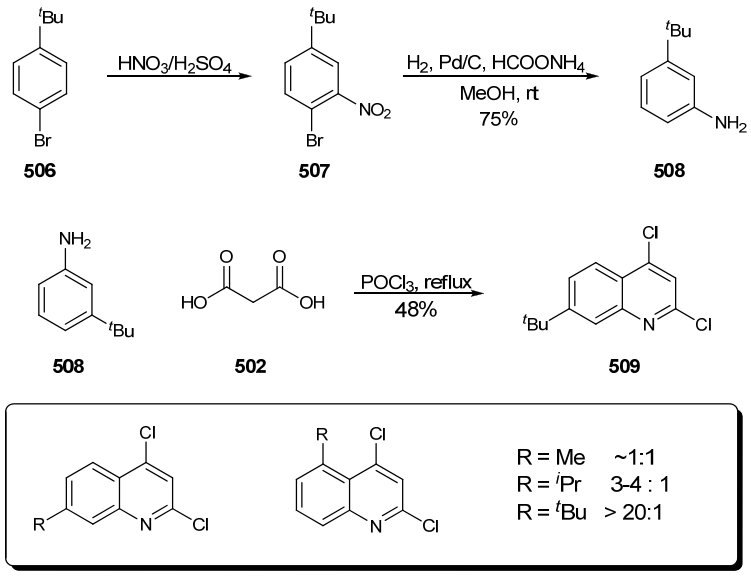



**501** **502** **503** **504** **503**

3.3 : 1

catalysts in which the reach of the chiral environment was extended. This could be achieved by installing substitutents on the 7-position of the quinoline ring as shown in Figure 40. 7-*tert*-Butyl and 7-isopropyl groups would be substitutions that could be incorporated using a reasonable number of steps. The requisite 7-isopropyl-2,4-dichloroquinoline was synthesized as shown in Scheme 134. The annulation of 7-isopropyl quinoline and malonic acid afforded a mixture of regioisomers that could be used to provide the desired 7-isopropylquinoline following a low temperature recrystallization. The corresponding annulations of 7-*tert*-butyl aniline with malonic acid resulted in the desired regioisomer as the sole product. The ratio of the desired to undesired regioisomer increases with the increasing steric bulk of the 7-substitutent as shown in Scheme 135.

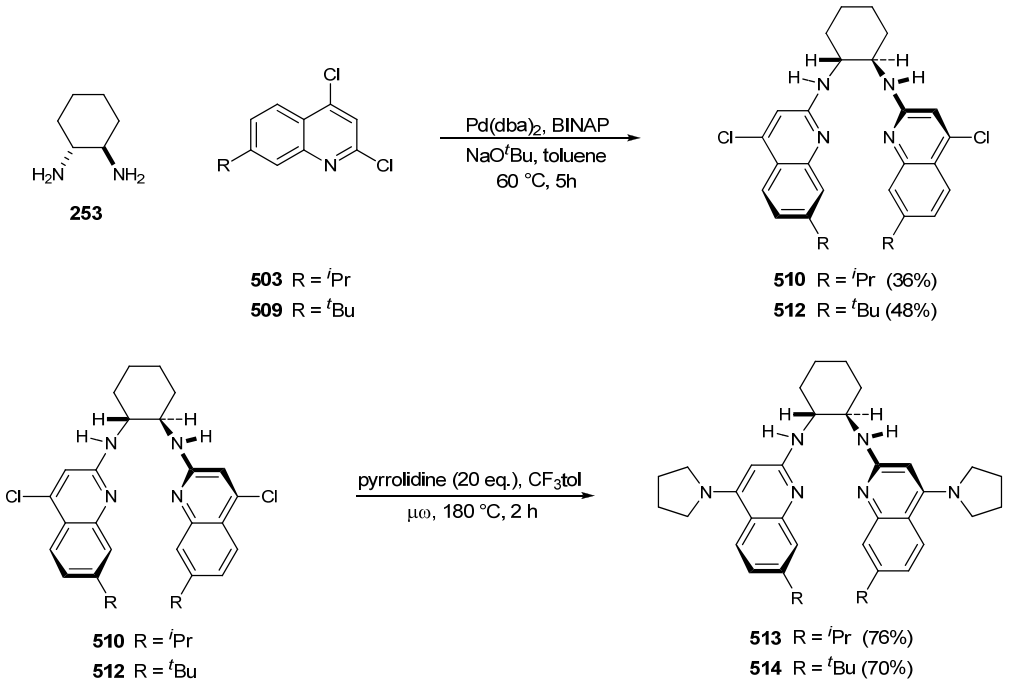
**Scheme 135.** Synthesis of 7-*tert*-Butyl-2,4-Dichlroquinoline and Effect of 7-Substitution on the Regioselectivity of the Annulation Reaction




The synthesis of the ligands was achieved as shown in Scheme 136. The Buchwald-Hartwig coupling of 2,4-dichloroquinolines with cyclohexyl diamine

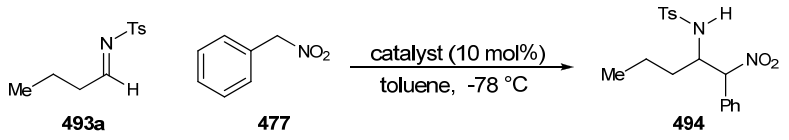
proceeded smoothly to afford the chloro bis(amidines) which could be converted to the corresponding 4-pyrrolidine derivatives in good yields.

**Scheme 136.** Synthesis of 7-iso-Propyl and 7-*tert*-Butyl Substituted PBAM Derivatives



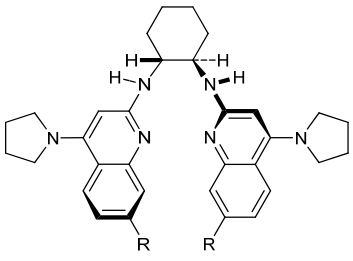

Unfortunately, however, these catalysts did not afford the increase in enantioselection that we desired. The reaction outcome was similar to that afforded by

**Table 19.** Evaluation of 7-Substituted PBAM Derivatives in Phenyl Nitromethane Additions




| entry | catalyst[a] | dr[b] | %ee[c] | %yield |
|---|---|---|---|---|
| 1 | $^{7i}$Pr-PBAM | 5:1 | 51 | 51 |
| 2 | $^{7i}$Pr-PBAM•HOTf | 14:1 | 72 | 72 |
| 3 | $^{7t}$Bu-PBAM•HOTf | 20:1 | 79 | 79 |

[a]All reactions are 0.5 M in imine and use 1.5 equivalents of the nitro alkane. [b]Diastereomer ratios were measured using 1H NMR. [c]Enantiomer ratios were measured using HPLC and a chiral stationary phase. Yields are for isolated product.

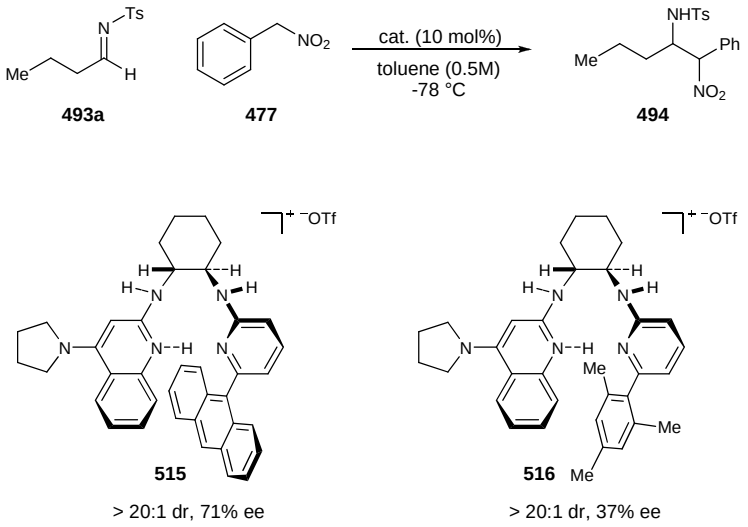


513 R = $^{i}$Pr
514 R = $^{t}$Bu

PBAM and its analogues as shown in Table 19. The failure of these catalysts to provide an increase in enantioselection suggests that the catalyst pocket needs to be further manipulated in order to achieve the optimal binding arrangement of the imine and the catalyst.

Continuing with the theme of catalyst optimization, we also attempted the use of catalysts with a hindered pocket, which include the anthracene and related derivatives. Unfortunately, these catalysts did not afford any increase in enantioselection. The anthracene containing catalyst afforded 71% ee which is only slightly lower than PBAM•HOTf but the mesitylene derived catalyst provided 37% ee indicating that the desired conformation around the reaction site had been altered by the bulky aromatic ring in an unproductive manner (Scheme 137).

**Scheme 137.** Performance of Unsymmetrical Catalysts featuring Hindered Pockets in the Addition of Phenyl Nitromethane to Alkyl Imines



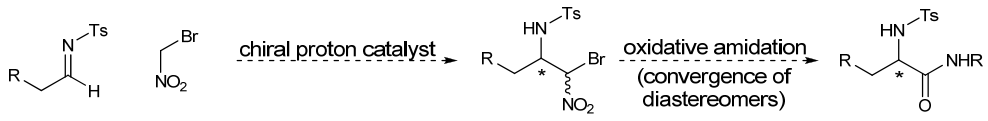

In conclusion, addition of phenyl nitromethane to alkyl *N*-tosyl imines affords adducts with excellent diastereoselection (>20:1) but moderate enantioselection (80%). Efforts to enhance facial selectivity using counterion effects, catalyst structure

modification, and imine structure modification have so far proven unsuccessful. The non-variant nature of enantioselection to subtle changes in structural characteristics of the reactants suggests that more pronounced changes to their steric profile needs to be effected in order to realize high enantioselection.

### *5.5 Enolizable Alkyl Imines in Chiral Proton Catalysis: Bromo Nitromethane Additions*

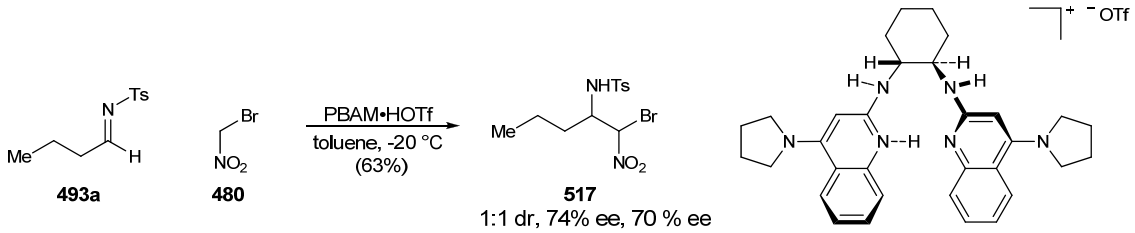
The use of bromo nitromethane as a nucleophilic carboxylate equivalent removes the need for high diastereoselection in these additions, since the subsequent transformation converts the nitromethyl carbon into an $sp^2$ center (Scheme 138). However, it is important that both diastereomers are formed with similar (high) enantioselection since they must convergence to a single enantiomer. As an example, if the adducts are formed as a 1:1 mixture of diastereomers with 90% and 40% ee

**Scheme 138.** Bromo Nitromethane as a Precursor to α-Amino Acids




respectively (with the same favored configuration at the β-carbon), the ee of the subsequent amide product will only be 65%.

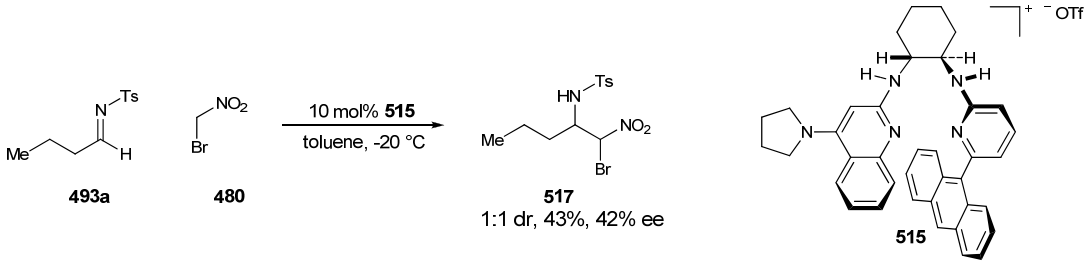
**Scheme 139.** PBAM•HOTf Catalyzed Bromo Nitromethane Addition to Alkyl Imine



An initial result with PBAM•HOTf was encouraging and showed that the reaction was catalyzed effectively affording the product as a 1:1 mixture of diastereomers with 74% and 70% ee. We were pleased to observe that the diastereomers were formed with similar enantioselection although the selectivity was moderate (Scheme 139).

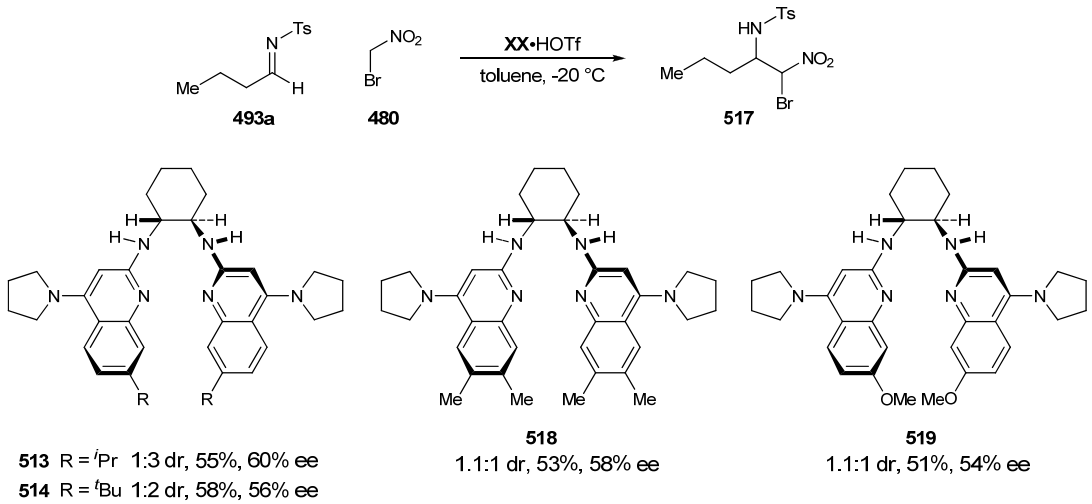
It was contemplated that catalyst structure might be used to influence (increase) enantioselection. The two motifs that we have identified so far towards this purpose are the anthracene derivatives and the 7-substituted PBAM derivatives as mentioned in the

**Scheme 141.** Poor Performance of Unsymmetrical Catalyst **515** in Catalyzing Bromo Nitromethane Addition to Alkyl Imine




previous section. Application of the unsymmetrical PBAM derivative **515** was found to be counterproductive, leading to lower enantioselection (Scheme 141). The high level of

**Scheme 140.** Evaluation of Catalysts with 7-Substituted Quinoline Rings: Attempt to Extend the Chiral Influence

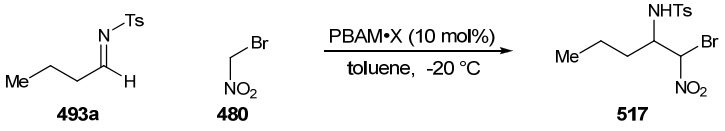


steric encumberance in the catalyst pocket which includes the anthracene ring and the tosyl group might serve to distort the optimal binding mode necessary for obtaining high enantioselection.

Application of various 7-substituted PBAM derivatives also yielded lower enantioselection as shown in Scheme 140. The steric bulk of the 7-substitution did not influence the outcome to a large extent as shown by the fact that the isopropyl, *tert*-butyl, and methyl substitutions afforded very similar enantioselection.

Based on the fact that these reactions impart enantioselection primarily through a Lewis acid activation mechanism, counterion effects may offer a simple but effective solution to the low enantioselection problem. A survey of various counterions revealed that triflate was the most effective (Table 20, entry 2) followed by the triflimide (Table 20, entry 3). The use of PBAM free base afforded lowest enantioselection suggesting that the proton plays a key role in stereoselection. Although most of the counterions were based on the sulfonic acid moiety, the sensitivity of the reaction to the changes was very

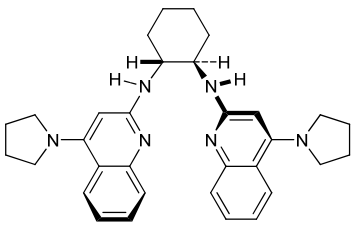
**Table 20.** Counter-ion Effects in the Chiral Proton Catalyzed Additions of Bromo Nitromethane to Alkyl Imines




493a 480 517

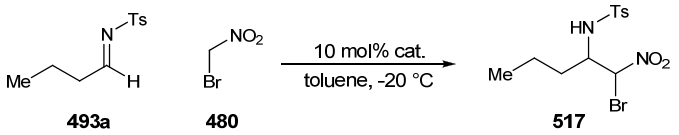
| entry[a] | X | dr[b] | %ee[c] | %yield[d] |
|---|---|---|---|---|
| 1 | none | 1.4:1 | 35,38 | 35,38 |
| 2 | TfOH | 1:1 | 74,70 | 74,70 |
| 3 | $HNTf_2$ | 1.3:1 | 68,68 | 68,68 |
| 4 | $CH_2Tf_2$ | 1:1 | 60,67 | 60,67 |
| 5 | CSA | 1:1 | 39,42 | 39,42 |
| 6 | $FSO_3H$ | 1:1 | 59,56 | 59,56 |
| 7 | $C_4H_9SO_3H$ | 1.1:1 | 55,62 | 55,62 |

[a]All reactions are 0.5 M in imine and use 1.5 equivalents of the nitro alkane. [b]Diastereomer ratios were measured using 1H NMR. [c]Enantiomer ratios were measured using HPLC and a chiral stationary phase. [d]Yields are for isolated product.




PBAM

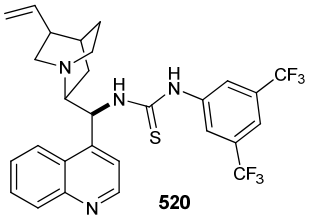
**Table 21.** Thiourea Catalyzed Additions of Bromo Nitromethane to Enolizable Alkyl Imines



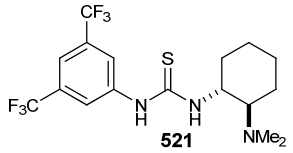

493a 480 517

| entry[a] | X | dr[b] | %ee[c] | %yield[d] |
|---|---|---|---|---|
| 1 | **1** | 1.2:1 | -19, -18 | 71 |
| 2 | **1**•HOTf | 1:1 | -53, -44 | 30 |
| 3 | **2** | 1.2:1 | 56, 56 | 69 |
| 4 | **2**•HOTf | 1:1 | -37,24 | 39 |

[a]All reactions are 0.5 M in imine and use 1.5 equivalents of the nitro alkane. [b]Diastereomer ratios were measured using 1H NMR. [c]Enantiomer ratios were measured using HPLC and a chiral stationary phase. Yields are for isolated product.




**520**



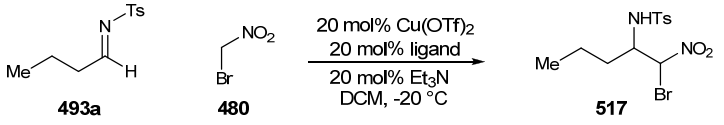

**521**

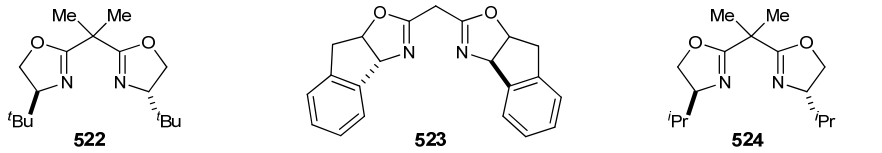
high as revealed by the broad spectrum of enantioselection obtained.

Since aza-Henry reactions have been successful with other organocatalysts also, attempts were made to perform this reaction using readily available catalyst systems such as the thioureas developed by Takemoto and Deng. Since these systems interact differently with the electrohphile and nucleophile, there is a possibility of obtaining better stereoselection. We employed the free amine form of these catalysts as well as the protonated versions (TfOH) in order to test their efficacy. It was discovered that neither of these thiourea catalysts afforded better stereoslection. Deng's catalyst **520** resulted in 19 and 18% ee for the two diastereomers favoring the *opposite* enantiomer compared to PBAM derivatives. The protonated form of this ligand provided higher enantioselection (still favoring the opposite enantiomer) than the free amine form but was lower than that given by PBAM. Takemoto's thiourea performed better when utilized as a free base (Table 21, entry 3). The sense of stereoinduction was same as that afforded by PBAM derivatives. Upon protonation, the reaction outcome changed dramatically with the two diastereomers being formed favoring opposite enantiomers. This suggests that the conformations of the protonated and unprotonated forms of this thiourea differ widely.

The plethora of Cu(II)-BOX catalysts reported for enantioselective Henry and aza-Henry reactions prompted to us to study the application of these systems in this reaction. A limited screen of BOX ligands in conjunction with Cu(II) triflate did not prove beneficial and since these catalysts fared worst in comparison to other systems, they were not pursued further (Scheme 142).

**Scheme 142.** Evaluation of Copper(II) Catalysis for Bromo Nitromethane Additions

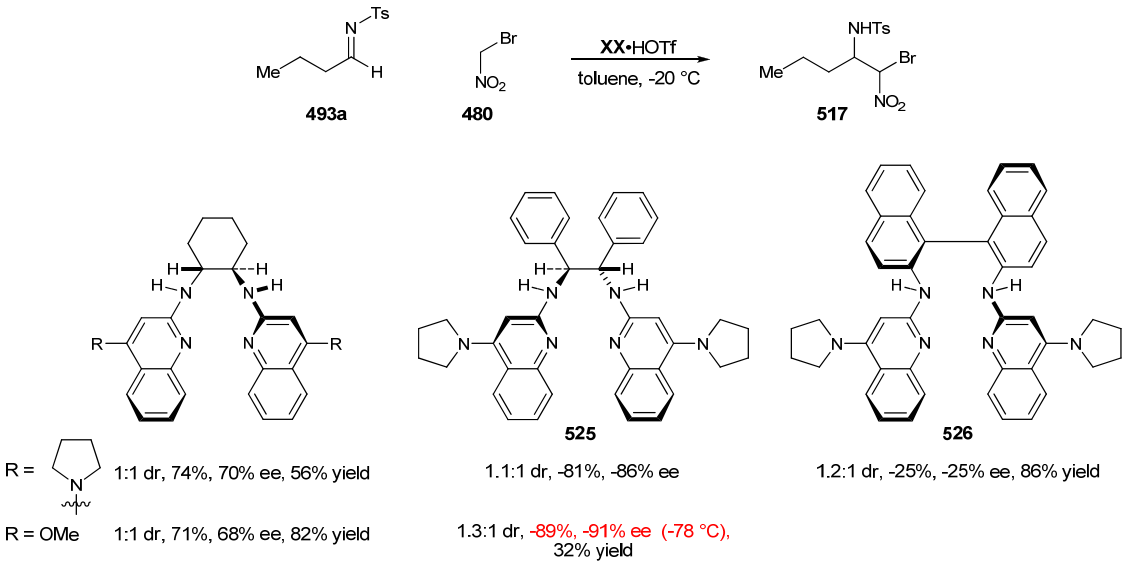



The superior performance of BAM catalysts compared to other systems prompted us to pursue suitable modifications that would afford the desired improvement in enantioselection. We turned our attention to a relatively unexplored area which is the use of BAM catalysts derived from different diamine backbones. It was decided to employ diamines that were easily accessible in enantiopure form such as BINAM and stilbene diamine. Scheme 143 illustrates the results from the PBAM derivatives of these catalysts. Although the BINAM derived catalyst **526** performed poorly (1.2:1 dr, -25, -25% ee), we were delighted to observe a significant increase in enantioselection with the stilbene derived catalyst **525**. Changes in the diamine backbone are ultimately expressed as the bite angle between the two quinoline rings. In a computationl study by Chin, the stilbene derivatives were found to have a smaller angle than cyclohexane diamine. We believe

that this change favorably modifies the binding of the imine in the catalyst pocket although an exact understanding of this phenomenon is not at hand yet.

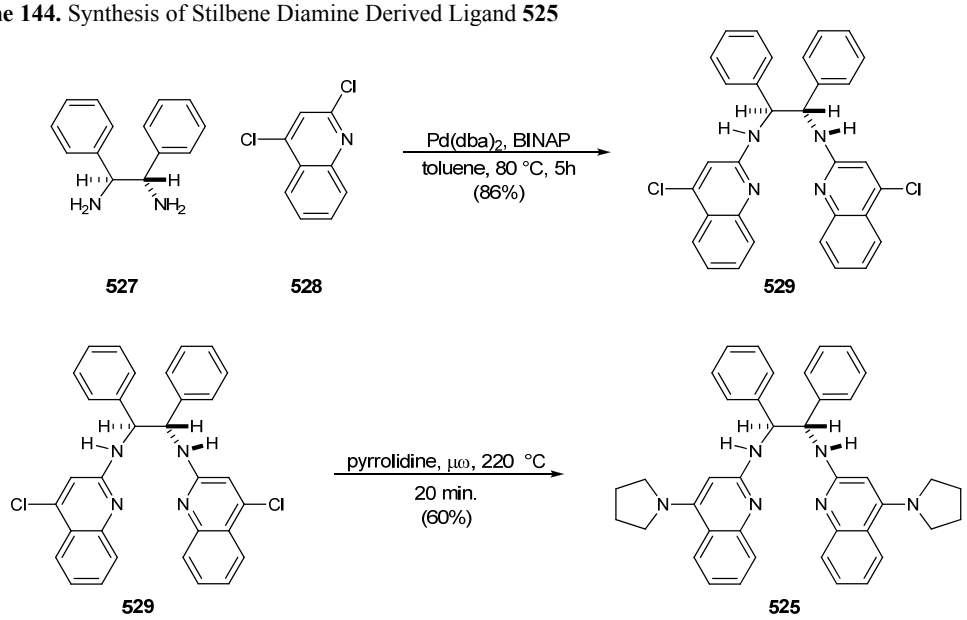
**Scheme 143.** Chiral Proton Catalyzed Additions of Bromo Nitromethane: Evaluations of Catalysts with Different Diamine Backbones




Performing the reaction at lower temperature resulted in the expected increase in enantioselection to 91% and 89% for the two diastereomers. Even though the enantioselection was high, a low yield (32%) of the product remained a concern. Crude NMR analysis of the reaction mixture revealed that the imine was consumed but possible decomposition resulted in low yield. A comparison between PBAM•HOTf and H,$^{4}$OMeQuin-BAM•HOTf revealed that the latter afforded cleaner reaction, higher yield but more importantly, similar enantioselection (three percent lower). Although this comparison was performed under unoptimized conditions (using cyclohexyl diamine derived catalysts), it underscores the difference in reactivity of these two catalysts. Extension of this behavior to stilbene derived catalysts will likely allow us to obtain high enantioselection in conjunction with high yields. The synthesis of the stilbene derived

ligands was achieved as shown in Scheme 144. The 4-chloro BAM **529** serves as the common template for the synthesis of the 4-pyrrolidine and the 4-methoxy derivatives and was synthesized in high yield following a Buchwald-Hartwig amination of stilbene diamine with 2,4-dichloroquinoline. Microwave assisted substitution of the chlorine with pyrrolidine (neat) afforded the appropriately substituted ligand.

**Scheme 144.** Synthesis of Stilbene Diamine Derived Ligand **525**




527 528 529 529 525

Concurrent to the catalyst modification attempts, we decided to investigate the effect of catalyst protonation state on the outcome of this reaction. Compared to catalysts derived from cyclohexyl diamine, we expected the stilbene derived catalysts to be conformationally more responsive to the changes in protonation state since the two parts of the molecule are not tethered (Figure 41).

**Figure 41.** Predicted Differences in Conformational Mobility of Catalysts Derived from Different Backbones

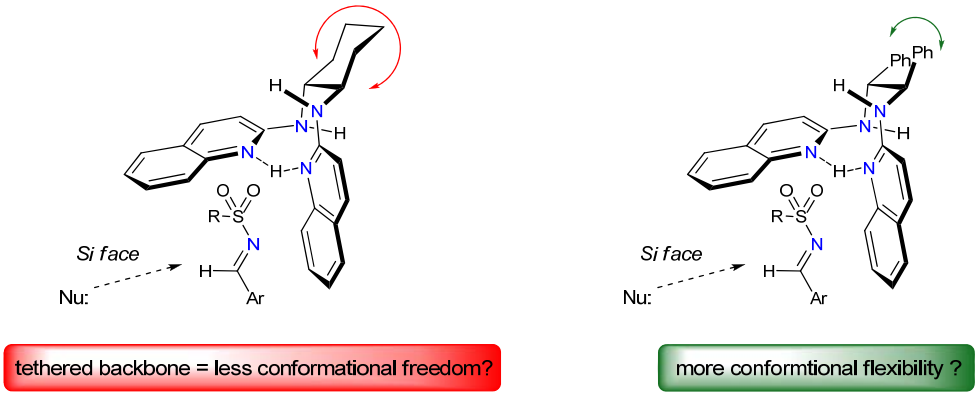
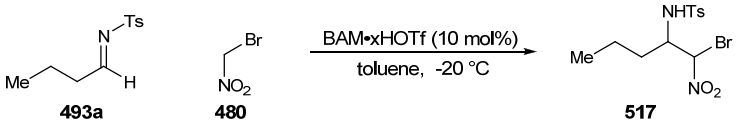


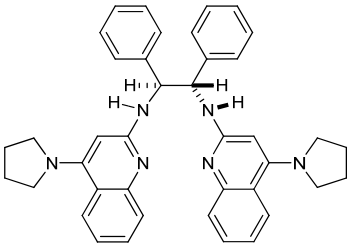

Table 22 illustrates the results of the protonation state study. It was discovered that the free ligand afforded low enantioselection indicating that the proton is key to high enantioselection. A steady increase in the proportion of triflic acid results in a gradual increase in enantioselection until a 1:1 ratio of ligand to triflic acid is reached. Further increase in the amount of trilflic acid (1:1.5 PBAM:HOTf) leads to slightly diminished

**Table 22.** Effect of Protonation State of the Catalyst on Enantioselection in the Chiral Proton Catalyzed Additions of Bromo Nitromethane to Alkyl Imines




| entry[a] | X | dr[b] | %ee[c] | %yield[d] |
|---|---|---|---|---|
| 1 | 0 | 1:1 | 47,44 | 39 |
| 2 | 0.5 | 1:1 | 69,70 | 53 |
| 3 | 0.75 | 1.3:1 | 79,80 | 51 |
| 4 | 1 | 1:1 | 81,86 | 61 |
| 5 | 1.5 | 1:1 | 81,82 | 70 |

[a]All reactions are 0.5 M in imine and use 1.5 equivalents of the nitro alkane. [b]Diastereomer ratios were measured using 1H NMR. [c]Enantiomer ratios were measured using HPLC and a chiral stationary phase. [d]Yields are for isolated product.



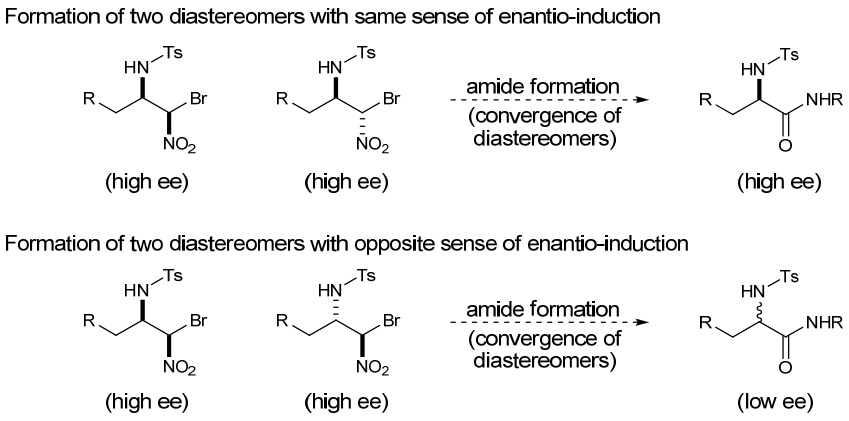

reactivity (90% conv. in 3 days) although crude NMR analysis revealed that a cleaner reaction occurred and this was reflected in the higher yield compared to the catalysts with

lower amounts of TfOH. In all cases, the enantioselection for both diastereomers remained similar.

### *5.6 Formation of Both Diastereomers with the Same Sense of Enantioselection*

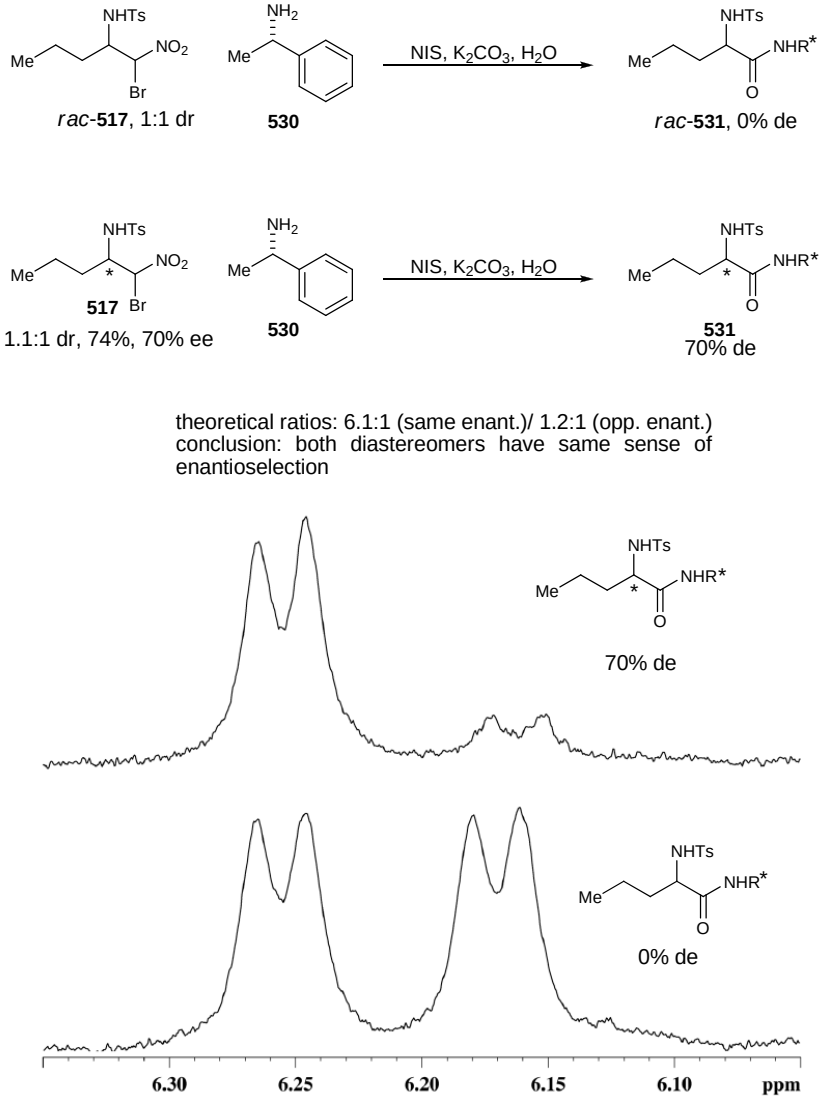
Since the diastereomeric products from these bromo nitromethane additions are converged to two enantiomers following the amide bond formation step, it is important that both diastereomers are formed with high ee *and* with the same sense of

**Figure 42.** Importance of Both Diastereomers Being Formed with the Same Sense of Enantioselection




enantioselection. As shown in Figure 42, if the diastereomers are formed with opposite configuration at Cα, the resulting amide product will be of low ee. In order to test which case was operative in these reactions, we decided to use enantiopure (*S*)-α-methylbenzylamine to form the amide because the dr of these products would allow us to determine whether the starting bromonitro adducts were formed with same sense of enantioselection or not. Comparision of the diastereomer ratios of the amide products indicated that the enantioenriched bromonitro adducts indeed had the same sense of enantioselection (70% de compared to the theoretical value of 72% de). If this had not been the case, we would have observed a 2% de for the formation of the amide.

**Figure 43.** Formation of the Bromo Nitromethane Adducts with Same Sense of Enantio-Induction: $^1$H NMR Analysis




In conclusion, we have shown that chiral proton catalysis can be applied to aza-Henry reactions involving enolizable alkyl imines. The best results achieved with phenyl nitromethane was the formation of adducts with >20:1 dr and 82% ee. In case of bromo nitromethane, the highest enantioselection obtained was 91%, 89% (for two diastereomers) although the yield was low (32%). The distereomeric bromonitro adducts were shown to be formed with the same sense of enantioselection by converting them to to the corresponding amides using (*S*)-α-methyl benzylamine. Improvements in yield has

been realized by the use of H,$^{4}$OMeQuin-BAM•HOTf as the catalyst and efforts are underway to optimize the reaction so that good yields and high enantioselection can be realized simultaneously using suitably substituted catalysts.

## *CHAPTER VI*

## *EXPERIMENTAL*

Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Diethyl ether ($Et_2O$), tetrahydrofuran (THF), dichloromethane ($CH_2Cl_2$), and toluene were dried by passage through a column of activated alumina as described by Grubbs.[178] Methanol was distilled from magnesium under $N_2$ immediately before use. Imines[179], $Pd(dba)_2$[180], 9-anthracenylboronic acid[181] and *tert*-Butyl nitroacetate[182] were prepared as reported in the literature. Buchwald's protocol was used for palladium-mediated aryl amination.[183]

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Scientific Adsorbents. UV light, and/or the use of ceric ammonium molybdate and potassium iodoplatinate solutions were used to visualize products.

IR spectra were recorded on a Thermo Nicolet IR100 spectrophotometer and are reported in wavenumbers ($cm^{-1}$). Liquids and oils were analyzed as neat films on a NaCl plate (transmission), whereas solids were applied to a diamond plate (ATR). Nuclear magnetic resonance spectra (NMR) were acquired on either a Bruker DRX-400 (400 MHz) or DRX-500 (500 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.1 ($CDCl_3$). Mass

[178] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520
[179] Kanazawa, A. M.; Denis, J.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238-1240.
[180] Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1992**, *28*, 110.
[181] Li, Z. H.; Wong, M. S.; Tao, Y.; D'lorio, M. *J. Org. Chem.* **2004**, *69*, 921.
[182] Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 875.
[183] Wagaw, S.; Rennels, R.; Buchwald, S. *J. Am. Chem. Soc.* **1997**, *119*, 8451-8458.

spectra were recorded on a Kratos MS-80 spectrometer by use of chemical ionization (CI). Absolute and relative configuration of *syn*-**384a** was determined by X-ray diffraction. This estabilished the configuration of *anti*-**384a** via epimerization. Absolute and relative configuration of the remaining products were assigned by analogy. Absolute and relative configuration of *syn*-**443d** was determined by X-ray diffraction. Single crystals were obtained by slow evaporation of a solution of **443d** in pentane. Absolute and relative configuration of the remaining products (**452**) were assigned by analogy.

**General Procedure for the Synthesis of Amines *anti*-385.** A solution of imine (1.0 equiv) and H,Quin($^{6}$($^{9}$Anth)$^{2}$Pyr)-BAM•HOTf (**2**)(0.05 equiv) in toluene (0.3 M) was cooled to -78 °C and treated with *tert*-butyl nitroacetate (1.1 equiv). The reaction was stirred at -78 °C until complete (as determined by TLC). The solution was concentrated at 0 °C and the product was immediately subjected to reduction. Diastereomeric excess of the adducts was determined by $^{1}$H NMR.

**General Procedure for the Reduction of Aza-Henry Products (384).** A solution of the nitroacetate adduct (1.0 equiv) and cobalt (II) chloride (1.0 equiv) in MeOH (0.1 M) was cooled to 0 °C followed by the addition of sodium borohydride (5.0 equiv). The resulting black suspension was stirred at 0 °C for 15 minutes and then at room temperature until complete (monitored by TLC). The reaction was quenched by the dropwise addition of 3M aq. HCl until pH 2 was reached. Then 1M aq. $NH_4OH$ was added dropwise until the solution attained pH 9. Methanol was removed, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, water, and then dried over magnesium sulfate. Filtration and concentration afforded the crude product which was subjected to purification by column chromatography.

**General Procedure for the Synthesis of Adducts *syn*-452a-j/443d.** A solution of imine (1.0 equiv) and H,$^{4}$OMeQuin($^{6}$($^{9}$Anth)$^{2}$Pyr)-BAM•HOTf (**446**) (0.05 equiv) in toluene (1.0 M) was cooled to -78 °C and treated with 2,6-diisopropylphenyl 2-nitrobutanoate (1.1 equiv). The reaction was stirred at -78 °C for 48 hours. The solution was concentrated and the product was purified by column chromatography. Diastereomeric ratios for each adduct were determined by $^{1}$H NMR.

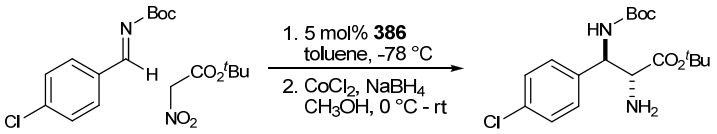
**General Procedure for the Reduction of Adducts *syn*-443d/452a.** To a solution of the nitroacetate adduct (1.0 equiv) in ethanol was added 3 M HCl (40 equiv) followed by zinc dust (40 equiv). The reaction was stirred at room temperature for 12 hours before it was quenched with satd aq sodium bicarbonate until pH 9 was achieved. Ethanol was removed and the reaction mixture was extracted with ethyl acetate. All organic extracts were combined, dried and concentrated to afford the crude product which was purified by column chromatography.

**General Procedure for the Synthesis of Adducts 443a-d.** A solution of imine (1.0 equiv) and H,$^{4}$OMeQuin($^{6}$($^{9}$Anth)$^{2}$Pyr)-BAM•HOTf (**446**) (0.05 equiv) in 1,2-dichloroethane (0.7 M) was cooled to -20 °C and treated with the appropriate nitroester (1.1 equiv). The reaction was stirred at -20 °C for 48 hours. The solution was concentrated and the product was purified by column chromatography. Diastereomer ratios for each adduct were determined by $^{1}$H NMR.

**General Procedure for the Saponification of Amino Esters**:[184] To a solution of the aminoester (1.0 eqiv) in ethanol/water (4:1) was added potassium hydroxide (25 equiv) and the reaction was refluxed for 5 hours. The reaction was cooled and neutralized with

[184](a) Miyano, S.; Koike, N.; Hayashizaka, N.; Suzuki, T.; Hattori, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3034. (b) Raju, B. *et al*. *Bioorg. Med. Chem. Lett.* **2004**, 14, 2103.

3.0 M HCl solution. Solvent was removed and the residue was extracted with chloroform. The residue was dried and then extracted with a solution of ethanol in dichloromethane (1:1). All extracts were combined and solvent removed to afford the amino acid.

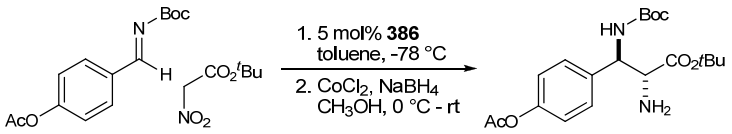



**(2*R*,3*R*)-*tert*-Butyl 2-amino-3-(*tert*-butoxycarbonylamino)-3-(4-chlorophenyl)propanoate (*anti*-385a)** According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (46.9 mg, 0.20 mmol) provided **385a** after flash column chromatography (40% ethyl acetate in hexanes) as a yellow oil (63.8 mg, 88%), which was determined to be 95% ee, 5:1 dr by chiral HPLC analysis (Chiralcel AD, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*anti*, major) = 14.8 min, $t_r$(*anti*, minor) = 9.7 min, $t_r$(*syn*, major) = 19.7 min, $t_r$(*syn*, minor) = 11.8 min).

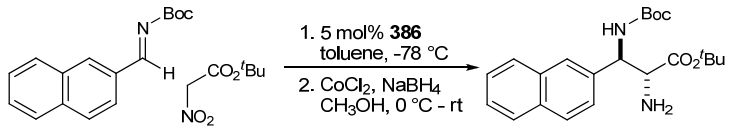
*anti*-**385a**: $R_f$ =0.07 (20% EtOAc/hexanes); IR (neat) 3394, 2975, 1713, 1511, 1155 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.28-7.21 (m, 4H), 5.89 (br d, $J$ = 7.7 Hz, 1H), 5.02 (br s, 1H), 3.67 (br d, $J$ = 4.0 Hz, 1H), 1.47 (br s, 2H), 1.41 (s, 9H), 1.38 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 172.1, 155.1, 137.2, 133.7, 128.7, 128.5, 82.3, 79.8, 58.6, 55.5, 28.5, 28.1. HRMS (CI): Exact mass calculated for $C_{18}H_{28}ClN_2O_4$ $[M+H]^+$ 371.1732. Found 371.1734.

*syn*-**385a**: $R_f$ = 0.10 (20% EtOAc/hexanes); IR (neat) 3381, 2981, 1711, 1507, 1156 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H), 5.72 (br d, $J$ = 1.9 Hz, 1H), 5.13 (br d, $J$ = 1.9 Hz, 1H), 3.74 (br s, 1H), 1.47 (s, 9H), 1.40 (s, 9H), 1.34 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 171.3, 155.0, 139.1, 133.1, 128.6, 127.9, 82.3, 79.5, 58.7,

55.8, 28.3, 27.9; HRMS (CI) Exact mass calculated for $C_{18}H_{28}ClN_2O_4$ $[M+H]^+$ 371.1738. Found 371.1720. *Anal.* Calcd for $C_{18}H_{27}ClN_2O_4$: C, 58.29; H, 7.34; N, 7.55. Found C, 58.04; H, 7.34; N, 7.47.

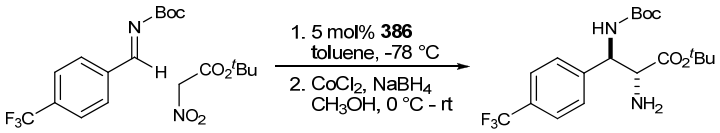



**(2*R*,3*R*)-*tert*-Butyl-3-(4-acetoxyphenyl)-2-amino-3-(*tert*-butoxycarbonylamino) propanoate (*anti*-385b):** According to the general procedure, *tert*-butyl 4-acetoxybenzylidenecarbamate (**239b**) (50 mg, 0.18 mmol) provided **385b** after flash column chromatography (20-40% ethyl acetate in hexanes) as a colorless oil (55.4 mg, 74%), which was determined to be 89% ee, 11:1 dr by chiral HPLC analysis (Chiralcel AD, 10% $^i$PrOH/hexanes, 1 mL/min, $t_r$(*anti*, major) = 19.7 min, $t_r$(*anti*, minor) = 14.5 min, $t_r$(*syn*, major) = 23.1 min, $t_r$(*syn*, minor) = 16.2 min). *anti*-**385b**: $R_f$=0.13 (40% EtOAc/hexanes); IR (neat) 3404, 2977, 1761, 1713, 1505, 1367, 1198 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 5.88 (br d, *J* = 8.1 Hz, 1H), 5.05 (br s, 1H), 3.67 (br d, *J* = 3.5 Hz, 1H), 2.26 (s, 3H), 1.53 (br s, 2H), 1.41 (s, 9H), 1.35 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 172.2, 169.3, 155.1, 150.2, 136.1, 128.2, 121.4, 82.2, 79.7, 58.8, 55.7, 28.4, 28.0, 21.2; HRMS (CI) Exact mass calculated for $C_{20}H_{31}N_2O_6$ $[M+H]^+$ 395.2177. Found 395.2182.



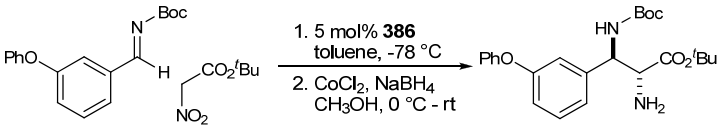

**(2*R*,3*R*)-*tert*-Butyl-2-amino-3-(*tert*-butoxycarbonylamino)-3-(naphthalen-2-yl) propanoate (*anti*-385c).** According to the general procedure, *tert*-butyl naphthalen-2-

ylmethylenecarbamate (**239c**) (50 mg, 0.20 mmol) provided **385c** after flash column chromatography (20-40% ethyl acetate in hexanes) as a colorless oil (60.5 mg, 80%), which was determined to be 91% ee, 11:1 dr by chiral HPLC analysis (Chiralcel AD, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*anti*, major) = 17.8 min, $t_r$(*anti*, minor) = 12.5 min, $t_r$(*syn*, major) = 26.9 min, $t_r$(*syn*, minor) = 14.5 min). *anti*-**6c**: $R_f$=0.23 (40% EtOAc/hexanes); IR (neat) 3393, 2976, 2926, 1712, 1493, 1367, 1249 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.79-7.74 (m, 4H), 7.46-7.42 (m, 3H), 6.03 (br d, *J* = 7.9 Hz, 1H), 5.23 (br s, 1H), 3.77 (br d, *J* = 3.8 Hz, 1H), 1.49 (s, 2H), 1.43 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 172.3, 155.2, 136.0, 133.2, 133.1, 128.2, 128.0, 127.7, 126.4, 126.2, 125.9, 125.2, 82.1, 79.7, 59.0, 56.3, 28.4, 28.1; HRMS (CI): Exact mass calculated for $C_{22}H_{31}N_2O_4$ $[M+H]^+$ 387.2284. Found 387.2278.

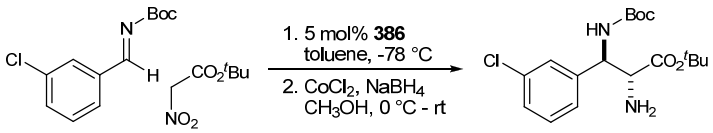



**(2*R*,3*R*)-*tert*-Butyl-2-amino-3-(*tert*-butoxycarbonylamino)-3-(4-(trifluoromethyl)phenyl) propanoate (*anti*-385e).** According to the general procedure, *tert*-butyl 4-trifluoromethylbenzylidenecarbamate (**239e**) (50 mg, 0.18 mmol) provided **6e** after flash column chromatography (20-40% ethyl acetate in hexanes) as a yellow oil (61.4 mg, 83%), which was determined to be 88% ee, 7:1 dr by chiral HPLC analysis (Chiralcel AD, 3% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*anti*, major) = 57.8 min, $t_r$(*anti*, minor) = 32.5 min, $t_r$(*syn*, major) = 69.5 min, $t_r$(*syn*, minor) = 41.7 min). *anti*-**6e**: $R_f$=0.26 (40% EtOAc/hexanes); IR (neat) 3383, 2977, 2925, 1714, 1492, 1368, 1326, 1297, 1161 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 2H), 5.95 (br

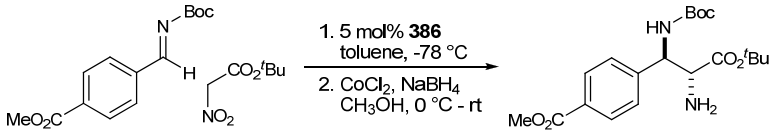
d, $J$ = 7.6 Hz, 1H), 5.10 (br s, 1H), 3.70 (br d, $J$ = 2.7 Hz, 1H), 1.48 (s, 2H), 1.42 (s, 9H), 1.38 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 172.0, 155.1, 142.8, 130.0 (q, $J$ = 32.5 Hz, 1C), 127.7, 125.3, 124.3 (q, $J$ = 272.3 Hz, 1 C), 82.5, 80.0, 58.6, 55.8, 28.5, 28.1; HRMS (CI): Exact mass calculated for $C_{19}H_{28}N_2O_4F_3$ $[M+H]^+$ 405.2001. Found 405.1996.




**(2*R*,3*R*)-*tert*-Butyl-2-amino-3-(*tert*-butoxycarbonylamino)-3-(3-phenoxyphenyl) propanoate (*anti*-385g):** According to the general procedure, *tert*-butyl 3-phenoxybenzylidenecarbamate (**239g**) (50 mg, 0.17 mmol) provided **385g** after flash column chromatography (20-40% ethyl acetate in hexanes) as a colorless oil (60.5 mg, 84%), which was determined to be 87% ee, 6:1 dr by chiral HPLC analysis (Chiralcel IA, 5% EtOH/hexanes, 1 mL/min, $t_r$(*anti*, major) = 17.5 min, $t_r$(*anti*, minor) = 12.5 min, $t_r$(*syn*, major) = 11.5 min, $t_r$(*syn*, minor) = 10.0 min). *anti*-**385g**: $R_f$=0.28 (40% EtOAc/hexanes); IR (neat) 3388, 2977, 2925, 1715, 1584, 1487, 1244, 1158 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, $J$ = 7.5, 7.5 Hz, 2H), 7.29-7.27 (m, 1H), 7.12 (t, $J$ = 7.4 Hz, 1H), 7.05 (d, $J$ = 7.7 Hz, 1H), 7.01-6.99 (m, 3H), 6.90 (d, $J$ = 7.9 Hz, 1H), 5.90 (br d, $J$ = 7.7 Hz, 1H), 5.07 (br s, 1H), 3.69 (br s, 1H), 1.57 (br s, 2H), 1.45 (s, 9H), 1.40 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 172.3, 157.2, 157.1, 155.1, 140.6, 129.8, 129.6, 123.3, 122.2, 119.0, 118.1, 117.8, 82.2, 79.7, 58.8, 55.9, 28.5, 28.1. HRMS (CI): Exact mass calculated for $C_{24}H_{33}N_2O_5$ $[M+H]^+$ 429.2389. Found 429.2384.

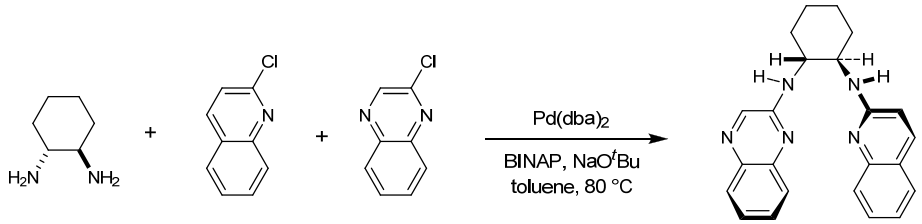



**(2*R*,3*R*)-*tert*-butyl-2-amino-3-(*tert*-butoxycarbonylamino)-3-(3-chlorophenyl) propanoate (*anti*-385h):** According to the general procedure, *tert*-butyl 3-chlorobenzylidenecarbamate (**239h**) (50 mg, 0.21 mmol) provided **385h** after flash column chromatography (20-40% ethyl acetate in hexanes) as a colorless oil (54.1 mg, 70%), which was determined to be 87% ee, 10:1 dr by chiral HPLC analysis (Chiralcel IA, 15% $^{i}$PrOH/hexanes, 0.5 mL/min, $t_r$(*anti*, major) = 15.1 min, $t_r$(*anti*, minor) = 12.2 min, $t_r$(*syn*, major) = 17.4 min, $t_r$(*syn*, minor) = 14.1 min). *anti*-**385h**: $R_f$=0.3 (40% EtOAc/hexanes); IR (neat) 3381, 2977, 2926, 1714, 1481, 1367, 1248, 1155 cm$^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.23-7.22 (m, 2H), 7.18-7.17 (m, 1H), 5.94 (br d, $J$ = 8.0 Hz, 1H), 5.03 (br d, $J$ = 3.5 Hz, 1H), 3.67 (br d, $J$ = 4.1 Hz, 1H), 1.47 (s, 2H), 1.42 (s, 9H), 1.39 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 171.9, 154.9, 140.5, 134.1, 129.5, 127.8, 127.4, 125.2, 82.3, 79.7, 58.5, 55.5, 28.3, 27.9. HRMS (CI): Exact mass calculated for $C_{18}H_{28}ClN_2O_4$ $[M+H]^+$ 371.1738. Found 371.1732.



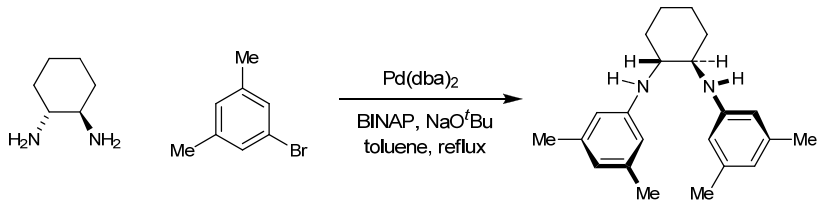

**Methyl 4-((1*R*,2*R*)-2-Amino-3-*tert*-butoxy-1-(*tert*-butoxycarbonylamino)-3-oxopropyl)benzoate (*anti*-385i)** According to the general procedure, methyl 4-((*tert*-butoxycarbonylimino)methyl)benzoate (**239i**) (50 mg, 0.19 mmol) provided **385i** after flash column chromatography (20-40% ethyl acetate in hexanes) as a pale yellow oil (62.9 mg, 84%), which was determined to be 95% ee, 8:1 dr by chiral HPLC analysis

(Chiralcel AD, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*anti*, major) = 25.6 min, $t_r$(*anti*, minor) = 17.7 min, $t_r$(*syn*, major) = 48.9 min, $t_r$(*syn*, minor) = 30.7 min). *anti*-**6i**: $R_f$=0.23 (40% EtOAc/hexanes); IR (neat) 3396, 2978, 1716, 1492, 1281, 1155 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 6.0 (br d, *J* = 8.3 Hz, 1H), 5.08 (br d, *J* = 3.4 Hz, 1H), 3.87 (s, 3H), 3.69 (br d, *J* = 2.77 Hz, 1H), 1.54 (br s, 2H), 1.39 (s, 9H), 1.35 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 172.0, 166.8, 155.0, 143.8, 129.6, 127.3, 126.6, 82.3, 79.8, 58.5, 55.9, 52.1, 28.3, 27.9; HRMS (CI): Exact mass calculated for $C_{20}H_{31}N_2O_6$ $[M+H]^+$ 395.2182. Found 395.2177.



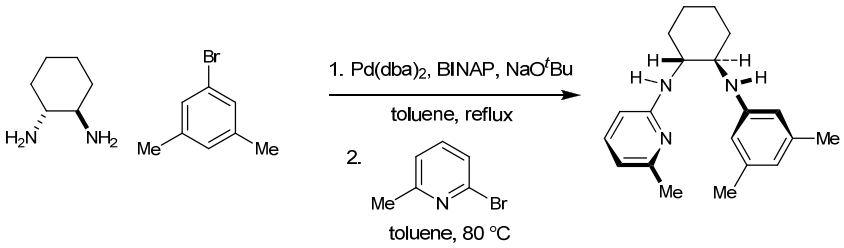

**H,Quinox(²Quin)-BAM (276).** $Pd(dba)_2$ (14.4 mg, 25.0 μmol), *rac*-BINAP (31.1 mg, 50.0 μmol), and NaO$^t$Bu (288.3 mg, 3.0 mmol) were combined in a round-bottomed flask in a glove box. Toluene (25 mL) was added to the mixture, followed by 1,2-(*R*,*R*)-*trans*-diaminocyclohexane (114.2 mg, 1.0 mmol) and 2-chloroquinoline (163.6 mg, 1.0 mmol). The reaction was stirred at 80 °C until TLC indicated complete consumption of the quinoline. Then 2-chloroquinoxaline was added and the reaction was stirred at 80 °C until TLC suggested complete conversion. The reaction was cooled to room temperature, concentrated, and purified by flash column chromatography on silica gel (gradient elution, 10-40% ethyl acetate in hexanes) to provide the desired ligand as a yellow solid (75 mg, 20%). Mp=154-157 °C; $[\alpha]_D^{20}$+614 (*c* 6.00, $CHCl_3$); $R_f$=0.32 (60% EtOAc/hexanes); IR (film) 3404, 3270, 3052, 2929, 2853, 1617, 1582, 1535, 1486, 1416,

1398, 1320 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.82-7.49 (m, 8H), 7.30-7.22 (m, 2H), 6.41 (d, *J* = 8.6 Hz, 1H), 5.22 (s, 1H), 4.27 (m, 1H), 3.95 (m, 1H), 2.56 (d, *J* = 12.0 Hz, 1H), 2.19 (d, *J* = 5.7 Hz, 1H), 1.83 (d, *J* = 13 Hz, 2H), 1.49-1.39 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ppm 157.1, 152.1, 147.2, 142.1, 139.8, 137.4, 136.8, 130.04, 129.7, 128.8, 127.6, 125.9, 125.4, 123.6, 123.4, 122.4, 112.7, 58.2, 54.6, 33.1, 32.0, 25.2, 24.4; HRMS (EI): Exact mass calcd for $C_{23}H_{24}N_5$ $[M+H]^+$ 370.1953. Found 370.2009.



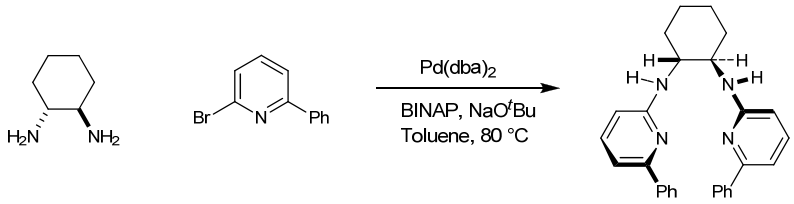

**(1*R*,2*R*)-$N^1$, $N^2$-bis(3,5-dimethylphenyl)cyclohexane-1,2-diamine (274).** $Pd(dba)_2$ (14.4 mg, 25.0 μmol), *rac*-BINAP (31.1 mg, 50.0 μmol), and $NaO^tBu$ (288.3 mg, 3.0 mmol) were combined in a round-bottomed flask in a glove box. Toluene (25 mL) was added to the mixture, followed by 1,2-(*R*,*R*)-*trans*-diaminocyclohexane (114.2 mg, 1.0 mmol) and 1-bromo-3,5-dimethylbenzene (370.14 mg, 2.0 mmol). The reaction was stirred at 80 °C until TLC indicated complete consumption of the bromoxylene. The reaction was cooled to room temperature, concentrated, and purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide the desired ligand as a brown wax (177 mg, 55%). $[\alpha]_D^{20}$ +21 (*c* 8.00, $CHCl_3$); $R_f$ = 0.74 (60% EtOAc/hexanes); IR (film) 3318, 3021, 2922, 2852, 1596, 1509, 1473, 1337, 1184, 1105 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 2H), 6.25 (s, 4H), 3.73 (br s, 2H), 3.18-3.15 (m, 2H), 2.24 (s, 12H), 1.78-1.75 (m, 2H), 1.46-1.39 (m, 2H), 1.26-1.24 (m, 4H); $^{13}C$

NMR (100 MHz, $CDCl_3$) ppm 147.9, 138.9, 119.5, 111.4, 57.1, 32.6, 24.6, 21.5; HRMS (EI): Exact mass calcd for $C_{22}H_{31}N_2$ $[M+H]^+$ 323.2409. Found 323.2478.

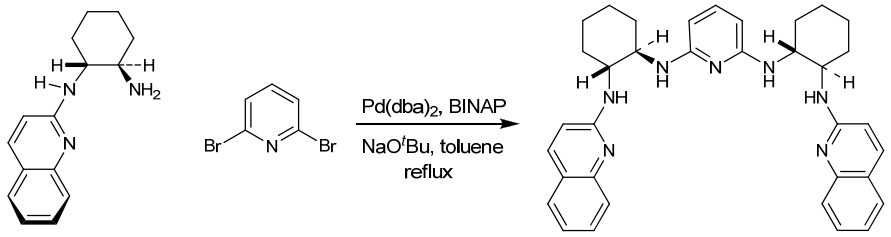



**(1*R*,2*R*)-N1-(3,5-dimethylphenyl)-N2-(6-methylpyridin-2-yl)cyclohexane-1,2-diamine.** $Pd(dba)_2$ (28.7 mg, 50.0 μmol), *rac*-BINAP (68.27 mg, 100.0 μmol), and $NaO^tBu$ (576.6 mg, 6.0 mmol) were combined in a round-bottomed flask in a glove box. Toluene (50 mL) was added to the mixture, followed by 1,2-(*R*,*R*)-*trans*-diaminocyclohexane (228.4 mg, 2.0 mmol) and 1-bromo-3,5-dimethylbenzene (370.1 mg, 2.0 mmol). The reaction was refluxed until TLC indicated complete consumption of the bromoxylene. Then 2-bromo-6-methyl pyridine (344.6 mg, 2.0 mmol) was added to the reaction and the reaction was stirred at 80 °C until TLC suggested complete conversion. The reaction was cooled to room temperature and filtered through a bed of Celite and silica gel. The filtrate was concentrated and then purified by flash column chromatography on silica gel (10-40% ethyl acetate in hexanes) to provide the desired ligand as a white solid (191.9 mg, 31%). Mp=116-118 °C; $[\alpha]_D^{20}$ +60 (*c* 1.00, $CHCl_3$); $R_f$=0.53 (60% EtOAc/hexanes); IR (film) 3392, 3014, 2925, 2853, 1600, 1502, 1461, 1332, 1187 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.42 (d, *J* = 7.3 Hz, 1H), 6.27 (s, 1H), 6.15-6.12 (m, 3H), 4.82 (br s, 1H), 4.38 (s, 1H), 3.80-3.71 (m, 1H), 3.15-3.07 (m, 1H), 2.24 (s, 6H), 2.15 (s, 3H), 1.77-1.71 (m, 3H); 1.46-1.24 (m,

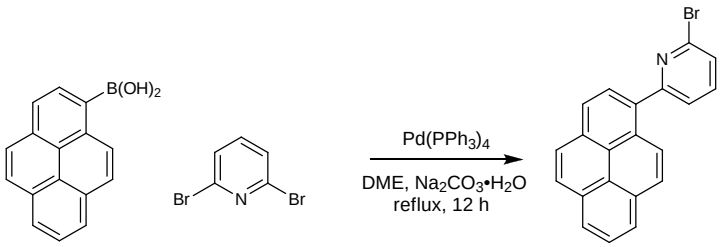
5H); $^{13}$C NMR (100 MHz, $CDCl_3$) ppm 158.3, 156.4, 148.2, 138.8, 137.6, 118.6, 111.9, 110.7, 104.8, 59.2, 54.3, 33.1, 32.6, 25.0, 24.5, 24.4, 21.6; HRMS (EI): Exact mass calcd for $C_{20}H_{28}N_3$ $[M+H]^+$ 310.2205. Found 310.2268.



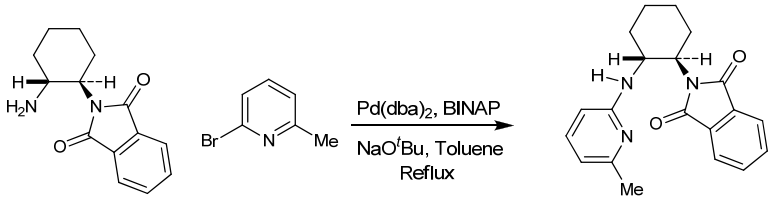

**H,$^6$Ph-BAM (260).** $Pd(dba)_2$ (42.44 mg, 73.9 μmol), *rac*-BINAP (92.0 mg, 148.0 μmol), and NaO$^t$Bu (852.0 mg, 8.86 mmol) were combined in a round-bottomed flask in a glove box. Toluene (40 mL) was added to the mixture, followed by 1,2-(*R*,*R*)-*trans*-diaminocyclohexane (337.43 mg, 2.955 mmol) and 2-bromo-6-phenylpyridine (1.0 g, 5.91 mmol). The reaction was stirred at 80 °C until TLC indicated complete consumption of the bromopyridine. The reaction was cooled to room temperature, filtered through Celite and silica gel, concentrated, and purified by flash column chromatography (10% ethyl acetate in hexanes) to provide the desired ligand as a solid (187.8 mg, 15%). Mp=162-164 °C; $[\alpha]_D^{20}$ +217 (*c* 9.00, $CHCl_3$); $R_f$=0.69 (40% EtOAc/hexanes); IR (film) 3314, 3109, 2936, 1652, 1624, 1602, 1576, 1442, 1288, 1238, 1028 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.30-7.22 (m, 2H), 7.47-7.45 (m, 6H), 6.87 (d, *J* = 7.3 Hz, 4H), 4.84 (br s, 2H), 3.89 (m, 2H), 2.20-2.17 (m, 2H), 1.86-1.84 (m, 2H), 1.63-1.45 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) ppm 155.4, 142.5, 130.8, 129.4, 127.0, 121.9, 118.8, 110.1, 108.4, 56.3, 31.9, 24.4; HRMS (EI): Exact mass calcd for $C_{28}H_{29}N_4$ $[M+H]^+$ 421.2381. Found 421.2387.




**(1*R*,1'*R*,2*R*,2'*R*)-N$^1$,N$^{1'}$-(pyridine-2,6-diyl)bis(N$^2$-(quinolin-2-yl)cyclohexane-1,2-diamine).** (1*R*,2*R*)-*N*$^1$-(quinolin-2-yl)cyclohexane-1,2-diamine (200.0 mg, 828.7 μmol), 2,6-dibromopyridine (98.16 mg, 414.3 μmol), $Pd_2(dba)_3$ (11.9 mg, 20.7 μmol), *rac*-BINAP (25.8 mg, 41.4 μmol) and NaO$^t$Bu (238.9 mg, 2.48 mmol) in toluene (30 mL) were heated to reflux for 12 hours (monitored by TLC). The mixture was cooled, diluted with ethyl acetate and filtered over a bed of Celite and silica gel. The filtrate was concentrated and then purified by flash column chromatography (silica gel, 20-40% ethyl acetate in hexanes) to provide the desired product as a yellow solid (153 mg, 65%). Mp=171-173 °C; $[\alpha]_D^{20}$ +490 (*c* 0.70, $CHCl_3$); $R_f$=0.10 (60% EtOAc/hexanes); IR (film) 3302, 3052, 2929, 2855, 1618, 1522, 1486, 1450, 1420 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.56-7.41 (m, 6H), 7.11 (dd, *J* = 7.0, 7.0 Hz, 2H), 6.87 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.20 (d, *J* = 8.5, 2H), 5.37 (d, *J* = 7.5 Hz, 4H), 5.17 (br s, 2H), 3.99-3.97 (m, 2H), 3.60 (br s, 2H), 2.24-2.18 (m, 4H), 1.83-1.71 (m, 4H), 1.42-1.31 (m, 6H), 1.18-1.11 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 158.0, 157.1, 147.9, 138.5, 136.8, 129.5, 127.4, 125.8, 123.5, 121.8, 113.0, 94.6, 56.6, 55.5, 33.3, 32.9, 24.99, 24.96; HRMS (EI): Exact mass calcd for $C_{35}H_{40}N_7$ $[M+H]^+$ 558.3261. Found 558.3260.

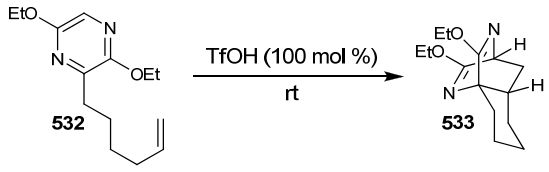



**2-bromo-6-(pyren-1-yl)pyridine (266).** 2,6-Dibromopyridine (80 mg, 338 μmol), pyren-1-ylboronic acid (100 mg, 406 μmol), $Pd(PPh_3)_4$ (15.6 mg, 40 μmol), and $Na_2CO_3 \cdot H_2O$ (96.4 mg, 774 μmol) in DME (10 mL) were heated to reflux for 16 hours (monitored by TLC). The mixture was cooled, diluted with ethyl acetate and water, and the layers were separated. The aqueous layer was further extracted with ethyl acetate and the combined organic extracts were dried over magnesium sulfate. The filtrate was concentrated and then purified by flash column chromatography (10% ethyl acetate in hexanes) to provide the desired product as a pale yellow solid (44.7 mg, 37%). Mp=146-148 °C; $R_f$=0.50 (40% EtOAc/hexanes); IR (film) 2922, 2852, 1573, 1549, 1425, 1440, 1163, 1116 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.38 (d, $J$ = 9.3 Hz, 1H), 8.26-8.01 (m, 7H), 8.04 (dd, $J$ = 7.6, 7.6 Hz, 1H), 7.75-7.69 (m, 2H), 7.59 (d, $J$ = 7.6 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 160.6, 142.1, 138.6, 133.9, 131.9, 131.4, 130.9, 128.7, 128.5, 128.3, 127.8, 127.5, 126.4, 126.2, 125.7, 125.4, 125.1, 124.9, 124.8, 124.6, 124.4; HRMS (EI): Exact mass calcd for $C_{21}H_{13}BrN$ $[M+H]^+$ 358.0231. Found 358.0226.



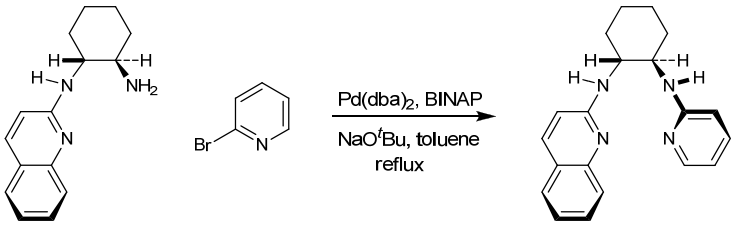

**2-((1*R*,2*R*)-2-(6-Methylpyridin-2-ylamino)cyclohexyl)isoindoline-1,2-dione.** 2-((1*R*,2*R*)-2-Aminocyclohexyl)isoindoline-1,3-dione (2.00 g, 8.29 mmol), 2-bromo-6-

methyl pyridine (1.43 g, 8.29 mmol), $Pd(dba)_2$ (190.4 mg, 331.5 μmol), *rac*-BINAP (206.0 mg, 331.5 μmol) and NaO$^t$Bu (1.194 g, 12.431 mmol) were dissolved in toluene (70mL) and heated to reflux until completon (as determined by TLC). The mixture was cooled and filtered over a bed of Celite and silica gel. The filtrate was concentrated and then purified by flash column chromatography (silica gel, 20%-40% ethyl acetate in hexanes) to provide the desired product as a white solid (1.042 g, 37%). Mp=180-183 °C; $[\alpha]_D^{20}$ +133 (*c* 2.00, $CHCl_3$); $R_f$=0.35 (40% EtOAc/hexanes); IR (film) 3407, 2934, 1702, 1597, 1463, 1390, 1374, 1330, 1074 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.70-7.69 (m, 2H), 7.60-7.58 (m, 2H), 7.07 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.10 (d, *J* = 7.7 Hz, 2H), 4.58 (ddd, *J* = 14.7, 10.9, 4.1 Hz, 1H) 4.09 (d, *J* = 10.2 Hz, 1H), 4.02-3.96 (m, 1H), 2.54-2.43 (m, 1H), 2.24-2.20 (m, 1H), 2.15 (s, 3H), 1.90-1.80 (m, 3H), 1.56-1.20 (m, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 168.8, 157.9, 156.6, 137.6, 133.5, 131.8, 122..8, 112.0, 103.8, 56.1, 51.8, 33.8, 29.3, 25.6, 25.0, 24.0. HRMS (EI): Exact mass calcd for $C_{20}H_{22}N_3O_2$ $[M+H]^+$ 336.1707. Found 336.1706.



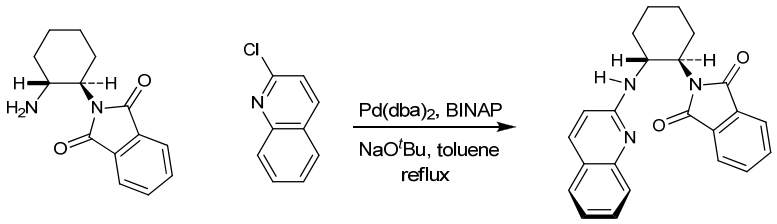

**(533).** A solution of 2,5-diethoxy-3-(hex-5-enyl)pyrazine (100 mg, 0.40 mmol) in dichloromethane (2 mL) was cooled to 0 °C followed by the addition of triflic acid (59.8 mg, 0.40 mmol). The reaction was stirred at room temperature until complete (as determined by TLC). Triethyl amine (55 μL, 0.60 mmol) was added to the reaction mixture followed by concentration and purification by flash column chromatography

(10% ethyl acetate in hexanes) to afford the product as a colorless oil (40 mg, 40%). $R_f$ = 0.63 (40% EtOAc/hexanes); IR (film) 2931, 2360, 1638, 1445, 1304, 1257, 1028 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.22-4.16 (m, 1H), 4.12-4.02 (m, 3H), 2.14-2.12 (m, 1H), 1.85-1.79 (m, 4H), 1.67-1.65 (m, 2H), 1.52-1.45 (m, 2H), 1.29 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.27 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.03-0.94 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 176.5, 173.6, 62.5, 62.4, 61.8, 56.5, 38.0, 32.5, 29.6 (2C), 25.8, 21.5, 14.3, 14.2; HRMS (EI): Exact mass calcd for $C_{14}H_{23}N_2O_2$ $[M+H]^+$ 251.1760. Found 251.1745.



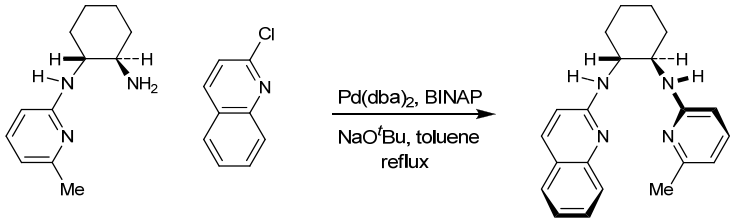

**H,Quin(²Pyr)-BAM.** $Pd(dba)_2$ (11.9 mg, 20.7 μmol), *rac*-BINAP (25.8 mg, 41.4 μmol), and $NaO^tBu$ (238.9 mg, 2.48 mmol) were combined in a round-bottomed flask in a glove box. Toluene (60 mL) was added to the mixture, followed by (1*R*,2*R*)-N1-(quinolin-2-yl)cyclohexane-1,2-diamine (**167**) (200 mg, 830 μmol) and 2-chloropyridine (94.98 mg, 830 μmol). The reaction was heated to reflux until TLC indicated complete consumption of the chloropyridine. The reaction was cooled to room temperature and filtered through a bed of Celite and silica gel. The filtrate was concentrated and purified by flash column chromatography on silica gel (20-40% ethyl acetate in hexanes) to afford the desired ligand as a yellow solid (197.5 mg, 75%). Mp=105-107 °C; $[\alpha]_D^{20}$ +537 (*c* 8.50, $CHCl_3$); $R_f$=0.39 (40% EtOAc/hexanes); IR (film) 3277, 3050, 2931, 1607, 1520, 1483, 1447,

1419, 1401 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1 H), 7.61 (d, *J* = 8.9 Hz, 1 H), 7.54-7.51 (m, 2H), 7.20-7.11 (m, 2H), 6.41 (dd, *J* = 5.3, 5.3 Hz, 1H), 6.36 (d, *J* = 8.9 Hz, 1H), 6.05 (d, *J* = 8.4 Hz, 1H), 5.94 (d, *J* = 5.8 Hz, 1H), 5.44 (d, *J* = 5.4 Hz, 1H), 4.15-4.07 (m, 1H), 3.83-3.79 (m, 1H), 2.32-2.23 (m, 2H), 1.78-1.76 (m, 2H), 1.48-1.34 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 158.8, 157.0, 147.7, 147.5, 136.8, 136.7, 129.4, 127.4, 125.8, 123.3, 121.8, 112.7, 111.9, 108.8, 56.8, 55.1, 32.9 (2C), 25.0, 24.7; HRMS (EI): Exact mass calcd for $C_{20}H_{23}N_4$ $[M+H]^+$ 319.1923. Found 319.1871.



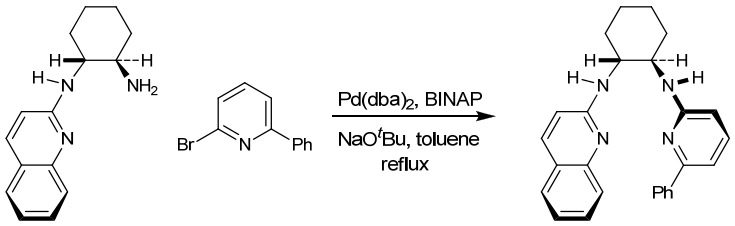

**2-((1*R*,2*R*)-2-(Quinolin-2-ylamino)cyclohexyl)isoindoline-1,2-dione (257)**. $Pd(dba)_2$ (190 mg, 330 μmol), *rac*-BINAP (206 mg, 330 μmol), and $NaO^tBu$ (1.19 g, 12.4 mmol) were combined in a round-bottomed flask in a glove box. Toluene (70 mL) was added to the mixture, followed by 2-((1*R*,2*R*)-2-aminocyclohexyl)isoindoline-1,3-dione (**179**) (2.00 g, 8.28 mmol) and 2-chloroquinoline (1.36 g, 8.28 mmol). The reaction was heated to reflux until TLC indicated complete consumption of the chloroquinoline. The mixture was cooled and filtered over a bed of Celite and silica gel using EtOAc. The filtrate was concentrated and then purified by flash column chromatography (silica gel, 20-40% EtOAc/hexanes) to provide the desired product as a yellow solid (1.13 g, 36%). Mp=169-171 °C; $[\alpha]_D^{20}$ +141 (*c* 6.30, $CHCl_3$); $R_f$=0.28 (40% EtOAc/hexanes); IR (film) 3400, 1702, 1622, 1573, 1529, 1484, 1398, 1375 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.53-7.47

(m, 4H), 7.36-7.26 (m, 4H), 7.01 (dd, $J$ = 7.3, 7.3 Hz, 1H), 6.45 (d, $J$ = 8.7, 1 H), 4.86 (br d, $J$ = 9.9 Hz, 1H), 4.45 (d, $J$ = 9.4 Hz, 1H) 4.08-4.03 (m, 1H), 2.69-2.62 (m, 1H), 2.27-2.24 (m, 1H), 1.92-1.83 (m, 3H), 1.62-1.55 (m, 1H), 1.39-1.33 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 169.0, 156.5, 147.5, 137.1, 133.2, 129.1, 126.9, 126.2, 122.9, 122.6 (2C), 121.8, 111.4, 56.4, 51.3, 33.2, 28.9, 25.7, 24.9; HRMS (EI): Exact mass calcd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 372.1707. Found 372.1697.



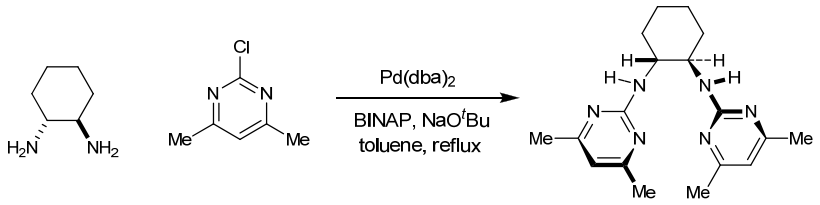

**H,$^2$Quin($^6$Me)-BAM (262).** $Pd(dba)_2$ (13.4 mg, 23.3 μmol), *rac*-BINAP (28.9 mg, 46.5 μmol), and NaO$^t$Bu (268.3 mg, 2.79 mmol) were combined in a round-bottomed flask in a glove box. Toluene (60 mL) was added to the mixture, followed by (1*R*,2*R*)-N$^1$-(6-methylpyridin-2-yl)cyclohexane-1,2-diamine (191 mg, 0.93 mmol) and 2-chloroquinoline (152.2 mg, 0.93 mmol). The reaction was heated to reflux until TLC indicated complete consumption of the chloroquinoline. The reaction was cooled to room temperature and filtered through a bed of Celite and silica gel. Concentration, followed by purification by flash column chromatography on silica gel (20-40% ethyl acetate in hexanes) provided the desired ligand as a yellow solid (190.5 mg, 62%). Mp=131-133 °C; $[\alpha]_D^{20}$ +276 (*c* 3.00, $CHCl_3$); $R_f$=0.30 (40% EtOAc/hexanes); IR (film) 3246, 3047, 2928, 2854, 1617, 1523, 1463, 1337, 1150 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J$ = 8.0 Hz, 1H), 7.63 (d, $J$ = 8.8 Hz, 1H), 7.52-7.49 (m, 2H), 7.18-7.12 (m, 2H), 6.38 (d, $J$ = 8.8 Hz, 1H),

6.35 (d, *J* = 7.2 Hz, 1H), 6.04 (d, *J* = 7.5 Hz, 1H), 5.92 (br s, 1H), 5.19 (br s, 1H), 4.03-4.01 (m, 1H), 3.85-3.83 (m, 1H) 2.40-2.38 (m, 4H), 2.24-2.22 (m, 1H), 1.80-1.79 (m, 2H), 1.51-1.33 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 158.4, 156.9, 156.2, 148.1, 137.3, 136.7, 129.3, 127.4, 126.0, 123.3, 121.6, 112.7, 111.4, 105.2, 56.0, 55.4, 32.8, 32.5, 24.9, 24.6, 24.6; HRMS (EI): Exact mass calcd for $C_{21}H_{25}N_4$ $[M+H]^+$ 333.2074. Found 333.2083.




**H,$^2$Quin($^6$Ph)-BAM (263).** $Pd(dba)_2$ (11.9 mg, 20.7 μmol), *rac*-BINAP (25.8 mg, 41.4 μmol), and NaO$^t$Bu (238.92 mg, 2.48 mmol) were combined in a round-bottomed flask in a glove box. Toluene (60 mL) was added to the mixture, followed by (1*R*,2*R*)-N1-(quinolin-2-yl)cyclohexane-1,2-diamine (**167**) (200 mg, 0.83 mmol) and 2-bromo-6-phenylpyridine (194 mg, 0.83 mmol). The reaction was heated to reflux until TLC indicated complete consumption of the bromopyridine. The reaction was cooled to room temperature and filtered through a bed of Celite and silica gel. Concentration to an oil, followed by it's purification by flash column chromatography on silica gel (20-40% ethyl acetate in hexanes) provided the desired ligand as a pale yellow solid (220 mg, 67%). Mp=122-125 °C; $[\alpha]_D^{20}$ +351 (*c* 10.0, $CHCl_3$); $R_f$=0.32 (40% EtOAc/hexanes); IR (film) 3238, 3052, 2929, 2854, 1617, 1575, 1510, 1490, 1450, 1427, 1349 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 1H), 7.6 (d, *J* = 8.7 Hz, 1H), 7.56-7.52 (m, 2H), 7.45 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.40 (dd, *J* = 6.9, 6.9 Hz, 1H),

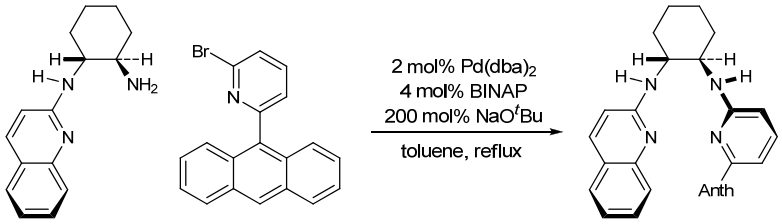
7.32-7.30 (m, 1H), 7.20 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.28 (d, *J* = 6.3 Hz, 1H), 6.13 (d, *J* = 6.5 Hz, 1H), 5.69 (br s, 2H), 4.18 (br s, 1H), 4.04 (br s, 1H), 2.41-2.39 (m, 2H), 1.87 (br s, 2H), 1.54-1.45 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 158.5, 157.1, 154.8, 147.9, 139.9, 137.6, 136.8, 129.3, 128.6 (2C), 128.4, 127.4, 126.7, 126.6, 125.9, 123.3, 121.7, 108.6, 56.5, 55.7, 33.0 (2C), 24.9 (2C); HRMS (EI): Exact mass calcd for $C_{26}H_{27}N_4$ $[M+H]^+$ 395.2230. Found 395.2214.



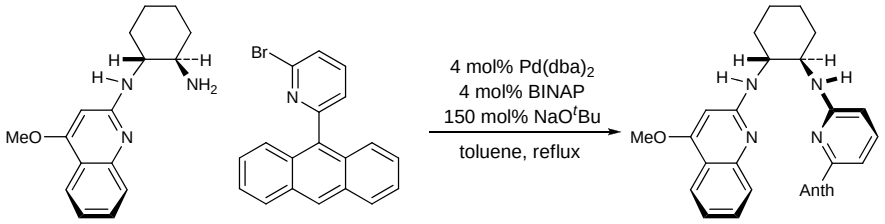

**H,$^{4,6}$Me$^2$Pyrazine-BAM (275).** $Pd(dba)_2$ (125 mg, 0.22 mmol), *rac*-BINAP (273 mg, 0.44 mmol), and NaO$^t$Bu (2.52 g, 26.3 mmol) were combined in a round-bottomed flask in a glove box. Toluene (70 mL) was added to the mixture, followed by 1,2-(*R*,*R*)-*trans*-diaminocyclohexane (1.0 g, 8.76 mmol) and 2-chloro-4,6-dimethylpyrazine (2.48 g, 8.76 mmol). The reaction was stirred at 80 °C until TLC indicated complete consumption of the chloropyrazine. The reaction was cooled to room temperature and filtered through a bed of celite and silica gel. The filtrate was concentrated and then purified by flash column chromatography on silica gel (20-50% ethyl acetate in hexanes) to provide the desired ligand as a solid (1.95 g, 68%). Mp = 146-148 °C; $[\alpha]_D^{20}$ +29 (*c* 6.00, $CHCl_3$); $R_f$=0.42 (60% EtOAc/hexanes); IR (film) 3250, 2922, 1567, 1544, 1463, 1379, 1334, 1174 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.29 (br s, 2H), 6.14 (s, 2H), 3.75 (br s, 2H), 2.28-2.25 (m, 2H), 2.21 (s, 12H), 1.74-1.72 (m, 2H), 1.41-1.37 (m, 2H), 1.24-1.22 (m,

2H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 166.6, 162.1, 108.3, 54.5, 33.21, 25.02, 23.84; HRMS (EI): Exact mass calcd for $C_{18}H_{27}N_6$ $[M+H]^+$ 327.2292. Found 327.2276.

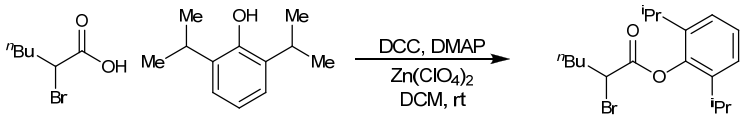

**2-(Anthracen-9-yl)-6-bromopyridine**. $Pd(PPh_3)_4$ (92.8 mg, 80.3 μmol) and $Ba(OH)_2 \cdot 8H_2O$ (950 mg, 3.01 mmol) were added into the solution of 9-anthracenylboronic acid (446 mg, 2.01 mmol) in 15 mL DME/$H_2O$ (2:1), followed by the addition of 2,6-dibromopyridine (571 mg, 2.41 mmol). The reaction was allowed to stir under reflux for 10 h. After cooling to room temperature, the reaction mixture was extracted with chloroform and the organic layer was dried, filtered, concentrated and purified by flash column chromatography on silica gel (3% ethyl acetate in hexanes) to give the bromopyridine as a yellow solid (503 mg, 75%). $R_f$=0.30 (10% EtOAc/ hexanes). IR (neat) 3056, 2921, 1577, 1546, 1119, 908, 731 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.04 (d, *J* = 9.5 Hz, 2H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 6.7 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.42-7.38 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.5, 142.3, 138.6, 133.3, 131.4, 130.0, 128.6, 128.2, 127.0, 126.3, 125.9, 125.7, 125.3; HRMS (CI): Exact mass calculated for $C_{19}H_{13}NBr$ $[M+H]^+$ 334.0226 Found 334.0210.



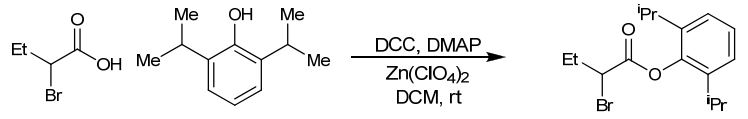

**H,Quin($^{6}$($^{9}$Anth)$^{2}$Pyr)-BAM**. $Pd(dba)_2$ (6.7 mg, 12 μmol), *rac*-BINAP (14.5 mg, 23.3 μmol), and $NaO^tBu$ (112 mg, 1.17 mmol) were loaded into a round bottom flask in a glove box. Toluene (5.8 mL) was added to the mixture followed by the amine (141 mg, 584 μmol) and 2-(anthracen-9-yl)-6-bromopyridine (195 mg, 584 μmol). The reaction was refluxed for 12 h, and then cooled to room temperature, filtered through Celite, concentrated, and purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes), to afford the desired bis(amidine) as a yellow solid (80.0 mg, 28%). Mp 116-117 °C; $R_f$=0.10 (20% ethyl acetate/hexanes). IR (neat) 2928, 1618, 1599, 1518, 1452, 755 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.06 (t, *J* = 8.4 Hz, 2H), 7.82 (t, *J* = 9.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.53-7.35 (m, 8H), 7.16 (t, *J* = 7.1 Hz, 1H), 6.70 (d, *J* = 7.0 Hz, 1H), 6.40 (br d, *J* = 7.3 Hz, 1H), 6.15 (br d, *J* = 8.2 Hz, 1H), 5.56 (br d, *J* = 6.0 Hz, 1H), 5.37 (br d, *J* = 6.6 Hz, 1H), 4.04 (br d, *J* = 8.0 Hz, 1H), 3.86 (br d, *J* = 8.0 Hz, 1H), 2.25 (br t, *J* = 8.0 Hz, 2H), 1.71-1.61(m, 2H), 1.45-1.32 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.8, 156.8, 155.8, 148.0, 137.0, 136.6, 136.5, 131.6, 131.5, 130.1, 129.9, 129.3, 128.5, 128.3, 127.4, 127.0, 126.9, 126.8, 126.0, 125.5, 125.4, 125.2, 125.1, 123.3, 121.6, 115.5, 113.1, 107.4, 55.6, 55.1, 32.7, 32.0, 24.6, 24.4; HRMS (CI): Exact mass calculated for $C_{34}H_{31}N_4$ $[M+H]^+$ 495.2543 Found 495.2529.




**H,$^{4}$OMeQuin($^{6}$($^{9}$Anth)$^{2}$Pyr)-BAM (451)**. $Pd(dba)_2$ (56.6 mg, 10.0 mmol), *rac*-BINAP (61.4 mg, 10.0 mmol), and NaO$^t$Bu (355 mg, 3.69 mmol) were loaded into a round bottom flask in a glove box. Toluene (45.0 mL) was added to the mixture followed by the amine (669 mg, 2.47 mmol) and 2-(anthracen-9-yl)-6-bromopyridine (824 mg, 2.47 mmol). The reaction was refluxed for 12 h, and then cooled to room temperature, filtered through Celite, concentrated, and purified by flash column chromatography on silica gel (20-40% ethyl acetate in hexanes), to afford the desired bis(amidine) as a brown solid (413.0 mg, 32%). Mp 146-148 °C; $R_f$ =0.15 (40% ethyl acetate/hexanes). $[\alpha]_D^{20}$ +381 (*c* 1.50, $CHCl_3$); IR (film) 3251, 3054, 2930, 2854, 1622, 1603, 1573, 1520, 1499 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.89-7.85 (m, 2H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 7.1, 7.1 Hz, 1H), 7.45-7.43 (m, 2H), 7.37-7.34 (m, 2H), 7.15 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.67 (d, *J* = 7.1 Hz, 1H), 6.39 (br s, 1H), 5.82 (br s, 1H), 5.56 (s, 1H), 5.26 (br s, 1H), 4.09 (br s, 1H), 3.79 (br s, 1H), 2.35 (br d, *J* = 11.9 Hz, 1H), 2.19 (br d, *J* = 11.2 Hz, 1H), 1.68(br d, *J* = 11.2 Hz, 2H), 1.43-1.39 (m, 2H), 1.22-1.18 (m, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 162.5, 158.9, 158.1, 155.6, 148.7, 136.9, 136.5, 131.6, 131.5, 130.2, 129.9, 128.5, 128.3, 127.0, 126.7, 125.6, 125.4, 125.2, 124.9, 121.7, 121.2, 117.8, 115.6, 107.3, 90.1, 56.4, 55.2, 55.1, 32.7, 32.5, 24.7, 24.6 (3 carbons overlapping); HRMS (CI): Exact mass calculated for $C_{35}H_{33}N_4O$ $[M+H]^+$ 525.2654, found 525.2656.



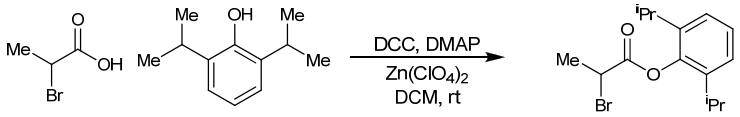

**2,6-Diisopropylphenyl 2-bromohexanoate.** 2-Bromohexanoic acid (5.00 g, 25.6 mmol), 2,6-diisopropyl phenol (5.48 g, 30.8 mmol), DCC (6.34 g, 30.8 mmol), and $Zn(ClO_4)_2$[185] (95 mg, 250 μmol) were dissolved in dichloromethane and then DMAP (251 mg, 2.05 mmol) was added. The reaction was stirred for 24 h, and then diluted with diethyl ether and filtered through Celite. The filtrate was concentrated to give the crude product which was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a colorless oil (5.3 g, 58%). $R_f$ = 0.64 (20% EtOAc/hexanes); IR (film) 3066, 3029, 2960, 2931, 2870, 1758, 1464, 1443 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25-7.22 (m, 1H), 7.18-7.16 (m, 2H), 4.49 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.99 (br s, 2H), 2.29-2.22 (m, 1H), 2.18-2.10 (m, 1H), 1.62-1.54 (m, 1H), 1.52-1.39 (m, 3H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 0.96 (dd, *J* = 7.1, 7.1 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 168.5, 145.1, 140.5, 127.0, 124.0, 45.2, 34.7, 29.6, 27.2, 23.8, 22.9, 22.1, 13.9; HRMS (CI): Exact mass calculated for $C_{18}H_{28}BrO_2$ $[M+H]^+$ 355.1267, found 355.1268.




**2,6-Diisopropylphenyl 2-bromobutanoate.** 2-Bromobutanoic acid (5.00 g, 29.9 mmol), 2,6-diisopropyl phenol (6.41 g, 35.9 mmol), DCC (7.41 g, 35.9 mmol) and $Zn(ClO_4)_2$ (111 mg, 299 μmol) were dissolved in dichloromethane. DMAP (292 mg, 2.39 mmol) was added and the reaction was allowed to stir for 24 h before it was diluted with diethyl

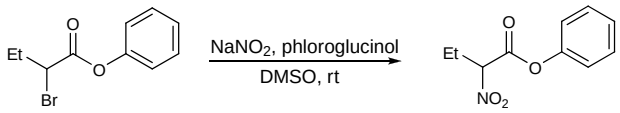
[185] Shivani; Gulhane, R.; Chakraborti, A. K., *J. Mol. Cat.* **2007**, 208.

ether and filtered through Celite. The filtrate was concentrated to give the crude product which was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a yellow oil (6.15 g, 63%). $R_f$ = 0.64 (20% EtOAc/hexanes); IR (neat) 2965, 2933, 1756, 1460, 1255, 1162 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25-7.22 (m, 1H), 7.18-7.16 (m, 2H), 4.44 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.00 (br s, 2H), 2.34-2.25 (m, 1H), 2.21-2.12 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 1.16 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 168.5, 145.2, 140.5, 127.0, 124.1, 47.4, 28.4, 27.2, 23.8, 22.8, 12.1; HRMS (CI): Exact mass calculated for $C_{16}H_{24}BrO_2$ $[M+H]^+$ 327.0954, found 327.0943.



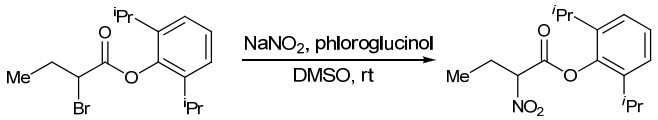

**2,6-Diisopropylphenyl 2-bromopropanoate.** 2-Bromopropanoic acid (5.00 g, 32.6 mmol), 2,6-diisopropyl phenol (3.87 g, 21.7 mmol), DCC (6.73 g, 32.6 mmol), and $Zn(ClO_4)_2$ (81 mg, 217 μmol) were dissolved in dichloromethane and then DMAP (213 mg, 1.74 mmol) was added. The reaction was stirred for 24 h, and then diluted with diethyl ether and filtered through Celite. The filtrate was concentrated to give the crude product, which was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a pink oil (5.64 g, 83%). $R_f$ = 0.63 (20% EtOAc/hexanes); IR (film) 2965, 2930, 1756, 1442, 1242, 1162 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25-7.23 (m, 1H), 7.18-7.17 (m, 2H), 4.65 (q, *J* = 6.9 Hz, 1H), 2.98 (br s, 2H), 2.00 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.7 Hz, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$)

ppm 168.9, 145.2, 140.5, 127.0, 124.1, 39.6, 27.3, 23.9, 22.8, 21.9; HRMS (CI): Exact mass calculated for $C_{15}H_{22}BrO_2$ $[M+H]^+$ 312.0719, found 312.0718.

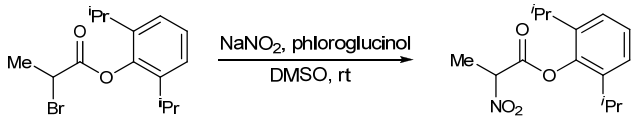



**Phenyl 2-nitrobutanoate (440c).** Phenyl 2-bromobutanoate (6.34 g, 26.1 mmol), sodium nitrite (3.11 g, 45.1 mmol), and phloroglucinol (3.48 g, 27.7 mmol) were dissolved in DMSO (50.0 mL) and the reaction was stirred at room temperature for 12 h.[186] The reaction was then poured into a diethyl ether/ice-water mixture and the solution was allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a yellow oil (3.87 g, 71%). $R_f$=0.56 (20% EtOAc/hexanes); IR (film) 3065, 2980, 2942, 1768, 1591, 1556, 1492, 1459 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.41 (t, $J$ = 7.9 Hz, 2H), 7.29 (t, $J$ = 7.5 Hz, 1H), 7.13 (d, $J$ = 8.5 Hz, 2H), 5.27 (dd, $J$ = 8.9, 5.9 Hz, 1H), 2.48-2.41 (m, 1H), 2.39-2.32 (m, 1H), 1.15 (dd, $J$ = 7.5, 7.5 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 163.1, 149.9, 129.8, 126.9, 121.0, 89.2, 24.1, 10.2; HRMS (CI): Exact mass calculated for $C_{10}H_{12}NO_4$ $[M+H]^+$ 210.0766, found 210.0762.

[186] Kornblum, N.; Blackwood, R. K.; Powers, J. W. *J. Am. Chem. Soc.* **1957**, 2507.

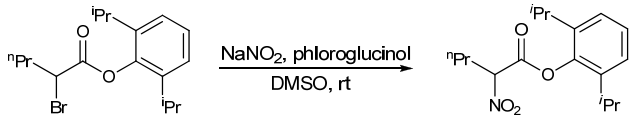



**2,6-Diisopropylphenyl 2-nitrobutanoate (440d).** 2,6-Diisopropylphenyl 2-bromobutanoate (6.15 g, 18.8 mmol), sodium nitrite (2.24 g, 32.5 mmol), and phloroglucinol (2.51 g, 19.9 mmol) were dissolved in DMSO (50.0 mL) and the reaction was stirred at room temperature for 12 h. The reaction was then poured into a diethyl ether/ice-water mixture and the solution was allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a colorless oil (3.1 g, 68%). $R_f$ =0.54 (20% EtOAc/hexanes); IR (neat) 3068, 3030, 2967, 2934, 1768, 1564, 1461, 1365 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25-7.24 (m, 1H), 7.18-7.17 (m, 2H), 5.34 (dd, $J$ = 9.5, 5.3 Hz, 1H), 2.87 (br s, 2H), 2.53-2.44 (m, 1H), 2.40-2.32 (m, 1H), 1.19 (d, $J$ = 7.1 Hz, 12H), 1.15 (dd, $J$ = 7.4, 7.4 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 163.3, 144.8, 140.1, 127.4, 124.2, 89.3, 27.5, 24.1, 23.7, 22.8, 10.3; HRMS (CI): Exact mass calculated for $C_{16}H_{24}NO_4$ $[M+H]^+$ 294.1700, found 294.1703.



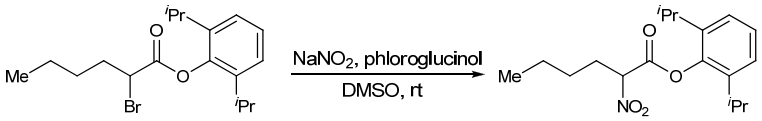

**2,6-Diisopropylphenyl 2-nitropropanoate (440e).** 2,6-Diisopropylphenyl 2-bromopropanoate (3.00 g, 9.58 mmol), sodium nitrite (1.14 g, 16.5 mmol), phloroglucinol (1.28 g, 10.1 mmol) were dissolved in DMSO (30 mL) and the reaction was allowed to proceed at room temperature for 12 h. The reaction was then poured into

a diethyl ether/ice-water mixture and the solution was allowed to warm to room temperature. The aqueous layer was then extracted with diethyl ether, the combined organic layers were washed with water, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography (5% ethyl acetate/hexanes) to afford the product as a colorless oil (1.68 g, 63%). $R_f$ =0.50 (20% EtOAc/hexanes); IR (neat) 2967, 2932, 1768, 1563, 1444, 1387, 1166 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.26-7.22 (m, 1H), 7.17-7.16 (m, 2H), 5.48 (q, *J* = 7.1 Hz, 1H), 2.86 (br s, 2H), 1.96 (d, *J* = 7.1, 3H), 1.18 (d, *J* = 6.9 Hz, 12H); $^{13}C$ NMR (150 MHz, $CDCl_3$) ppm 164.0, 144.9, 140.2, 127.5, 124.3, 83.1, 27.5, 24.8, 22.7, 15.9; HRMS (CI): Exact mass calculated for $C_{15}H_{22}NO_4$ $[M+H]^+$ 280.1543, found 280.1537.

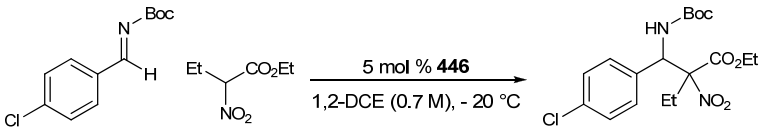



**2,6-Diisopropylphenyl 2-nitropentanoate (440f).** 2,6-Diisopropylphenyl 2-bromopentanoate (5.26 g, 15.4 mmol), sodium nitrite (1.84 g, 26.7 mmol), and phloroglucinol (2.06 g, 16.3 mmol) were dissolved in DMSO (50.0 mL) and the reaction was stirred at room temperature for 12 h. The reaction was then poured into a diethyl ether/ice-water mixture and the solution was allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a yellow oil (3.12 g, 68%). $R_f$ =0.57 (20% EtOAc/hexanes); IR (film) 2966, 2934, 2873, 1768, 1564, 1463, 1442 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 2H),

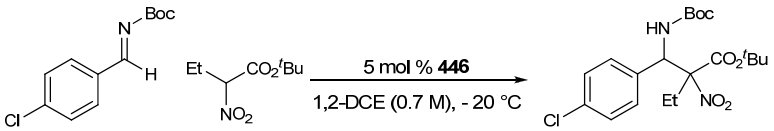
5.41 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.85 (br s, 2H), 2.51-2.44 (m, 1H), 2.30-2.24 (m, 1H), 1.60-1.51 (m, 2H), 1.19 (d, *J* = 6.9 Hz, 12H), 1.07 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.5, 144.8, 140.3, 127.5, 124.3, 87.9, 32.3, 27.5, 23.7, 22.8, 19.2, 13.3; HRMS (CI): Exact mass calculated for $C_{17}H_{26}NO_4$ $[M+H]^+$ 308.1856, found 308.1848.



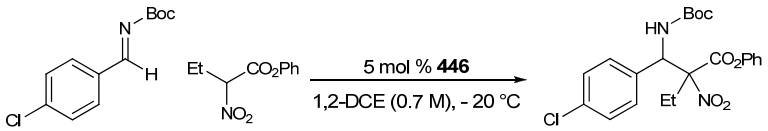

**2,6-Diisopropylphenyl 2-nitrohexanoate (440g).** 2,6-Diisopropylphenyl 2-bromohexanoate (4.50 g, 12.7 mmol), sodium nitrite (1.51 g, 21.9 mmol), and phloroglucinol (1.69 g, 13.4 mmol) were dissolved in DMSO (45.0 mL) and the reaction was stirred at room temperature for 18 h. The reaction was then poured into a diethyl ether/ice-water mixture and the solution was allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a colorless oil (1.62 g, 40%). $R_f$ = 0.59 (20% EtOAc/hexanes); IR (film) 2965, 2933, 1755, 1459, 1255, 1196, 1162 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1H), 7.18-7.17 (m, 2H), 5.38 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.85 (br s, 2H), 2.51-2.43 (m, 1H), 2.34-2.27 (m, 1H), 1.51-1.43 (m, 4H), 1.19 (d, *J* = 6.9 Hz, 12H), 0.97 (dd, *J* = 7.0, 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 163.5, 144.8, 140.2, 127.4, 124.2, 88.1, 30.1, 27.8, 27.5, 23.7, 22.8, 22.0, 13.7; HRMS (CI): Exact mass calculated for $C_{18}H_{28}NO_4$ $[M+H]^+$ 322.2013, found 322.2012.



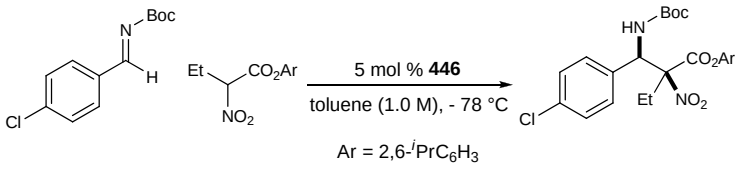

**Ethyl 2-((*tert*-butoxycarbonylamino)(4-chlorophenyl)methyl)-2-nitrobutanoate (443a)**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (50.0 mg, 208 μmol) provided **443a** after flash column chromatography (10% ethyl acetate in hexanes) as a colorless oil (76.9 mg, 92%), the major diasteremer of which was determined to be 73% ee by chiral HPLC analysis (Chiralcel AD, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(major) = 7.1 min, $t_r$(minor) = 5.9 min). *major diastereomer*: $R_f$ =0.30 (20% EtOAc/hexanes); IR (film) 3448, 2979, 1752, 1718, 1558, 1488 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.43 (d, *J* = 9.7 Hz, 1H), 5.42 (d, *J* = 9.9 Hz, 1H), 4.40-4.28 (m, 2H), 2.09 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.97 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.39 (s, 9H), 1.34 (dd, *J* = 7.1, 7.1 Hz, 3H), 1.02 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 165.3, 154.5, 134.9, 134.0, 129.2, 129.1, 99.9, 80.5, 66.3, 58.2, 28.4, 28.3, 14.1, 9.1. *minor diastereomer*: $R_f$ = 0.36 (20% EtOAc/hexanes); IR (film) 3425, 2980, 1720, 1556, 1493, 1367, 1241 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.36 (d, *J* = 8.6 Hz, 1H), 5.53 (d, *J* = 9.2 Hz, 1H), 4.38-4.24 (m, 2H), 2.10-2.00 (m, 2H), 1.38 (s, 9H), 1.27 (dd, *J* = 7.1, 7.1 Hz, 3H), 0.97 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 165.5, 154.7, 134.8, 129.5, 128.9, 98.1, 80.5, 63.2, 58.3, 29.2, 28.3, 13.8, 8.9 (one carbon overlapping); HRMS (CI): Exact mass calculated for $C_{18}H_{25}ClN_2O_6Na$ $[M+Na]^+$ 423.1299, found 423.1304.




***tert*-Butyl 2-((*tert*-butoxycarbonylamino)(4-chlorophenyl)methyl)-2-nitrobutanoate (443b)**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (25.0 mg, 100 μmol) provided **443b** after flash column chromatography (10% ethyl acetate in hexanes) as a colorless oil (39.8 mg, 89%), the major diasteremer of which was determined to be 97% ee by chiral HPLC analysis (Chiralcel AD, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$( major) = 7.1 min, $t_r$(minor) = 5.9 min). *major diastereomer*: $R_f$=0.38 (20% EtOAc/hexanes); IR (neat) 3427, 2979, 2935, 1721, 1556, 1492, 1369 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, $J$ = 8.5 Hz, 2H), 7.03 (d, $J$ = 6.9 Hz, 2H), 6.28 (d, $J$ = 8.6 Hz, 1H), 5.26 (d, $J$ = 9.1 Hz, 1H), 1.81-1.70 (m, 2H), 1.26 (s, 9H), 1.15 (s, 9H), 0.74 (dd, $J$ = 7.1, 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 164.4, 154.7, 134.9, 134.7, 129.7, 128.9, 98.2, 85.7, 80.3, 58.3, 29.5, 28.3, 27.7, 8.9. *minor diastereomer*: $R_f$=0.32 (20% EtOAc/hexanes); IR (neat) 3452, 2979, 2936, 1746, 1718, 1556, 1486 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, $J$ = 8.4 Hz, 2H), 7.12 (d, $J$ = 8.3 Hz, 2H), 6.51 (d, $J$ = 9.8 Hz, 1H), 5.34 (d, $J$ = 9.9 Hz, 1H), 2.04 (dq, $J$ = 14.6, 7.3 Hz, 1H), 1.92 (dq, $J$ = 14.8, 7.4 Hz, 1H), 1.54 (s, 9H), 1.40 (s, 9H), 1.06 (dd, $J$ = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) ppm 164.0, 154.6, 134.9, 134.3, 129.2, 129.1, 100.1, 85.4, 80.4, 58.5, 28.5, 28.4, 27.9, 9.1. HRMS (CI): Exact mass calculated for $C_{20}H_{29}ClN_2O_6$ $[M+Na]^+$ 451.1612, found 451.1632.

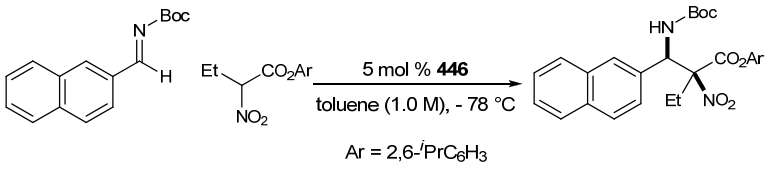



**Phenyl 2-((*tert*-butoxycarbonylamino)(4-chlorophenyl)methyl)-2-nitrobutanoate (443c)**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (25.0 mg, 104 μmol) provided **443c** after flash column chromatography (10% ethyl acetate in hexanes) as a colorless oil (76.9 mg, 92%), the major diasteremer of which was determined to be 73% ee by chiral HPLC analysis (Chiralcel AD, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(major) = 29.7 min, $t_r$(minor) = 13.4 min. *major diastereomer*: $R_f$=0.42 (20% EtOAc/hexanes); IR (film) 3430, 2978, 1779, 1719, 1558, 1492 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 10.1 Hz, 1H), 5.61 (d, *J* = 10.1 Hz, 1H), 2.27-2.18 (m, 2H), 1.39 (s, 9H), 1.19 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.9, 154.6, 149.9, 135.2, 133.7, 129.7, 129.3, 129.2, 126.9, 121.1, 99.9, 80.9, 58.6, 28.6, 28.4, 9.3. *minor diastereomer*: $R_f$=0.47 (20% EtOAc/hexanes); IR (film) 3406, 2978, 1770, 1700, 1559, 1492, 1225 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.27-7.25 (m, 3H), 6.98 (d, *J* = 7.9, 2H), 6.25 (d, *J* = 9.7 Hz, 1H), 5.59 (d, *J* = 9.8 Hz, 1H), 2.26-2.22 (m, 1H), 2.19-2.15 (m, 1H), 1.32 (s, 9H), 1.02 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.3, 154.6, 149.6, 135.0, 134.4, 129.9, 129.7, 129.1, 127.2, 121.0, 98.5, 80.7, 58.3, 29.4, 28.3, 8.9 (one carbon overlapping); HRMS (CI): Exact mass calculated for $C_{22}H_{25}ClN_2O_6$ $[M+H]^+$ 449.1479, found 449.1470.




**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-chlorophenyl)methyl)-2-nitrobutanoate (443d)**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (50.0 mg, 210 μmol) provided **443d** after flash column chromatography (5% ethyl acetate in hexanes) as a white solid (92.2 mg, 83%), which was determined to be 98% ee, >20:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 8.0 min, $t_r$(*syn*, minor) = 4.3 min, $t_r$(*anti*, major) = 5.3 min, $t_r$(*anti*, minor) = 9.3 min). Mp 91-93 °C; $R_f$=0.41 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –33 (*c* 3.00, $CHCl_3$); IR (film) 3454, 2969, 2931, 1767, 1722, 1557, 1483 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.28-7.25 (m, 1H), 7.21-7.18 (m, 4H), 6.51 (d, *J* = 9.9 Hz, 1H), 5.59 (d, *J* = 9.9 Hz, 1H), 3.04 (br s, 1H), 2.85 (br s, 1H), 2.42 (dq, *J* = 14.6, 7.2 Hz, 1H), 2.05 (dq, *J* = 15.1, 7.5 Hz, 1H), 1.36 (s, 9H), 1.23 (dd, *J* = 7.5, 7.5 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.3, 154.5, 144.4, 140.5/139.9*, 134.9, 133.8, 129.2, 128.9, 127.4, 124.1, 98.9, 80.4, 55.6, 28.2, 27.3, 27.1, 23.8, 23.2/22.9*, 8.6; HRMS (CI): Exact mass calculated for $C_{28}H_{38}ClN_2O_6$ $[M+Na]^+$ 555.2238, found 555.2253.

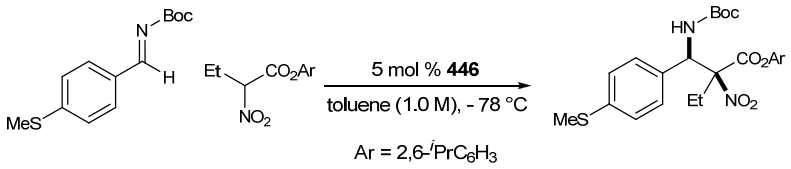
* Broadened peaks due to restricted rotation of aryl ester.




**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino)(naphthalene-2-yl)methyl)-2-nitrobutanoate (452a).** According to the general procedure, *tert*-butyl

naphthalene-2-ylmethylenecarbamate (53.3 mg, 210 μmol) provided **452a** after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (96.0 mg, 80%), which was determined to be 96% ee, >20:1 dr by chiral HPLC analysis (Chiralcel IA, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.3 min, $t_r$(*syn*, minor) = 4.4 min, $t_r$(*anti*, major) = 8.2 min, $t_r$(*anti*, minor) = 4.9 min). $R_f$=0.45 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –37 (*c* 6.65, $CHCl_3$); IR (neat) 3455, 2968, 2931, 1767, 1721, 1557, 1483 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.87-7.86 (m, 3H), 7.79 (s, 1H), 7.54-7.52 (m, 2H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.30-7.27 (m, 1H), 7.22 (br s, 2H), 6.69 (d, *J* = 9.9 Hz, 1H), 5.83 (d, *J* = 9.9 Hz, 1H), 3.13 (br s, 1H), 2.89 (br s, 1H), 2.46 (dq, *J* = 14.9, 7.4 Hz, 1H), 2.13 (dq, *J* = 15.1, 7.6 Hz, 1H), 1.39 (s, 9H), 1.31 (dd, *J* = 7.5, 7.5 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.6, 154.7, 144.7, 140.7/140.0*, 133.4, 133.2, 132.7, 129.1, 128.4, 127.7, 127.6, 127.5, 126.8, 126.7, 124.5, 124.3, 99.2, 80.4, 55.4, 28.4, 27.5, 27.2, 23.9, 23.4/23.0*, 8.8. HRMS (CI): Exact mass calculated for $C_{32}H_{41}N_2O_6$ $[M+H]^+$ 549.2959, found 549.2949.

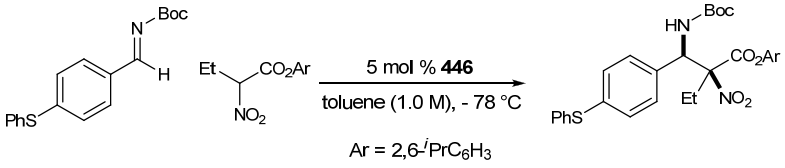
* Broadened peaks due to restricted rotation of aryl ester.




**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-(methylthio)phenyl)methyl)-2-nitrobutanoate (452b).** According to the general procedure, *tert*-butyl 4-(thiomethyl)benzylidenecarbamate (52.3 mg, 210 μmol) provided **452b** after flash column chromatography (20% ethyl acetate in hexanes) as a colorless oil (91.7 mg, 81%), which was determined to be 98% ee, 13:1 dr by chiral HPLC analysis

(Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 8.4 min, $t_r$(*syn*, minor) = 4.8 min, $t_r$(*anti*, major) = 14.4 min, $t_r$(*anti*, minor) = 6.3 min). $R_f$=0.40 (20% EtOAc/hexanes); IR (film) 3455, 2968, 2928, 2870, 1766, 1722, 1556, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.19-7.16 (m, 4H), 6.52 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 9.9 Hz, 1H), 3.07 (br s, 1H), 2.84 (br s, 1H), 2.48 (s, 3H), 2.41 (dq, *J* = 15.1, 7.6 Hz, 1H), 2.06 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.37 (s, 9H), 1.24-1.21 (m, 3H), 1.21 (d, *J* = 6.9 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.5, 154.7, 144.6, 139.8, 131.8, 129.2, 128.0, 127.5, 126.5, 124.2, 99.2, 80.4, 55.8, 28.4, 27.4, 27.2, 23.9, 23.3/23.0*, 15.4, 8.7. HRMS (CI): Exact mass calculated for $C_{29}H_{41}N_2O_6S$ $[M+H]^+$ 545.2685, found 545.2670.

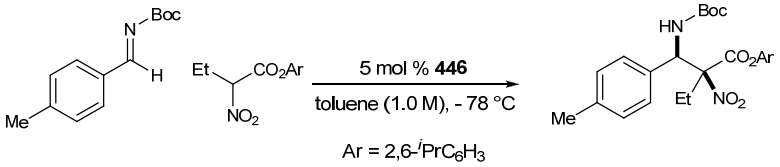
* Broadened peaks due to restricted rotation of aryl ester.




**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino)(4-(phenylthio)phenyl)methyl)-2-nitrobutanoate (452c).** According to the general procedure, *tert*-butyl 4-(phenylthio)benzylidenecarbamate (50.0 mg, 160 μmol) provided **452c** after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (57.1 mg, 59%), which was determined to be 97% ee, 15:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 8.5 min, $t_r$(*syn*, minor) = 5.4 min, $t_r$(*anti*, major) = 15.2 min, $t_r$(*anti*, minor) = 7.1 min). $R_f$=0.50 (20% EtOAc/hexanes); IR (neat) 3457, 2968, 2929, 2872, 1766, 1722, 1556, 1481 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.1 Hz, 2H), 7.37-7.31 (m, 3H), 7.27-7.24 (m,

1H), 7.21 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.51 (d, *J* = 9.9 Hz, 1H), 5.58 (d, *J* = 9.9 Hz, 1H), 3.05 (br s, 1H), 2.84 (br s, 1H), 2.42 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.07 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.38 (s, 9H), 1.24-1.20 (m, 3H), 1.21 (d, *J* = 6.8 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.5, 154.7, 144.6, 138.3, 133.8, 133.5, 132.8, 129.7, 129.5, 128.4, 124.1, 127.5, 124.7, 99.1, 80.5, 55.8, 29.8, 28.3, 27.2, 23.9*, 23.1*, 8.7 (one carbon overlapping). HRMS (CI): Exact mass calculated for $C_{34}H_{43}N_2O_6S$ $[M+H]^+$ 607.2742, found 607.2764 .

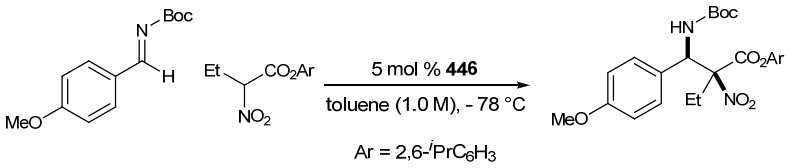
* Broadened peaks due to restricted rotation of aryl ester.




**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-methylphenyl)methyl)-2-nitrobutanoate (452e).** According to the general procedure with the exception of a reaction time of 3.5 days, *tert*-butyl 4-(methyl)benzylidenecarbamate (50.0 mg, 230 μmol) provided **8e** after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (93.5 mg, 80%), which was determined to be 97% ee, 17:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^i$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.5 min, $t_r$(*syn*, minor) = 3.9 min, $t_r$(*anti*, major) = 6.7 min, $t_r$(*anti*, minor) = 4.7 min). $R_f$ = 0.51 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –42 (*c* 4.00, $CHCl_3$); IR (film) 3458, 2969, 2931, 1767, 1723, 1557, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1H), 7.18-7.17 (m, 2H), 7.15-7.13 (m, 4H), 6.52 (d, *J* = 10.0 Hz, 1H), 5.59 (d, *J* = 10.0 Hz, 1H), 3.09 (br s, 1H), 2.85 (br s, 1H), 2.40 (dq, *J* = 14.9, 7.4 Hz, 1H), 2.34 (s, 3H), 2.07 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.37 (s, 9H), 1.25-1.21 (m, 3H), 1.22 (d, *J* = 6.9 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.6, 154.7,

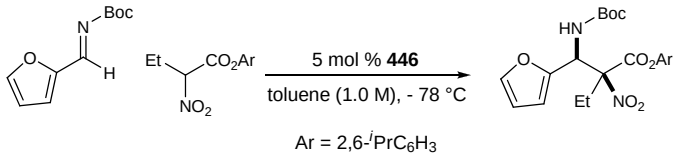
144.7, 140.6/140.1*, 138.9, 132.4, 129.7, 127.48, 127.45, 124.2, 99.3, 80.2, 55.9, 28.4, 27.3, 27.2, 23.9, 23.3/23.0*, 21.2, 8.7. HRMS (CI): Exact mass calculated for $C_{29}H_{41}N_2O_6Na$ $[M+Na]^+$ 535.2784, found 535.2782.

* Broadened peaks due to restricted rotation of aryl ester.

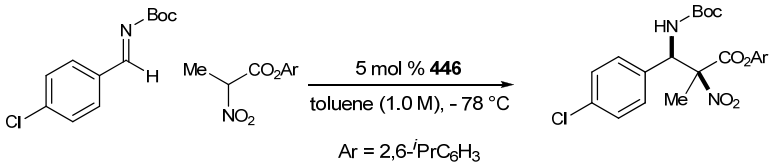



**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-methoxyphenyl)methyl)-2-nitrobutanoate (8f).** According to the general procedure, *tert*-butyl 4-methoxybenzylidenecarbamate (50.0 mg, 210 μmol) provided **452f** after flash column chromatography (20% ethyl acetate in hexanes) as a colorless oil (82.0 mg, 73%), which was determined to be 95% ee, 12:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% $^i$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.5 min, $t_r$(*syn*, minor) = 3.9 min, $t_r$(*anti*, major) = 8.9 min, $t_r$(*anti*, minor) = 4.7 min). $R_f$=0.36 (20% EtOAc/hexanes); IR (film) 3456, 2968, 2932, 1765, 1722, 1557, 1514, 1483 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.28-7.23 (m, 1H), 7.19-7.16 (m, 4H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.49 (d, *J* = 9.8 Hz, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 3.80 (s, 3H), 3.06 (br s, 1H), 2.86 (br s, 1H), 2.45-2.36 (m, 1H), 2.06 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.37 (s, 9H), 1.25-1.20 (m, 3H), 1.22 (d, *J* = 6.9 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) ppm 163.6, 159.9, 154.7, 144.6, 130.0, 128.8, 127.5, 127.4, 124.2, 114.4, 99.4, 80.2, 55.7, 55.3, 28.4, 27.4, 27.2, 23.9 (2C)*, 8.7. HRMS (CI): Exact mass calculated for $C_{29}H_{41}N_2O_7$ $[M+H]^+$ 529.2914, found 529.2908.

* Broadened peaks due to restricted rotation of aryl ester.



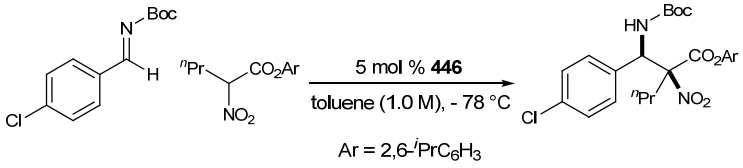

**(*S*)-2,6-Diisopropylphenyl 2-((*S*)-(*tert*-butoxycarbonylamino)(furan-2-yl)methyl)-2-nitrobutanoate (452g)**. According to the general procedure, *tert*-butyl furan-2-ylmethyenecarbamate (50.0 mg, 260 μmol) provided **452g** after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (107 mg, 86%), which was determined to be 94% ee, 5:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 4.7 min, $t_r$(*syn*, minor) = 4.0 min, $t_r$(*anti*, major) = 4.4 min, $t_r$(*anti*, minor) = 4.4 min). $R_f$=0.54 (20% EtOAc/hexanes); IR (film) 3455, 2970, 2971, 1766, 1725, 1561, 1482, 1365 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 1H), 7.24 (d, *J* = 7.68 Hz, 1H), 7.18-7.16 (m, 3H), 6.38-6.32 (m, 2H), 5.81 (d, *J* = 10.2 Hz, 1H), 3.00 (br s, 1H), 2.85 (br s, 1H), 2.51 (dq, *J* = 14.8 ,7.3 Hz, 1H), 2.19 (dq, *J* = 15.1, 7.6, 1H), 1.41 (s, 9H), 1.22-1.19 (m, 3H), 1.19 (d, *J* = 6.8 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) ppm 163.1, 154.6, 148.8, 144.5, 142.9, 127.3, 124.2, 110.7, 110.5, 109.3, 97.9, 80.4, 50.5, 28.2, 27.5, 27.1, 23.6, 23.2/22.8*, 8.7; HRMS (CI): Exact mass calculated for $C_{26}H_{37}N_2O_7$ $[M+H]^+$ 489.2587, found 489.259.




**(2*S*, 3*R*)-2,6-Diisopropylphenyl 3-(*tert*-butoxycarbonylamino)-3-(4-chlorophenyl)-2-methyl)-2-nitropropanoate (425h).** According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (12.5 mg, 50 μmol) provided **452h** after flash

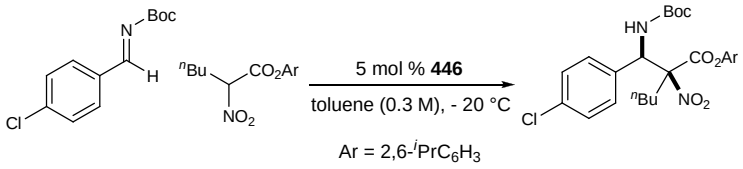
column chromatography (5% ethyl acetate in hexanes) as a colorless oil (22.2 mg, 82%), which was determined to be 99% ee, 12:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 23.5 min, $t_r$(*syn*, minor) = 9.2 min, $t_r$(*anti*, major) = 13.5 min, $t_r$(*anti*, minor) = 7.5 min). $R_f$=0.54 (20% EtOAc/hexanes); IR (film) 3448, 2969, 2968, 1766, 1722, 1559, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.28-7.25 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.19-7.17 (br d, *J* = 7.3 Hz 2H), 6.55 (d, *J* = 9.7 Hz, 1H), 5.50 (d, *J* = 11.1 Hz, 1H), 3.00 (br s, 1H), 2.83 (br s, 1H), 1.92 (s, 3H), 1.39 (s, 9H), 1.21 (br d, *J* = 3.1 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 165.1, 154.7, 144.8, 140.4/140.0*, 135.1, 133.8, 129.6, 129.2, 127.6, 124.3, 95.3, 80.8, 58.8, 28.4, 27.3, 23.8/23.7*, 23.1/22.8*, 22.3. HRMS (CI): Exact mass calculated for $C_{27}H_{36}ClN_2O_6$ $[M+H]^+$ 519.2262, found 519.2256.

* Broadened peaks due to restricted rotation of aryl ester.



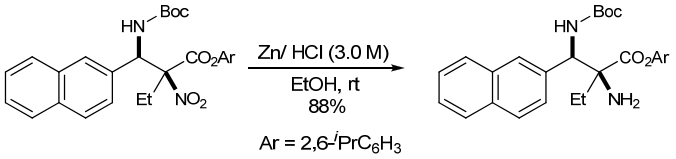

**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino)(4-chlorophenyl)methyl)-2-nitropentanoate (452i)**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (12.5 mg, 52 μmol) provided **452i** after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (23.5 mg, 82%), which was determined to be 97% ee, >20:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 14.2 min, $t_r$(*syn*, minor) = 5.3 min, $t_r$(*anti*, major) = 10.6 min, $t_r$(*anti*, minor) = 8.4 min). $R_f$=0.57 (20% EtOAc/hexanes); IR (film) 3454, 2969, 2933, 2872, 1767, 1722, 1557, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 2H), 7.27-7.25 (m, 1H), 7.18 (br d, *J* = 8.0 Hz, 4H), 6.51

(d, $J$ = 9.7 Hz, 1H), 5.59 (d, $J$ = 9.8 Hz, 1H), 3.04 (br s, 1H), 2.80 (br s, 1H), 2.30-2.25 (m, 1H), 1.97 (ddd, $J$ = 13.7, 13.7, 4.2 Hz, 1H), 1.73-1.68 (m, 1H), 1.61-1.59 (m, 1H), 1.37 (s, 9H), 1.21 (d, $J$ = 6.9 Hz, 12H), 1.01 (dd, $J$ = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.6, 154.7, 144.6, 140.7/140.0*, 135.1, 134.0, 129.3, 128.9, 127.6, 124.3, 98.6, 80.5, 55.9, 36.0, 28.3, 27.2, 23.9, 23.3/22.8*, 17.7, 14.0; HRMS (CI): Exact mass calculated for $C_{29}H_{40}ClN_2O_6$ $[M+H]^+$ 547.2560, found 547.2569.



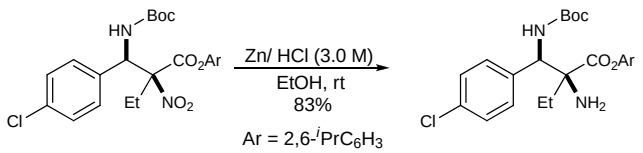

**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino)(4-chlorophenyl)methyl)-2-nitrohexanoate (452j)**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (25.0 mg, 104 μmol) provided **452j** after flash column chromatography (3% ethyl acetate in hexanes) as a colorless oil (51.5 mg, 88%), which was determined to be 97% ee, 16:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^i$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.9 min, $t_r$(*syn*, minor) = 3.8 min, $t_r$(*anti*, major) = 5.1 min, $t_r$(*anti*, minor) = 5.1 min). $R_f$ =0.50 (20% EtOAc/hexanes); IR (film) 3456, 2966, 2932, 2872, 1766, 1723, 1558, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, $J$ = 7.3 Hz, 2H), 7.27-7.25 (m, 1H), 7.18 (d, $J$ = 7.3 Hz, 4H), 6.50 (d, $J$ = 9.7 Hz, 1H), 5.60 (d, $J$ = 9.8 Hz, 1H), 3.04 (br s, 1H), 2.80 (br s, 1H), 2.30 (dd, $J$ = 12.8, 12.8 Hz, 1H), 1.98 (ddd, $J$ = 13.3, 13.3, 3.4 Hz, 1H), 1.66 (br s, 1H), 1.54 (br s, 1H), 1.41-1.37 (m, 2H), 1.37 (s, 9H), 1.21 (d, $J$ = 5.8 Hz, 12H), 0.96 (dd, $J$ = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.6, 154.7, 144.6, 140.7/140.0*, 135.1, 134.0, 129.4, 129.0, 127.6, 124.3, 98.6, 80.6, 55.9, 33.9, 28.4, 27.2, 26.3, 24.0 (2C)*, 22.9, 13.8;

HRMS (CI): Exact mass calculated for $C_{30}H_{41}ClN_2O_6$ $[M+Na]^+$ 583.2551, found 583.2579.

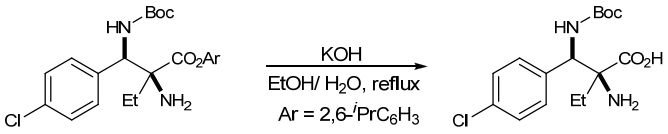



**(*S*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino)(naphthalene-2-yl)methyl)-2-aminobutanoate (453a)**. According to the general procedure, **452a** (25.0 mg, 0.05 mmol) provided **453a** after flash column chromatography (20% ethyl acetate in hexanes) as a white paste (20.9 mg, 88%), which was determined to be 96% ee, >20:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^i$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 20.6 min, $t_r$(*syn*, minor) = 40.1 min, $t_r$(*anti*, major) = 29.3 min, $t_r$(*anti*, minor) = 14.2 min). $R_f$=0.32 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –59 (*c* 1.50, $CHCl_3$); IR (neat) 3396, 3057, 2968, 2931, 1749, 1715, 1468, 1365 $cm^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) □ 7.89-7.83 (m, 4H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.49-7.48 (m, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.19 (br s, 2H), 6.54 (d, *J* = 9.0 Hz, 1H), 5.29 (d, *J* = 9.0 Hz, 1H), 3.07 (br s, 1H), 2.76 (br s, 1H), 2.07 (dq, *J* = 14.5, 7.2 Hz, 1H), 1.66 (br s, 2H), 1.48-1.43 (m, 1H), 1.36 (s, 9H), 1.21 (br s, 12H), 0.97 (dd, *J* = 7.4, 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 173.6, 155.2, 145.3, 137.0, 133.2, 133.1, 128.2, 127.9, 127.7, 127.4, 126.9, 126.2, 126.1, 126.0, 124.2, 123.9, 79.4, 64.8, 59.9, 32.4, 28.5, 28.1, 27.0, 24.4/24.2*, 23.1/22.7*, 7.8. HRMS (CI): Exact mass calculated for $C_{32}H_{43}N_2O_4$ $[M+H]^+$ 519.3217, found 519.3206.

* Broadened peaks due to restricted rotation of aryl ester.

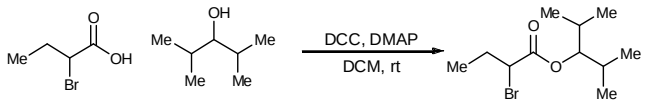



**(*S*)-2,6-Diisopropylphenyl 2-amino-2-((*R*)-(*tert*-butoxycarbonylamino) (4-chlorophenyl)methyl)-2-butanoate (453d).** According to the general procedure, **443d** (30.0 mg, 60.0 μmol) provided **453d** after flash column chromatography (20% ethyl acetate in hexanes) as a white paste (23.3 mg, 83%), which was determined to be 97% ee, >20:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 13.8 min, $t_r$(*syn*, minor) = 8.3 min, $t_r$(*anti*, major) = 5.8 min, $t_r$(*anti*, minor) = 5.4 min). $R_f$=0.14 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ –28 (*c* 2.00, $CHCl_3$); IR (film) 3397, 2969, 2930, 1749, 1716, 1489, 1467 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.17 (br s, 2H), 6.37 (d, *J* = 8.9 Hz, 1H), 5.07 (d, *J* = 8.9 Hz, 1H), 3.01 (br s, 1H), 2.85 (br s, 1H), 2.74 (br s, 1H), 1.99 (dq, *J* = 14.6, 7.3 Hz, 2H), 1.58 (br s, 2H), 1.37 (s, 9H), 1.18 (d, *J* = 3.8 Hz, 12H), 0.97 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 173.4, 155.1, 145.2, 138.1, 133.6, 129.6, 128.5, 126.9, 124.2, 123.9, 79.6, 64.5, 59.2, 32.2, 28.5, 27.0, 24.2, 23.0, 7.7. HRMS (CI): Exact mass calculated for $C_{28}H_{40}ClN_2O_4$ $[M+H]^+$ 503.2677, found 503.2663.



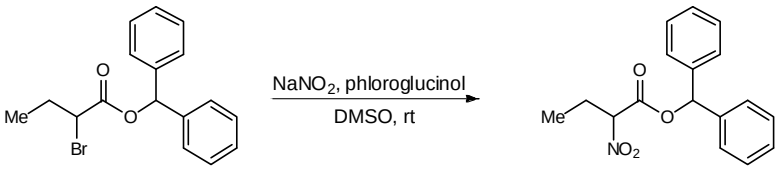

**(*S*)-2-Amino-2-((R)-(*tert*-butoxycarbonylamino)(4-chlorophenyl)methyl)butanoic acid (454)**. The amino ester (**443d**) (15.0 mg, 30 μmol) was dissolved in ethanol (3.00 mL) and then water (0.5 mL) was added followed by potassium hydroxide (41.8 mg, 745

μmol). The reaction was refluxed for 5 h before it was cooled and neutralized with 3.0 M HCl solution. Solvent was removed and the residue was extracted with chloroform. The residue was dried and then extracted with a solution of ethanol in dichloromethane (1:1). All extracts were combined and solvent removed to afford the amino acid as a white foam (7.9 mg, 77%). $R_f$=0.57 (20% EtOAc/hexanes); IR (neat) 3414, 3270, 2972, 1690, 1641, 1598, 1493 $cm^{-1}$; $^1H$ NMR (500 MHz, $D_2O$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.07 (dq, *J* = 14.7, 7.5 Hz, 1H), 1.77 (dq, *J* = 14.7, 6.9 Hz, 1H), 1.25 (br s, 9H), 0.86 (dd, *J* = 7.4, 7.4 Hz, 3H) (benzylic proton eclipsed by $H_2O$ peak); $^{13}C$ NMR (150 MHz, MeOD) ppm 171.9, 156.8, 137.7, 135.9, 130.9, 130.2, 81.5, 58.9, 57.5, 30.7, 28.5, 7.9; HRMS (CI): Exact mass calculated for $C_{16}H_{23}ClN_2O_4$ $[M+Na]^+$ 365.1244, found 365.1245.

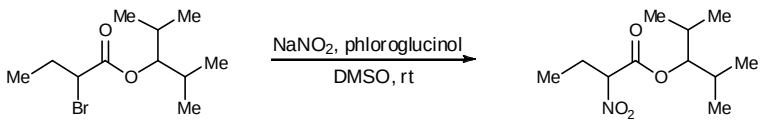



**2,4-Dimethylpentan-3-yl 2-bromobutanoate**. 2-Bromobutanoic acid (7.00 g, 41.9 mmol), 2,4-dimethylpentan-3-ol (3.25 g, 27.9 mmol), DCC (8.65 g, 41.9 mmol) were dissolved in dichloromethane and then DMAP (274 mg, 2.24 mmol) was added. The reaction was stirred for 8 h, and then diluted with diethyl ether and filtered through Celite. The filtrate was concentrated to give the crude product which was purified by column chromatography ($SiO_2$, 10% ethyl acetate in hexanes) to afford the product as a colorless oil (6.1 g, 82%). $R_f$=0.66 (20% EtOAc/hexanes); IR (film) 2968, 2937, 2877, 1737, 1463, 1388 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 4.62 (dd, *J* = 6.2 Hz, 1H), 4.16 (dd, *J* = 7.4 Hz, 1H), 2.12 (dq, *J* = 7.2, 14.4 Hz, 1H), 2.03-1.90 (m, 3H), 1.03 (dd, *J* = 7.6

Hz, 3H), 0.91-0.86 (m, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 169.8, 84.4, 48.3, 29.7, 29.5, 28.5, 19.6, 19.5, 17.2, 17.1, 12.1.

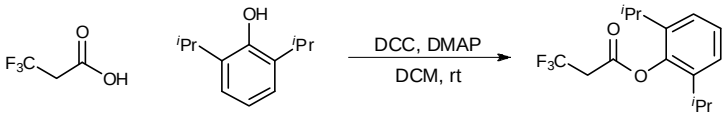



**Benzhydryl 2-nitrobutanoate**. Benzhydryl 2-bromobutanoate (5.50 g, 16.5 mmol), sodium nitrite (1.97 g, 28.8 mmol), and phloroglucinol (2.21 g, 17.5 mmol) were dissolved in DMSO (40 mL) and the reaction was allowed to proceed at room temperature for 15 h. The reaction was then poured into a diethyl ether/ice-water mixture and the solution was allowed to warm to room temperature. The aqueous layer was then extracted with diethyl ether, the combined organic layers were washed with water, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography (5% ethyl acetate/hexanes) to afford the product as a colorless oil (3.31 g, 67%). $R_f$=0.49 (20% EtOAc/hexanes); IR (neat) 3064, 3033, 2978, 2941, 1752, 1560, 1495 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 10H), 6.95 (s, 1H), 5.15 (dd, $J$ = 9.3, 5.4 Hz, 1H), 2.39-2.17 (m, 2H), 1.02 (dd, $J$ = 7.4, 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 163.6, 138.8, 138.7, 128.8, 128.7, 128.5, 128.4, 127.2, 126.9, 89.6, 79.5, 23.9, 10.1; HRMS (CI): Exact mass calculated for $C_{17}H_{18}NO_4$ $[M]^+$ 299.1158, found 299.1246.



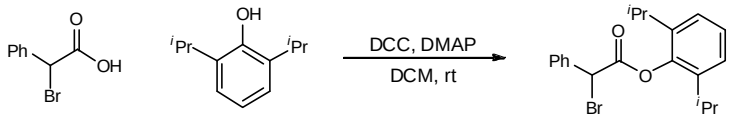

**2,4-Dimethylpentan-3-yl 2-nitrobutanoate**. 2,4-Dimethylpentan-3-yl 2-bromobutanoate (5.50 g, 16.5 mmol), sodium nitrite (2.48 g, 35.9 mmol), and phloroglucinol (2.77 g, 21.9

mmol) were dissolved in DMSO (40 mL) and the reaction was allowed to proceed at room temperature for 15 h. The reaction was then poured into a diethyl ether/ice-water mixture and the solution was allowed to warm to room temperature. The aqueous layer was then extracted with diethyl ether, the combined organic layers were washed with water, dried ($Na_2SO_4$), and concentrated. The crude product was purified by column chromatography (gradient elution, 5-20% ethyl acetate/hexanes) to afford the product as a colorless oil (3.27 g, 68%). $R_f$=0.59 (20% EtOAc/hexanes); IR (neat) 2970, 2880, 1747, 1562, 1465, 1371 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.06 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.67 (dd, *J* = 6.1 Hz, 1H), 2.39-2.29 (m, 1H), 2.27-2.15 (m, 1H), 1.93 (qq, *J* = 6.7, 6.7 Hz, 2H), 1.06 (dd, *J* = 7.4, 7.4 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 6H), 0.85 (d *J* = 6.7 Hz, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$) ppm 164.6, 89.7, 86.2, 29.4, 29.3, 24.0, 19.4, 19.3, 17.0, 16.9, 10.3; HRMS (CI): Exact mass calculated for $C_{11}H_{22}NO_4$ $[M]^+$ 231.1471, found 231.1524.

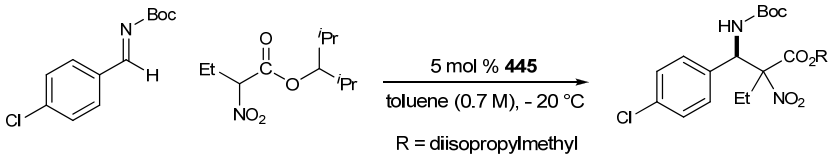



**2,6-Diisopropylphenyl 3,3,3-trifluoropropanoate.** 3,3,3-trifluoropropanoic acid (1.00 g, 7.81 mmol), 2,6-diisopropyl phenol (1.67 g, 9.37 mmol), DCC (1.93 g, 9.37 mmol) were dissolved in dichloromethane and then DMAP (77 mg, 0.66 mmol) was added. The reaction was stirred for 12 h, and then diluted with diethyl ether and filtered through Celite. The filtrate was concentrated to give the crude product which was purified by column chromatography (neutral alumina, 5% diethyl ether in hexanes) to afford the product as a white solid (1.82 g, 81%). $R_f$=0.61 (20% EtOAc/hexanes); IR (film) 3067,

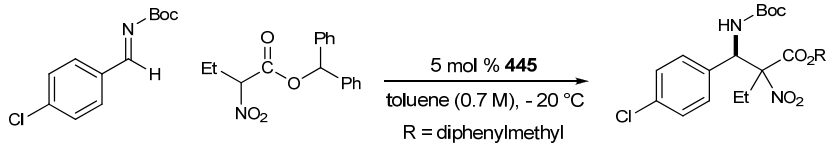
2973, 2933, 2873, 1758, 1463, 1363 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.25-7.23 (m, 1H), 7.19-7.17 (m, 2H), 3.48 (q, *J* = 10.1 Hz, 2H), 2.89 (qq, J = 6.9, 6.9 Hz, 2H), 1.20 (d, *J* = 7.5 Hz, 12H); $^{13}C$ NMR (150 MHz, $CDCl_3$) ppm 162.8 (q, *J* = 4.2 Hz, 1C), 145.1, 140.2, 127.2, 124.2, 123.5 (q, *J* = 276.4 Hz, 1C), 39.74 (q, *J* = 31.6 Hz, 1C), 27.6, 23.7, 22.7; HRMS (CI): Exact mass calculated for $C_{15}H_{19}F_3O_2$ $[M+H]^+$ 288.1337, found 288.1332.




**2,6-Diisopropylphenyl 2-bromo-2-phenylacetate.** α-Bromophenylacetic acid (6.41 g, 29.8 mmol), 2,6-diisopropyl phenol (3.54 g, 19.9 mmol), DCC (6.15 g, 29.8 mmol) were dissolved in dichloromethane and then DMAP (292 mg, 2.38 mmol) was added. The reaction was stirred for 12 h, and then diluted with diethyl ether and filtered through Celite. The filtrate was concentrated to give the crude product which was purified by column chromatography (5% ethyl acetate in hexanes) to afford the product as a yellow oil (1.1 g, 15%) in addition to 5.64 g contaminated with the phenol. $R_f$=0.61 (20% EtOAc/hexanes); IR (film) 3065, 2965, 2930, 2870, 1765, 1455, 1230 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.72-7.69 (m, 2H), 7.44-7.40 (m, 3H), 7.23-7.14 (m, 1H), 7.12-7.11 (m, 2H), 5.62 (s, 1H), 2.75-2.69 (m, 2H), 1.10-1.06 (m, 12H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 166.9, 145.2, 140.5, 135.2, 129.6 (2C), 128.9, 127.0, 124.1, 46.7, 27.2, 23.7, 22.7; HRMS (CI): Exact mass calculated for $C_{20}H_{24}BrO_2$ $[M+Na]^+$ 397.0779, found 397.0787.

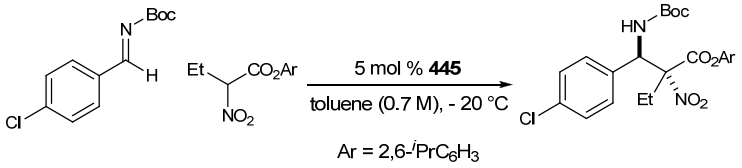



**2,4-Dimethylpentan-3-yl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-chlorophenyl)methyl)-2-nitrobutanoate**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (50.0 mg, 210 μmol) provided the adduct after flash column chromatography (5% ethyl acetate in hexanes) as a white solid (83.0 mg, 84%), which was determined to be 72%, 72% ee, 2.5:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 23.0 min, $t_r$(*syn*, minor) = 7.7 min, $t_r$(*anti*, major) = 8.4 min, $t_r$(*anti*, minor) = 6.0 min).; $R_f$=0.52 (20% EtOAc/hexanes); IR (film) 3454, 2971, 2937, 1746, 1722, 1557, 1485 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.48 (d, *J* = 9.7 Hz, 1H), 5.44 (d, *J* = 9.8 Hz, 1H), 4.76 (t, *J* = 5.9 Hz, 1H), 2.15-2.09 (m, 1H), 2.00-1.88 (m, 3H), 1.38 (s, 9H), 1.09 (t, *J* = 7.5 Hz, 3H), 0.95 (d, *J* = 6.9 Hz , 3H), 0.92 (dd, *J* = 6.6, 6.6 Hz, 6H), 0.87 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.9, 154.5, 134.8, 134.3, 129.18, 129.15, 99.7, 87.4, 80.3, 57.0, 29.7, 29.6, 28.3, 28.1, 19.8, 19.7, 17.7, 17.1, 9.2; HRMS (CI): Exact mass calculated for $C_{23}H_{36}ClN_2O_6$ $[M+H]^+$ 471.2262, found 471.2253.



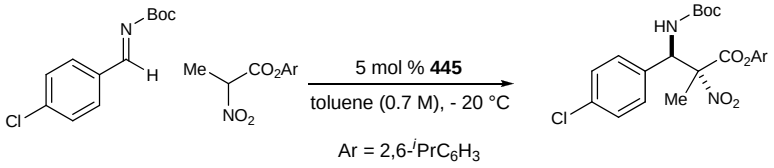

**Benzhydryl 2-((*R*)-(tert-butoxycarbonylamino)(4-chlorophenyl)methyl)-2-nitrobutanoate**. According to the general procedure, *tert*-butyl 4-

chlorobenzylidenecarbamate (**239a**) (50.0 mg, 210 μmol) provided the adduct after flash column chromatography (5% ethyl acetate in hexanes) as a white solid (91.0 mg, 81%), which was determined to be 89% ee, 3.6:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 22.8 min, $t_r$(*syn*, minor) = 29.7 min, $t_r$(*anti*, major) = 31.6 min, $t_r$(*anti*, minor) = 10.9 min).; $R_f$=0.56 (20% EtOAc/hexanes); IR (film) 3454, 2971, 2937, 1746, 1722, 1557, 1485 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.15-7.12 (m, 7H), 7.09-7.06 (m, 3H), 7.04 (d, *J* = 2.7 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 6.17 (d, *J* = 9.4 Hz, 1H), 5.25 (d, *J* = 9.6 Hz, 1H), 1.91-1.81 (m, 1H), 1.77-1.69 (m, 1H), 1.08 (s, 9H), 0.54 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.9, 154.5, 134.8, 134.3, 129.18, 129.15, 99.7, 87.4, 80.3, 57.0, 29.7, 29.6, 28.3, 28.1, 19.8, 19.7, 17.7, 17.1, 9.2; HRMS (CI): Exact mass calculated for $C_{29}H_{32}ClN_2O_6$ $[M+H]^+$ 539.1949, found 539.1949.

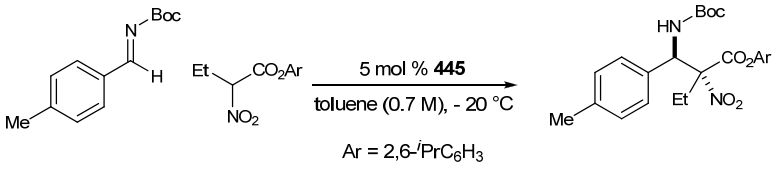



**(*R*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-chlorophenyl)methyl)-2-nitrobutanoate**. According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (25.0 mg, 105 μmol) provided *anti*-**452a** after flash column chromatography (5% ethyl acetate in hexanes) as a white solid (46.0 mg, 83%), which was determined to be 92% ee, 10:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 8.0 min, $t_r$(*syn*, minor) = 4.3 min, $t_r$(*anti*, major) = 5.3 min, $t_r$(*anti*, minor) = 9.3 min).; $R_f$=0.41 (20% EtOAc/hexanes); IR (film) 3440, 2969, 2931, 2871, 1767, 1746, 1722, 1562, 1483 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 4H), 7.24-7.21 (m, 2H), 7.09 (d, *J* = 5.6 Hz, 1H), 6.59 (d, *J* = 9.3 Hz,

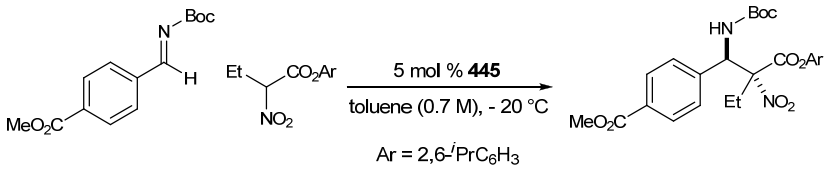
1H), 5.68 (d, $J$ = 9.7 Hz, 1H), 3.16 (br s, 1H), 2.39-2.34 (m, 2H), 1.74 (br s, 1H), 1.38 (s, 9H), 1.26-1.23 (m, 6H), 1.14 (d, $J$ = 6.1 Hz, 3H), 1.02 (d, $J$ = 5.7 Hz, 3H), 0.81 (d, $J$ = 5.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.6, 154.6, 144.7, 140.9, 139.1, 134.9, 134.1, 130.2, 128.9, 127.6, 124.6, 123.8, 98.9, 80.6, 59.4, 29.9, 28.3, 27.4, 26.7, 24.4, 24.3, 22.8, 21.5, 9.5; HRMS (CI): Exact mass calculated for $C_{28}H_{38}ClN_2O_6$ $[M+Na]^+$ 555.2238, found 555.2253.




**(2*R*, 3*R*)-2,6-Diisopropylphenyl 3-(*tert*-butoxycarbonylamino)-3-(4-chlorophenyl)-2-methyl)-2-nitropropanoate.** According to the general procedure, *tert*-butyl 4-chlorobenzylidenecarbamate (**239a**) (24 mg, 100 μmol) provided the adduct after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (45 mg, 86%), which was determined to be 92% ee, 10:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^i$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 23.5 min, $t_r$(*syn*, minor) = 9.2 min, $t_r$(*anti*, major) = 13.5 min, $t_r$(*anti*, minor) = 7.5 min). $R_f$=0.54 (20% EtOAc/hexanes); IR (film) 3448, 2969, 2968, 1766, 1722, 1559, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.18-7.15 (m, 2H), 7.13-7.09 (m, 2H), 7.02 (br d, $J$ = 6.7 Hz 1H), 6.36 (s, 1H), 5.51 (d, $J$ = 7.6 Hz, 1H), 3.04 (br s, 1H), 1.93 (s, 3H), 1.86 (br s, 1H), 1.29 (s, 9H), 1.17 (d, $J$ = 2.5 Hz, 3H), 1.05 (d, $J$ = 6.3 Hz, 3H), 0.92 (d, $J$ = 6.1 Hz, 3H), 0.79 (d, $J$= 6.1 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.6, 154.7, 144.8, 140.9, 139.3, 135.0, 133.9, 130.4, 128.8, 127.6, 124.6, 123.9, 94.9, 80.7, 60.1, 28.3, 27.4, 26.7, 24.1, 23.9, 22.9, 22.8, 21.8. HRMS (CI): Exact mass calculated for $C_{27}H_{36}ClN_2O_6$ $[M+H]^+$ 519.2262, found 519.2256.

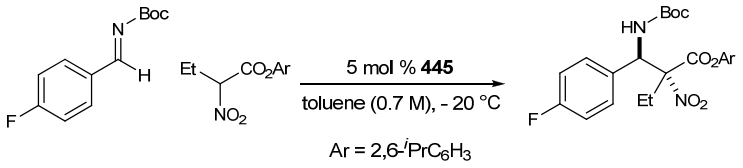



**(*R*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-methylphenyl)methyl)-2-nitrobutanoate.** According to the general procedure, *tert*-butyl 4-(methyl)benzylidenecarbamate (22.0 mg, 100 μmol) provided the adduct after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (44 mg, 86%), which was determined to be 97% ee, 6:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.5 min, $t_r$(*syn*, minor) = 3.9 min, $t_r$(*anti*, major) = 6.7 min, $t_r$(*anti*, minor) = 4.7 min). $R_f$=0.51 (20% EtOAc/hexanes); IR (film) 3458, 2969, 2931, 1767, 1723, 1557, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.28-7.24 (m, 4H), 7.25 (d, *J* = 7.4 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 9.5 Hz, 1H), 5.69 (d, *J* = 9.8 Hz, 1H), 3.23 (br s, 1H), 2.43-2.37 (m, 5H), 1.80 (br s, 1H), 1.39 (s, 9H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.25 (dd, *J* = 7.3, 7.1 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.00 (d, *J* = 5.9 Hz, 3H), 0.78 (d, *J* = 5.6 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.7, 154.7, 144.8, 141.0, 139.3, 138.6, 132.4, 129.4, 128.7, 127.4, 124.5, 123.7, 99.2, 80.2, 59.8, 29.9, 28.3, 27.2, 26.7, 24.2, 22.8, 21.5, 21.2, 9.5. HRMS (CI): Exact mass calculated for $C_{29}H_{41}N_2O_6Na$ $[M+Na]^+$ 535.2784, found 535.2782.



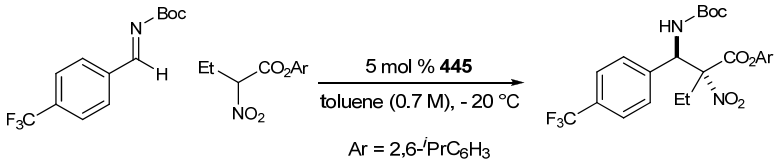

**Methyl-4-((1*R*,2*R*)-1-(*tert*-butoxycarbonylamino)-2-((2,6-di-isopropylphenoxy) carbonyl)-2-nitrobutyl)benzoate.** According to the general procedure, *tert*-butyl 4-

(methoxycarbonyl)benzylidenecarbamate (26.0 mg, 100 μmol) provided the adduct after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (51 mg, 82%), which was determined to be 96% ee, 7:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.5 min, $t_r$(*syn*, minor) = 3.9 min, $t_r$(*anti*, major) = 6.7 min, $t_r$(*anti*, minor) = 4.7 min). $R_f$=0.50 (20% EtOAc/hexanes); IR (film) 3454, 2974, 2928, 1764, 1718, 1560, 1491 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.25-7.22 (m, 2H), 7.07 (br s, 1H), 6.65 (d, *J* = 9.1 Hz, 1H), 5.76 (d, *J* = 9.5 Hz, 1H), 3.93 (s, 3H), 3.17 (br s, 1H), 2.43-2.32 (m, 2H), 1.74 (br s, 1H), 1.37 (s, 9H), 1.25-1.21 (m, 6H), 1.13 (d, *J* = 4.8 Hz, 3H), 0.95 (d, *J* = 3.6 Hz, 3H), 0.76 (br s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 166.4, 164.5, 154.6, 144.7, 140.9, 140.5, 139.1, 130.7, 129.9, 128.9, 127.6, 124.6, 123.8, 98.9, 80.7, 59.8, 52.4, 29.8, 28.3, 27.3, 26.7, 24.3, 22.8, 21.6, 9.4. HRMS (CI): Exact mass calculated for $C_{30}H_{41}N_2O_8$ $[M+H]^+$ 557.2863, found 557.2863.



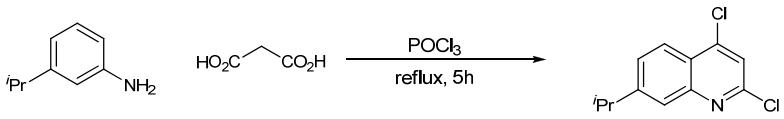

**(*R*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino)(4-fluorophenyl)methyl)-2-nitrobutanoate.** According to the general procedure, *tert*-butyl 4-(fluoro)benzylidenecarbamate (22.0 mg, 100 μmol) provided the adduct after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (36.6 mg, 73%), which was determined to be 96% ee, 8:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.9 min, $t_r$(*syn*, minor) = 4.3 min, $t_r$(*anti*, major) = 8.8 min, $t_r$(*anti*, minor) = 5.1 min). $R_f$=0.53 (20% EtOAc/hexanes); IR (film) 3458, 2969, 2931, 1767, 1723, 1557, 1483 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.40-7.37

(m, 2H), 7.27-7.19 (m, 2H), 7.11-7.04 (m, 3H), 6.61 (d, $J$ = 9.2 Hz, 1H), 5.69 (d, $J$ = 9.6 Hz, 1H), 3.18 (br d, $J$ = 5.9 Hz, 1H), 2.46-2.30 (m, 2H), 1.78 (br s, 1H), 1.39 (s, 9H), 1.27-1.24 (m, 6H), 1.15 (d, $J$ = 6.5 Hz, 3H), 1.02 (d, $J$ = 5.7 Hz, 3H), 0.82 (d, $J$ = 5.5 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.5, 162.8 (d, $J$ = 248.7 Hz, 1C), 154.5, 144.6, 140.9, 139.0, 131.3, 130.6 (d, $J$ = 8.2 Hz, 1C), 127.4, 124.5, 123.7, 115.5 (d, $J$ = 21.5 Hz, 1C), 98.9, 80.5, 59.2, 29.8, 28.2, 27.2, 26.6, 24.2, 24.1, 22.7, 21.5, 9.3; HRMS (CI): Exact mass calculated for $C_{27}H_{36}FN_2O_6$ $[M+Na]^+$ 539.2541, found 539.2529.

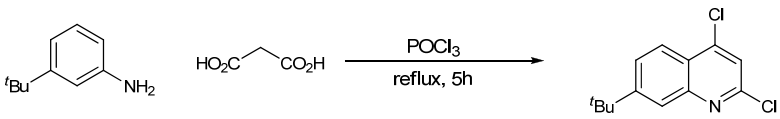



**(*R*)-2,6-Diisopropylphenyl 2-((*R*)-(*tert*-butoxycarbonylamino) (4-(trifluoromethyl)phenyl)methyl)-2-nitrobutanoate.** According to the general procedure, *tert*-butyl 4-(trifluoromethyl)benzylidenecarbamate (27.3 mg, 100 μmol) provided the adduct after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (39.2 mg, 70%), which was determined to be 85% ee, 7:1 dr by chiral HPLC analysis (Chiralcel AD-H, 5% $^i$PrOH/hexanes, 1 mL/min, $t_r$(*syn*, major) = 6.9 min, $t_r$(*syn*, minor) = 4.3 min, $t_r$(*anti*, major) = 8.8 min, $t_r$(*anti*, minor) = 5.1 min). $R_f$=0.54 (20% EtOAc/hexanes); IR (film) 3462, 2966, 2936, 1769, 1723, 1557, 1481 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, $J$ = 8.3 Hz, 2H), 7.54 (d, $J$ = 8.2 Hz, 2H), 7.25-7.20 (m, 2H), 7.09 (d, $J$ = 6.1 Hz, 1H), 6.64 (d, $J$ = 9.1 Hz, 1H), 5.78 (d, $J$ = 9.6 Hz, 1H), 3.16 (br s, 1H), 2.46-2.38 (m, 1H), 2.38-2.32 (m, 1H), 1.79 (br s, 1H), 1.39 (s, 9H), 1.28-1.25 (m, 6H), 1.14 (d, $J$ = 5.5 Hz, 3H), 0.97 (d, $J$ = 5.3 Hz, 3H), 0.78 (d, $J$ = 4.7 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 164.5, 154.6, 144.7, 140.9, 139.8, 139.1, 131.1 (q, $J$ = 32.8 Hz, 1C), 129.4, 127.6, 125.6, 125.5, 124.7, 123.8, 123.6 (q, $J$ = 202 Hz, 1C), 98.8,

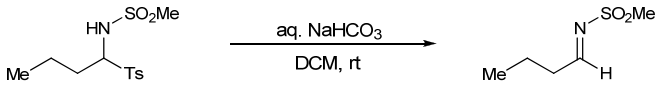
80.8, 59.5, 29.8, 28.3, 27.4, 26.7, 24.2, 22.8, 21.5, 9.4; HRMS (CI): Exact mass calculated for $C_{29}H_{38}F_3N_2O_6$ $[M+H]^+$ 589.2501, found 589.2489.




**2,4-Dichloro-7-isopropylquinoline (503).** Malonic acid (3.1 g, 29.5 mmol), 3-isopropylaniline (5.0 g, 36.9 mmol), and phosphorous oxychloride (40 mL) were combined in a round bottomed flask and the reaction was heated to reflux for 5h. The reaction was cooled to room temperature, neutralized to pH 9 using 6.0 M NaOH solution, and extracted with dichloromethane. The organic extracts were collected, dried, and concentrated to afford the crude product which was purified by flash column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the desired product as a mixture with the 7-isopropyl regio-isomer. Recrystallization from hexanes at -78 °C provided the desired product as a viscous oil (3.6 g, 48%). $R_f$=0.61 (20% EtOAc/ hexanes); IR (film) 2962, 2930, 2872, 1620, 1574, 1550, 1492 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 1.4 Hz, 1H), 7.49 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.37 (s, 1H), 3.08 (qq, *J* = 6.9, 6.9 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ppm 152.9, 149.7, 148.5, 144.0, 127.9, 125.2, 123.9, 123.5, 121.0, 34.2, 23.6; HRMS (EI): Exact mass calcd for $C_{12}H_{12}Cl_2N$ $[M+H]^+$ 240.0347, found 240.0339.

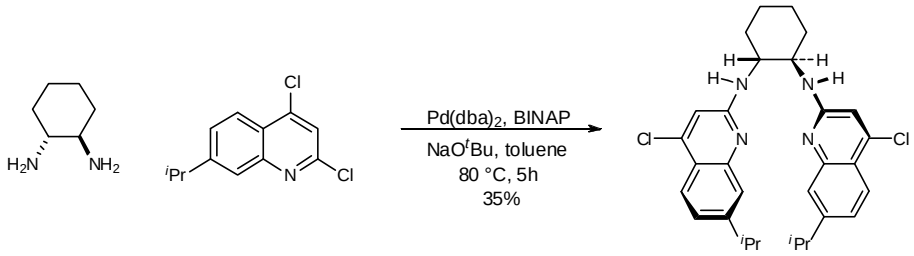



**7-*tert*-Butyl-2,4-dichloroquinoline (509).** Malonic acid (0.45 g, 4.29 mmol), 3-*tert*-butylaniline (0.8 g, 5.36 mmol), and phosphorous oxychloride (15 mL) were combined in a round bottomed flask and the reaction was heated to reflux for 6h. The reaction was cooled to room temperature, neutralized to pH 9 using 6.0 M NaOH solution, and extracted with dichloromethane. The organic extracts were collected, dried, and concentrated to afford the crude product which was purified by flash column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the desired product as a pale yellow solid (569 mg, 52%). Mp 149-151 °C; $R_f$=0.65 (20% EtOAc/ hexanes); IR (film) 2960, 2926, 2907, 2865, 1619, 1573, 1550, 1490 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 1H), 7.98 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.41 (s, 1H), 1.40 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ppm 155.4, 149.7, 148.4, 144.0, 126.8, 124.5, 123.7, 123.2, 121.2, 35.3, 31.0; HRMS (EI): Exact mass calcd for $C_{13}H_{14}Cl_2N$ $[M+H]^+$ 254.0503, found 254.0501.



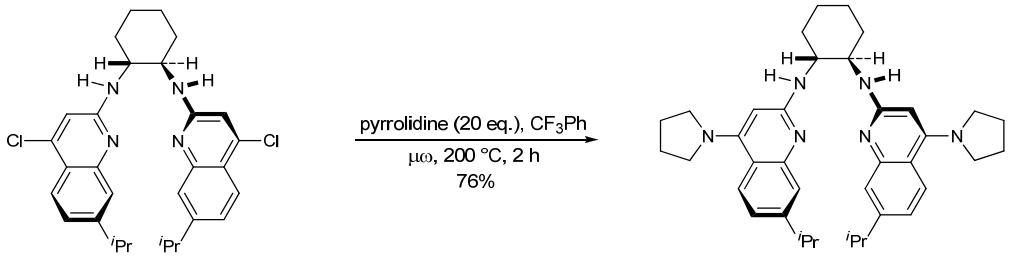

**(*E*)-*N*-Butylidenemethanesulfonamide.** *N*-(1-Tosylbutyl)methanesulfonamide (50.0 mg, 164 μmol) was dissolved in dichloromethane (6.0 mL) and sat. aq. sodium bicarbonate solution (50 μL) was added. The reaction was stirred at room temperature and an additional 50 μL of $NaHCO_3$ solution was added. Reaction was stirred for 30 min. and then extracted with dichloromethane. All organic extracts were combined, dried, and concentrated to provide the product as a colorless oil (5.0 mg, 21%). IR (film) 3280,

2964, 2936, 1634, 1312, 1150 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.64 (t, *J* = 4.4 Hz, 1H), 3.04 (s, 3H), 2.54 (td, *J* = 7.3, 4.4 Hz, 2H), 1.71 (tq, *J* = 7.4, 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ppm 180.2, 39.9, 37.8, 18.1, 13.7; HRMS (EI): Exact mass calcd for $C_5H_{12}NO_2S$ $[M+H]^+$ 150.0589, found 150.0587.



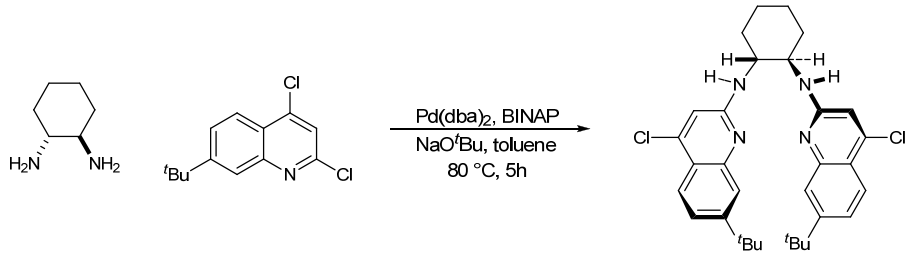

***(1R,2R)-N*[1]*, N*[2]*-bis(4-Chloro-7-isopropylquinolin-2-yl)cyclohexane-1,2-diamine.*** $Pd(dba)_2$ (9.00 mg, 16.0 μmol), *rac*-BINAP (10.0 mg, 16.0 μmol), and $NaO^tBu$ (91.0 mg, 945 μmol) were combined in a round-bottomed flask in a glove box. Toluene (8 mL) was added to the mixture, followed by 1,2-(*R*,*R*)-*trans*-diaminocyclohexane (71.0 mg, 630 μmol) and 2,4-dichloro-7-isopropylquinoline (300 mg, 1.25 mmol). The reaction was stirred at 50 °C until TLC indicated complete consumption of the chloroquinoline. The reaction was cooled to room temperature, filtered through Celite and silica gel, concentrated, and purified by flash column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the desired product as a light brown solid (117 mg, 35%). Mp 162-164 °C; $[\alpha]_D^{20}$ +613 (*c* 2.0, $CHCl_3$); $R_f$=0.69 (40% EtOAc/ hexanes); IR (film) 3220, 2960, 2933, 1601, 1624, 1510, 1445 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.55 (s, 2H), 7.17 (dd, *J* = 8.4, 1.4 Hz, 2H), 6.41 (s, 2H), 5.84 (br s, 2H), 4.08 (br s, 2H), 3.06 (qq, *J* = 7.0, 7.0 Hz, 2H), 2.38 (d, *J* = 12.4 Hz, 2H), 1.85-1.83 (m, 4H), 1.35 (d, *J* = 6.9 Hz, 12 H), 1.27-1.26 (m, 2H); $^{13}C$ NMR (100 MHz,

$CDCl_3$) ppm 156.7, 151.9, 148.8, 142.3, 124.0, 122.9, 122.3, 119.9, 111.5, 56.2, 34.4, 32.8, 24.9, 24.0, 23.9; HRMS (EI): Exact mass calcd for $C_{30}H_{35}Cl_2N_4$ $[M+H]^+$ 521.2239. found 521.2239.

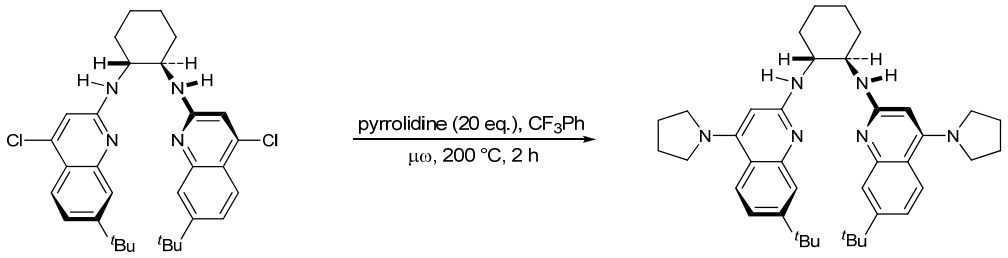



**(1*R*, 2*R*)-*N*$^1$, *N*$^2$-Bis(7-isopropyl-4-(pyrrolidin-1-yl)quinolin-2-yl)cyclohexane-1,2-diamine (513)**. A 0.5-2.0 mL microwave vial was charged with H,$^4$Cl,$^{7i}$Pr-BAM (150 mg, 0.29 mmol), pyrrolidine (480 μL, 5.75 mmol), and trifluoromethylbenzene (1 mL). This suspension was heated at 200 °C in the microwave for 2 h with stirring. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and washed with 3M NaOH. The combined organic layers were dried over sodium sulfate and concentrated to afford the desired product as a light brown powder (129 mg, 76%). Mp 212-213 °C; $[\alpha]_D^{20}$ +489 (*c* 2.0, $CHCl_3$); $R_f$=0.38 (10% MeOH/$CH_2Cl_2$); IR (film) 3259, 2958, 2928, 2865, 1590, 1524 $cm^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.49 (s, 2H), 6.91 (dd, *J* = 8.6, 1.7 Hz, 2H), 5.55 (br s, 2H), 5.24 (s, 2H), 4.09 (s, 2H), 3.29-3.28 (m, 4H), 3.11-3.10 (m, 4H), 2.98 (qq, *J* = 6.9 Hz, 2H), 2.29 (d, *J* = 12 Hz, 2H), 1.82-1.81 (m, 10H), 1.51-1.41 (m, 4H), 1.32 (d, *J* = 6.9 Hz, 6H), 1.31 (d, *J* = 6.9 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 158.7, 153.1, 150.3, 149.2, 124.7, 123.3, 118.7, 116.9, 92.4, 56.4, 51.6, 34.1, 33.6, 25.6, 25.3,

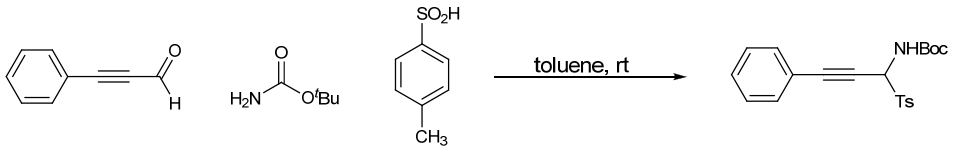
24.1, 23.8; HRMS (ESI): Exact mass calcd for $C_{38}H_{51}N_6[M+H]^+$ 591.4175, found 591.4167.



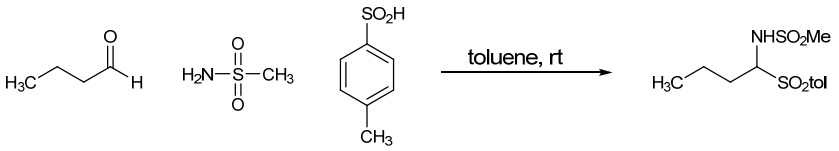

**(*1R,2R*)-$N^1$, $N^2$-bis(4-Chloro-7-*tert*-butyl-quinolin-2-yl)cyclohexane-1,2-diamine.** $Pd(dba)_2$ (6.00 mg, 10.0 μmol), *rac*-BINAP (6.00 mg, 10.0 μmol), and NaO$^t$Bu (58.0 mg, 600 μmol) were combined in a round-bottomed flask in a glove box. Toluene (5 mL) was added to the mixture, followed by 1,2-(*R,R*)-*trans*-diaminocyclohexane (45.0 mg, 400 μmol) and 2,4-dichloro-7-*tert*-butylquinoline (200 mg, 790 μmol). The reaction was stirred at 50 °C until TLC indicated complete consumption of the chloroquinoline. The reaction was cooled to room temperature, filtered through Celite and silica gel, concentrated, and purified by flash column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the desired product as a light yellow solid (105 mg, 48%). Mp 189-191 °C; $[\alpha]_D^{20}$ +491 (*c* 2.0, $CHCl_3$); $R_f$=0.73 (40% EtOAc/ hexanes); IR (film) 3222, 3055, 2963, 2934, 1614, 1624, 1512, 1445 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.68 (s, 2H), 7.35 (dd, *J* = 8.4, 1.1 Hz, 2H), 6.40 (s, 2H), 5.84 (br s, 2H), 4.07 (br s, 2H), 2.39 (d, *J* = 12.1 Hz, 2H), 1.85 (d, *J* = 7.6 Hz, 2H), 1.52-1.46 (m, 2H), 1.46-1.42 (m, 20H); $^{13}C$ NMR (150 MHz, $CDCl_3$) ppm 156.7, 154.1, 148.6, 142.1, 123.7, 121.9, 121.2, 119.4, 111.7, 56.3, 35.1, 32.8, 31.3, 24.9; HRMS (EI): Exact mass calcd for $C_{32}H_{39}Cl_2N_4$ $[M+H]^+$ 549.2552, found 549.2535.




**(1*R*, 2*R*)-$N^1$, $N^2$-bis(7-*tert*-butyl-4-(pyrrolidin-1-yl)quinolin-2-yl)cyclohexane-1,2-diamine (514)**. A 0.5-2.0 mL microwave vial was charged with H,$^4$Cl,$^{7t}$Bu-BAM (80.0 mg, 0.15 mmol), pyrrolidine (243 μL, 2.91 mmol), and trifluoromethylbenzene (1 mL). This suspension was heated at 200 °C in the microwave for 2 h with stirring. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and washed with 3M NaOH. The combined organic layers were dried over sodium sulfate and concentrated to afford the desired product as a light brown powder (64 mg, 71%). Mp 201-203 °C; $[\alpha]_D^{20}$ +506 (*c* 2.0, $CHCl_3$); $R_f$=0.42 (10% MeOH/$CH_2Cl_2$); IR (film) 3236, 2963, 2866, 1589, 1520, 1434 $cm^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 1.9 Hz, 2H), 7.07 (dd, *J* = 8.8, 2.0 Hz, 2H), 5.53 (br s, 2H), 5.21 (s, 2H), 4.09 (s, 2H), 3.29-3.28 (m, 4H), 3.10-3.09 (m, 4H), 2.29 (d, *J* = 12 Hz, 2H), 1.82-1.79 (m, 10H), 1.51-1.41 (m, 4H), 1.39 (s, 18H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 158.7, 152.9, 151.4, 150.1, 124.4, 122.3, 117.7, 116.4, 92.4, 56.4, 51.5, 34.7, 33.6, 31.3, 25.6, 25.3; HRMS (ESI): Exact mass calcd for $C_{40}H_{55}N_6[M+H]^+$ 619.4488, found 619.4514.

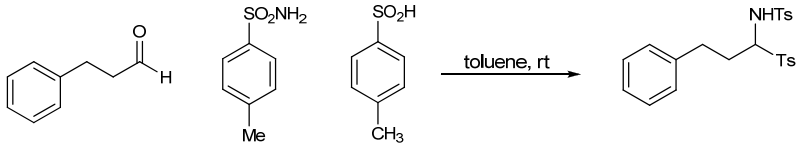



***tert*-Butyl 3-phenyl-1-(phenylsulfonyl)prop-2-ynylcarbamate**. 3-Phenylpropiolaldehyde (656 mg, 5.04 mmol), *tert*-butyl carbamate (500 mg, 4.20 mmol), 4-methylbenzenesulfinic acid (787 mg, 5.04 mmol), and toluene (15 mL) were combined in a round-bottomed flask and stirred at room temperature for 48 h, resulting in the precipitation of a solid. The reaction mixture was filtered, and the filtrate was washed with toluene to afford the product as a white solid (967 mg, 50%). $R_f$=0.38 (10% EtOAc/hexanes); Mp 186-188 °C; IR (film) 3336, 2980, 2930, 1720, 1510 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.39-7.31 (m, 5H), 5.84 (d, *J* = 10.2, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 2.44 (s, 3H), 1.33 (s, 9H); $^{13}C$ NMR (150 MHz, $CDCl_3$) ppm 153.3, 145.6, 132.9, 132.2, 130.0, 129.9, 129.5, 128.5, 121.1, 89.2, 81.7, 78.3, 64.8, 28.1, 21.8.

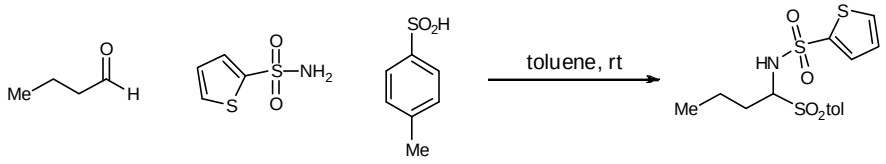



***N*-(1-Tosylbutyl)methanesulfonamide**. Butyraldehyde (910 mg, 13.0 mmol), methane sulfonamide (1.00 g, 11.0 mmol), 4-methylbenzenesulfinic acid (1.97 g, 13.0 mmol), and toluene (25 mL) were combined in a round-bottomed flask, and the reaction was stirred at room temperature for 48 h. The resulting clear solution was cooled to -78 °C, resulting in the precipitation of a solid. The reaction mixture was filtered and the filtrate was washed with cold toluene and pentane to afford the product as a white solid (2.25 g, 70%); Mp

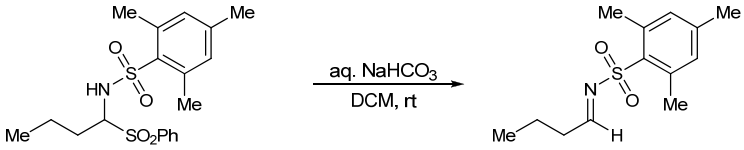
179-181 °C; $R_f$=0.38 (10% EtOAc/hexanes); IR (film) 3256, 2963, 1323, 1289, 1150, 1082 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.29 (d, *J* = 9.8, 1H), 4.62 (ddd, *J* = 10.8, 10.8, 3.1 Hz, 1H), 2.98 (s, 3H), 2.45 (s, 3H), 1.95-1.87 (m, 1H), 1.66-1.49 (m, 2H), 1.44-1.34 (m, 1H), 0.91 (dd, *J* = 7.1, 7.1 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ppm 145.8, 132.7, 130.2, 129.6, 74.2, 42.8, 31.2, 21.8, 18.6, 13.3.




**4-Methyl-*N*-(3-phenyl-1-tosylpropyl)benzenesulfonamide**. 3-Phenylpropanal (940 mg, 7.01 mmol), 4-methyl benzenesulfonamide (1.00 g, 5.84 mmol), 4-methyl benzenesulfinic acid (1.09 g, 7.01 mmol), and toluene (25 mL) were combined in a round-bottomed flask and stirred at room temperature for 22 h. The reaction mixture was filtered, and the solid collected was washed with toluene and diethyl ether to afford the product as a white solid (2.34 g, 90%); Mp 185-186 °C; $R_f$=0.15 (20% EtOAc/hexanes); IR (film) 3234, 2958, 2933, 1596, 1454, 1435, 1328 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.27-7.24 (m, 4H), 7.21-7.19 (m, 3H), 7.05-7.03 (m, 2H), 5.45 (d, *J* = 10.6 Hz, 1H), 4.59 (m, 1H), 2.70-2.63 (m, 1H), 2.56-2.46 (m, 2H), 2.44 (s, 3H), 2.41 (s, 3H), 2.00-1.90 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ppm 145.8, 132.7, 130.2, 129.6, 74.2, 42.8, 31.2, 21.8, 18.6, 13.3.

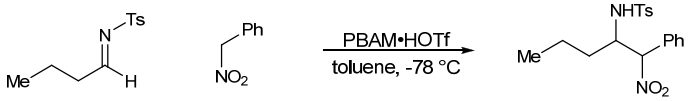



***N*-(1-Tosylbutyl)thiophene-2-sulfonamide.** Butanal (530 mg, 7.35 mmol), thiophene-2-sulfonamide (1.00 g, 6.13 mmol), and toluenesulfinic acid (1.15 g, 7.35 mmol) were dissolved in toluene (20.0 mL) and the reaction was stirred at room temperature for 12 h. The reaction was then diluted with water and filtered. The solid collected was washed with water (2x10 mL) and pentane (10 mL), and then dried to afford the product as a white solid (1.01 g, 80%). $R_f$=0.06 (20% EtOAc/hexanes); IR (neat) 3255, 3103, 2964, 2933, 2875, 1597, 1457 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.54 (d, *J* = 5.0 Hz, 1H) , 7.44 (d, *J* = 3.6 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 3.9, 3.9 Hz, 1H), 5.35 (d, *J* = 10.2 Hz, 1H), 4.58 (ddd, *J* = 10.0, 10.0, 3.5 Hz, 1H), 2.45 (s, 3H), 2.17-2.08 (m, 1H), 7.54 (dddd, *J* = 14.6, 10.0, 10.0, 4.8 Hz, 1H), 1.43-1.31 (m, 1H), 1.28-1.17 (m, 1H), 0.87 (dd, *J* = 7.2, Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) ppm 145.4, 141.5, 132.6, 132.4, 129.8, 129.6, 127.3, 73.6, 30.4, 21.7, 18.3, 13.5.

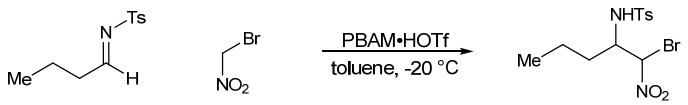



**(*E*)-*N*-Butylidene-2,4,6-trimethylbenzenesulfonamide (494d).** 2,4,6-trimethyl-*N*-(1-(phenylsulfonyl)butyl)benzenesulfonamide was dissolved in dichloromethane (10 mL) and sat. aq. sodium bicarbonate solution (5 mL) was added. Reaction was stirred for 2 h at room tmperature and then extracted with dichloromethane. All organic extracts were combined, dried, and concentrated to provide the product as a white solid (233 mg, 91%).

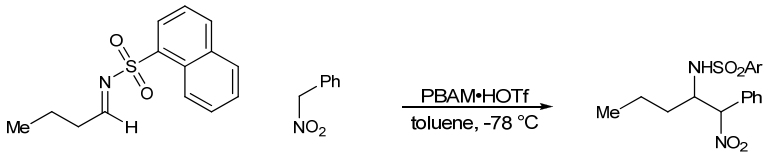
Mp 147-148 °C; IR (film) 2965, 2957, 2875, 1629, 1320 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.59 (t, *J* = 6.5 Hz, 1H), 6.96 (s, 2H), 2.62 (s, 6H), 2.49 (ddd, *J* = 7.3, 7.3, 4.5 Hz, 2H), 2.3 (s, 3H), 1.66 (tq, *J* = 7.4, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ppm 176.9, 143.4, 140.3, 131.9, 37.8, 22.9, 21.09, 18.3, 13.7.



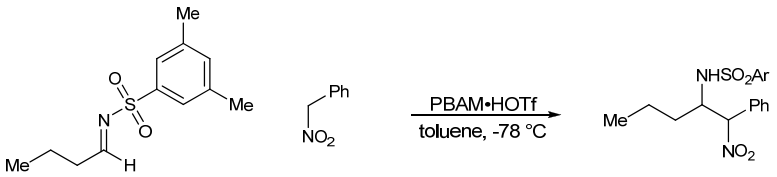

**4-Methyl-*N*-(1-nitro-1phenylpentan-2-yl)benzenesulfonamide (494a).** A solution of (*E*)-*N*-butylidene-4-methylbenzenesulfonamide (23.0 mg, 10.0 μmol) and PBAM•HOTf (**457**) (7.00 mg, 1.00 μmol) in toluene (200 μL) was cooled to -78 °C and treated with phenyl nitromethane (21.0 mg, 15.0 μmol). The reaction was stirred at -78 °C for 48 hours. The solution was concentrated and purified by column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the product as a colorless oil (31 mg, 85%) which was determined to be 79% ee, >20:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% $^i$PrOH/hexanes, 1 mL/min, $t_r$(major, major) = 19.5 min, $t_r$(major, minor) = 15.4 min, $t_r$(minor, major) = 17.2 min, $t_r$(minor, minor) = 21.7 min). $R_f$=0.19 (20% EtOAc/Hexanes); IR (film) 3279, 2962, 2931, 1554, 1456, 1360 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.33-7.32 (m, 1H), 7.29-7.25 (m, 4H), 7.19 (d, *J* = 8.1 Hz, 2H), 5.49 (d, *J* = 7.0 Hz, 1H), 4.76 (d, *J* = 8.8 Hz, 1H), 4.13-4.08 (m, 1H), 2.39 (s, 3H), 1.55-1.51 (m, 2H), 1.39-1.29 (m, 1H), 1.19-1.11 (m, 1H), 0.75 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) ppm 143.7, 137.6, 131.5, 129.8, 129.7, 129.2, 129.0, 128.4, 126.9, 93.1, 56.6, 33.4, 21.6, 18.5, 13.5; HRMS (ESI): Exact mass calcd for $C_{18}H_{23}N_2O_4S[M+Na]^+$ 385.1198, found 385.1209.



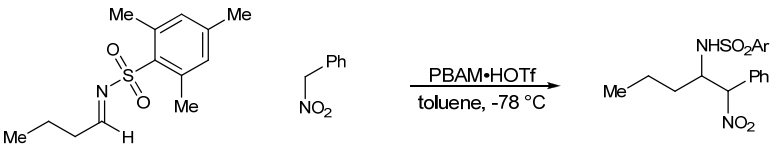

***N*-((2*R*)-1-Bromo-1-nitropentan-2-yl)-4-methylbenzenesulfonamide (517).** A solution of (*E*)-*N*-Butylidene-4-methylbenzenesulfonamide (23.0 mg, 10.0 μmol) and PBAM•HOTf (**457**) (7.00 mg, 1.00 μmol) in toluene (200 μL) was cooled to -78 °C and treated with bromo nitromethane (21.0 mg, 15.0 μmol). The reaction was stirred at -20 °C for 48 hours. The solution was concentrated and purified by column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the product as a colorless oil (31 mg, 85%) which was determined to be 74%, 70% ee, 1:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(major, major) = 11.9 min, $t_r$(major, minor) = 10.7 min, $t_r$(minor, major) = 13.1 min, $t_r$(minor, minor) = 14.9 min). $R_f$=0.41 (20% EtOAc/Hexanes); IR (film) 3279, 2962, 2931, 1554, 1456, 1360 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.35-7.32 (m, 4H), 6.15 (d, *J* = 4.0 Hz, 1H), 6.15 (d, *J* = 4.0 Hz, 1H), 6.06 (d, *J* = 2.8 Hz, 1H), 4.95 (d, *J* = 9.5 Hz, 1H), 4.86 (d, *J* = 9.1 Hz, 1H), 4.02-3.95 (m, 2H), 2.45 (s, 3H), 2.44 (s, 3H), 1.77-1.71 (m, 1H), 1.56-1.50 (m, 3H), 1.43-1.38 (m, 1H), 1.37-1.31 (m, 1H), 1.19-1.33 (m, 1H), 1.10-1.09 (m, 1H), 0.84 (dd, *J* = 7.3, 7.3 Hz, 3H), 0.75 (dd, *J* = 7.4, 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 144.5, 144.4, 137.1, 136.8, 130.0, 129.9, 127.2, 127.1, 85.3, 84.1, 57.8, 56.5, 33.6, 32.6, 29.8, 21.7, 18.9, 18.2, 13.4, 13.3; HRMS (ESI): Exact mass calcd for $C_{12}H_{17}BrN_2O_4S[M+Na]^+$ 386.9990, found 387.0009.




***N*-(1-Nitro-1-phenylpentan-2-yl)naphthalene-1-sulfonamide (494c).** A solution of (*E*)-*N*-butylidenenaphthalene-1-sulfonamide (26.0 mg, 10.0 μmol) and PBAM•HOTf (**457**) (7.00 mg, 1.00 μmol) in toluene (200 μL) was cooled to -78 °C and treated with phenyl nitromethane (21.0 mg, 15.0 μmol). The reaction was stirred at -78 °C for 24 hours. The solution was concentrated and purified by column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the product as a colorless oil (30 mg, 75%) which was determined to be 50% ee, >20:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(major, major) = 14.7 min, $t_r$(major, minor) = 26.6 min, $t_r$(minor, major) = 17.9 min, $t_r$(minor, minor) = 30.9 min). $R_f$=0.22 (20% EtOAc/Hexanes); IR (film) 3293, 2962, 2933, 1552, 1456, 1361 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 8.36-8.35 (m, 1H), 8.19 (dd, *J* = 7.4, 1.1 Hz, 1H ), 8.03 (d, *J* = 8.3 Hz, 1H), 7.90-7.89 (m, 1H), 7.57-7.56 (m, 2H), 7.49 (dd, *J* = 8.0, 8.0 Hz, 1H) 7.09-7.05 (m, 3H), 7.02-7.00 (m, 2H), 5.39 (d, *J* = 9.0 Hz, 1H), 4.86 (d, *J* = 9.0 Hz, 1H), 4.14-4.09 (m, 1H), 1.54-1.50 (m, 2H), 1.30-1.23 (m, 1H), 1.14-1.05 (m, 1H), 0.65 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 143.7, 137.6, 131.5, 129.8, 129.7, 129.2, 129.0, 128.4, 126.9, 93.1, 56.6, 33.4, 21.6, 18.5, 13.5; HRMS (ESI): Exact mass calcd for $C_{21}H_{23}N_2O_4S[M+Na]^+$ 421.1198, found 421.1219.




**3,5-Dimethyl-*N*-(1-nitro-1-phenylpentan-2-yl)benzenesulfonamide (494d).** A solution of (*E*)-*N*-butylidene-3,5-dimethylbenzenesulfonamide (24.0 mg, 10.0 μmol) and PBAM•HOTf (**457**) (7.00 mg, 1.00 μmol) in toluene (200 μL) was cooled to -78 °C and treated with phenyl nitromethane (21.0 mg, 15.0 μmol). The reaction was stirred at -78 °C for 24 hours. The solution was concentrated and purified by column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the product as a colorless oil (30 mg, 80%) which was determined to be 82% ee, >20:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(major, major) = 9.6 min, $t_r$(major, minor) = 14.4 min, $t_r$(minor, major) = 12.1 min, $t_r$(minor, minor) = 27.4 min). $R_f$=0.33 (20% EtOAc/Hexanes); IR (film) 3278, 2962, 2926, 1554, 1456, 1360 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.46-7.45 (m, 1H), 7.43-7.39 (m, 4H), 7.37-7.36 (m, 3H), 5.57 (d, *J* = 7.1 Hz, 1H), 4.65 (d, *J* = 8.8 Hz, 1H), 4.27-4.22 (m, 1H), 2.43 (s, 6H), 1.73-1.63 (m, 2H), 1.54-1.46 (m, 1H), 1.36-1.28 (m, 1H), 0.91 (dd, *J* = 7.3, 7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 140.2, 139.2, 134.6, 131.4, 129.9, 128.9, 128.4, 124.5, 93.2, 56.5, 33.5, 21.3, 18.5, 13.6; HRMS (ESI): Exact mass calcd for $C_{19}H_{25}N_2O_4S[M+H]^+$ 399.1354, found 399.1371.




**2,4,6-Trimethyl-*N*-(1-nitro-1-phenylpentan-2-yl)benzenesulfonamide (494b).** A solution of 2,4,6-trimethyl-*N*-(1-nitro-1-phenylpentan-2-yl)benzenesulfonamide (25.0

mg, 10.0 μmol) and PBAM•HOTf (7.00 mg, 1.00 μmol) in toluene (1.00 mL) was cooled to -78 °C and treated with phenyl nitromethane (21.0 mg, 15.0 μmol). The reaction was stirred at -78 °C for 24 hours. The solution was concentrated and purified by column chromatography (gradient elution, 10-20% ethyl acetate in hexanes) to provide the product as a colorless oil (35 mg, 91%) which was determined to be 14:1 dr, 8%, 24% ee, by chiral HPLC analysis (Chiralcel AD-H, 10% $^{i}$PrOH/hexanes, 1 mL/min, $t_r$(major, major) = 9.5 min, $t_r$(major, minor) = 11.9 min, $t_r$(minor, major) = 10.5 min, $t_r$(minor, minor) = 14.3 min). $R_f$=0.45 (20% EtOAc/Hexanes); IR (film) 3290, 2963, 2937, 2874, 1552, 1456 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.27-7.25 (m, 1H), 7.21-7.20 (m, 4H) 6.84 (s, 2H), 5.47 (d, $J$ = 7.4 Hz, 1H), 4.67 (d, $J$ = 9.1 Hz, 1H), 4.12-4.06 (m, 1H), 2.50 (s, 6H), 2.28 (s, 3H), 1.66-1.55 (m, 2H), 1.47-1.38 (m, 1H), 1.31-1.23 (m, 1H), 0.80 (dd, $J$ = 7.4, 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) ppm 142.4, 138.7, 134.4, 132.1, 131.6, 129.8, 128.9, 127.9, 93.2, 56.7, 33.6, 23.3, 20.9, 18.4, 13.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{27}N_2O_4S[M+Na]^+$ 413.1511, found 413.1525.

## *Appendix*

## (*S*)-2,6-Diisopropylphenyl-2-((*R*)-(*tert*-butoxycarbonylamino)-(4-chlorophenyl)methyl)-2-nitrobutanoate (443d)

**Table 1. Crystal data and structure refinement for 07155.**

| | | |
|---|---|---|
| Empirical formula | C28 H37 Cl N2 O6 | |
| Formula weight | 533.05 | |
| Crystal color, shape, size Temperature | colorless, flat needle, 0.25 · 0.10 · 0.05 $mm^3$ | |
| | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system, space group Unit cell dimensions | Orthorhombic, $P2_12_12_1$ | |
| | a = 9.6521(7) Å | α= 90°. |
| | b = 11.1645(8) Å | β= 90°. |
| | c = 27.4646(18) Å | γ = 90°. |
| Volume | 2959.6(4) | |
| Z | $Å^3$ 4 | |
| Density (calculated) | 1.196 $Mg/m^3$ | |
| Absorption coefficient | 0.170 $mm^{-1}$ | |
| F(000) | 1136 | |

***Data collection***

| | |
|---|---|
| Diffractometer | APEX II Kappa Duo, |
| Theta range for data collection | Bruker 2.24 to 26.39°. |
| Index ranges | -9<=h<=12, -13<=k<=13, -34<=l<=34 |
| Reflections collected | 29147 |
| Independent reflections | 6017 [R(int) = 0.0460] |
| Observed Reflections | 4621 |
| Completeness to theta = 26.39° | 99.5 % |

***Solution and Refinement***

| | |
|---|---|
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9916 and 0.9588 |
| Solution | Direct methods |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Weighting scheme | $w = [\sigma^2 Fo^2 + AP^2 + BP]^{-1}$, with $P = (Fo^2 + 2\,Fc^2)/3$, A = 0.0456, B = 0.4416 |
| Data / restraints / parameters | 6017 / 81 / 361 |
| Goodness-of-fit on $F^2$ | 1.020 |
| Final R indices [I>2sigma(I)] | R1 = 0.0400, wR2 = 0.0864 |
| R indices (all data) | R1 = 0.0625, wR2 = 0.0965 |
| Absolute structure parameter | -0.02(7) |
| Largest diff. peak and hole | 0.254 and -0.348 e.$Å^{-3}$ |

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Goodness-of-fit = $[\Sigma[w(F_o^2 - F_c^2)^2]/N_{observns} - N_{params})]^{1/2}$, all data.

$R1 = \Sigma(|F_o| - |F_c|) / \Sigma |F_o|$. $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2]]^{1/2}$.

**Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 07155. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Cl1 | 4729(1) | 4320(1) | 4425(1) | 64(1) |
| O1 | 8731(2) | 3906(1) | 6891(1) | 41(1) |
| O3 | 11498(2) | 4010(2) | 5354(1) | 49(1) |
| O4 | 11334(2) | 5709(2) | 4982(1) | 64(1) |
| O5 | 11327(2) | 5490(1) | 6616(1) | 40(1) |
| O6 | 12854(1) | 5782(1) | 6004(1) | 34(1) |
| N1 | 9628(2) | 3631(2) | 6131(1) | 34(1) |
| N2 | 11158(2) | 5067(2) | 5335(1) | 40(1) |
| C1 | 9227(2) | 4799(2) | 5946(1) | 30(1) |
| C2 | 10474(2) | 5597(2) | 5793(1) | 32(1) |
| C3 | 11578(2) | 5586(2) | 6192(1) | 31(1) |
| C4 | 9215(2) | 3265(2) | 6583(1) | 34(1) |
| O2 | 9792(10) | 2148(6) | 6622(5) | 39(1) |
| C5 | 9524(12) | 1435(11) | 7079(5) | 38(1) |
| C6 | 10363(18) | 298(9) | 6998(5) | 84(2) |
| C7 | 10090(30) | 2120(30) | 7516(9) | 55(2) |
| C8 | 7993(12) | 1225(12) | 7139(5) | 54(1) |
| O2D | 9309(5) | 2063(3) | 6630(2) | 39(1) |
| C5D | 9078(6) | 1475(5) | 7109(2) | 38(1) |
| C6D | 9381(10) | 178(4) | 6978(2) | 84(2) |
| C7D | 10143(15) | 1912(12) | 7469(4) | 55(2) |
| C8D | 7596(6) | 1628(5) | 7273(2) | 54(1) |
| C9 | 8131(2) | 4711(2) | 5547(1) | 30(1) |
| C10 | 6967(2) | 5451(2) | 5559(1) | 35(1) |
| C11 | 5925(2) | 5349(2) | 5212(1) | 39(1) |
| C12 | 6059(2) | 4502(2) | 4852(1) | 39(1) |
| C13 | 7196(3) | 3766(2) | 4824(1) | 42(1) |
| C14 | 8232(2) | 3869(2) | 5171(1) | 36(1) |
| C15 | 10044(2) | 6897(2) | 5686(1) | 38(1) |
| C16 | 9438(3) | 7558(2) | 6122(1) | 47(1) |
| C17 | 13966(2) | 5817(2) | 6346(1) | 35(1) |
| C18 | 14409(2) | 6954(2) | 6497(1) | 41(1) |
| C19 | 15550(3) | 6973(3) | 6807(1) | 52(1) |
| C20 | 16189(3) | 5921(3) | 6954(1) | 56(1) |
| C21 | 15703(2) | 4828(2) | 6798(1) | 49(1) |
| C22 | 14568(2) | 4744(2) | 6485(1) | 39(1) |
| C23 | 13684(3) | 8076(2) | 6325(1) | 51(1) |

| | | | | |
|---|---|---|---|---|
| C25 | 14120(5) | 8396(3) | 5816(1) | 105(1) |
| C26 | 14035(2) | 3532(2) | 6319(1) | 49(1) |
| C27 | 13357(3) | 2868(3) | 6745(1) | 81(1) |
| C28 | 15156(3) | 2756(2) | 6086(1) | 56(1) |

**Table 3. Bond lengths [Å] and angles [°] for 07155.**

| | | | |
|---|---|---|---|
| Cl1-C12 | 1.749(2) | O1-C4 | 1.204(2) |
| O3-N2 | 1.226(2) | O4-N2 | 1.217(2) |
| O5-C3 | 1.195(2) | O6-C3 | 1.353(2) |
| O6-C17 | 1.427(2) | N1-C4 | 1.365(3) |
| N1-C1 | 1.452(2) | N1-H1N | 0.8800 |
| N2-C2 | 1.539(3) | C1-C9 | 1.527(3) |
| C1-C2 | 1.555(3) | C1-H1 | 1.0000 |
| C2-C3 | 1.528(3) | C2-C15 | 1.538(3) |
| C4-O2D | 1.351(4) | C4-O2 | 1.370(7) |
| O2-C5 | 1.508(11) | C5-C8 | 1.506(11) |
| C5-C7 | 1.520(13) | C5-C6 | 1.522(12) |
| C6-H6A | 0.9800 | C6-H6B | 0.9800 |
| C6-H6C | 0.9800 | C7-H7A | 0.9800 |
| C7-H7B | 0.9800 | C7-H7C | 0.9800 |
| C8-H8A | 0.9800 | C8-H8B | 0.9800 |
| C8-H8C | 0.9800 | O2D-C5D | 1.488(5) |
| C5D-C7D | 1.508(8) | C5D-C8D | 1.509(5) |
| C5D-C6D | 1.520(6) | C6D-H6DA | 0.9800 |
| C6D-H6DB | 0.9800 | C6D-H6DC | 0.9800 |
| C7D-H7DA | 0.9800 | C7D-H7DB | 0.9800 |
| C7D-H7DC | 0.9800 | C8D-H8DA | 0.9800 |
| C8D-H8DB | 0.9800 | C8D-H8DC | 0.9800 |
| C9-C10 | 1.395(3) | C9-C14 | 1.400(3) |
| C10-C11 | 1.391(3) | C10-H10 | 0.9500 |
| C11-C12 | 1.375(3) | C11-H11 | 0.9500 |
| C12-C13 | 1.373(3) | C13-C14 | 1.384(3) |
| C13-H13 | 0.9500 | C14-H14 | 0.9500 |
| C15-C16 | 1.523(3) | C15-H15A | 0.9900 |
| C15-H15B | 0.9900 | C16-H16A | 0.9800 |
| C16-H16B | 0.9800 | C16-H16C | 0.9800 |
| C17-C22 | 1.385(3) | C17-C18 | 1.402(3) |
| C18-C19 | 1.391(3) | C18-C23 | 1.511(4) |
| C19-C20 | 1.388(4) | C19-H19 | 0.9500 |
| C20-C21 | 1.376(4) | C20-H20 | 0.9500 |
| C21-C22 | 1.396(3) | C21-H21A | 0.9500 |
| C22-C26 | 1.518(3) | C23-C25 | 1.505(4) |
| C23-C24 | 1.523(4) | C23-H23 | 1.0000 |
| C24-H24A | 0.9800 | C24-H24B | 0.9800 |
| C24-H24C | 0.9800 | C25-H25A | 0.9800 |
| C25-H25B | 0.9800 | C25-H25C | 0.9800 |
| C26-C28 | 1.527(4) | C26-C27 | 1.531(4) |

| | | | |
|---|---|---|---|
| C13-C14-H14 | 119.6 | C9-C14-H14 | 119.6 |
| C16-C15-C2 | 114.33(17) | C16-C15-H15A | 108.7 |
| C2-C15-H15A | 108.7 | C16-C15-H15B | 108.7 |
| C2-C15-H15B | 108.7 | H15A-C15-H15B | 107.6 |
| C15-C16-H16A | 109.5 | C15-C16-H16B | 109.5 |
| H16A-C16-H16B | 109.5 | C15-C16-H16C | 109.5 |
| H16A-C16-H16C | 109.5 | H16B-C16-H16C | 109.5 |
| C22-C17-C18 | 124.9(2) | C22-C17-O6 | 118.23(19) |
| C18-C17-O6 | 116.74(19) | C19-C18-C17 | 115.9(2) |
| C19-C18-C23 | 123.0(2) | C17-C18-C23 | 121.1(2) |
| C20-C19-C18 | 121.2(2) | C20-C19-H19 | 119.4 |
| C18-C19-H19 | 119.4 | C21-C20-C19 | 120.5(2) |
| C21-C20-H20 | 119.8 | C19-C20-H20 | 119.8 |
| C20-C21-C22 | 121.3(2) | C20-C21-H21A | 119.3 |
| C22-C21-H21A | 119.3 | C17-C22-C21 | 116.2(2) |
| C17-C22-C26 | 123.14(19) | C21-C22-C26 | 120.7(2) |
| C25-C23-C18 | 111.0(2) | C25-C23-C24 | 111.5(3) |
| C18-C23-C24 | 113.8(3) | C25-C23-H23 | 106.7 |
| C18-C23-H23 | 106.7 | C24-C23-H23 | 106.7 |
| C23-C24-H24A | 109.5 | C23-C24-H24B | 109.5 |
| H24A-C24-H24B | 109.5 | C23-C24-H24C | 109.5 |
| H24A-C24-H24C | 109.5 | H24B-C24-H24C | 109.5 |
| C23-C25-H25A | 109.5 | C23-C25-H25B | 109.5 |
| H25A-C25-H25B | 109.5 | C23-C25-H25C | 109.5 |
| H25A-C25-H25C | 109.5 | H25B-C25-H25C | 109.5 |
| C22-C26-C28 | 113.0(2) | C22-C26-C27 | 110.3(2) |
| C28-C26-C27 | 110.4(2) | C22-C26-H26 | 107.6 |
| C28-C26-H26 | 107.6 | C27-C26-H26 | 107.6 |
| C26-C27-H27A | 109.5 | C26-C27-H27B | 109.5 |
| H27A-C27-H27B | 109.5 | C26-C27-H27C | 109.5 |
| H27A-C27-H27C | 109.5 | H27B-C27-H27C | 109.5 |
| C26-C28-H28A | 109.5 | C26-C28-H28B | 109.5 |
| H28A-C28-H28B | 109.5 | C26-C28-H28C | 109.5 |
| H28A-C28-H28C | 109.5 | H28B-C28-H28C | 109.5 |

**Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 07155. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$**

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Cl1 | 89(1) | 45(1) | 57(1) | -1(1) | -42(1) | -6(1) |
| O1 | 55(1) | 36(1) | 31(1) | 2(1) | 7(1) | 10(1) |
| O3 | 62(1) | 41(1) | 44(1) | -9(1) | 13(1) | 7(1) |
| O4 | 83(1) | 81(1) | 28(1) | 17(1) | 9(1) | 20(1) |
| O5 | 40(1) | 52(1) | 27(1) | -2(1) | 1(1) | 1(1) |
| O6 | 36(1) | 36(1) | 30(1) | 6(1) | 1(1) | 0(1) |
| N1 | 51(1) | 25(1) | 25(1) | 1(1) | 3(1) | 7(1) |
| N2 | 43(1) | 50(1) | 28(1) | 1(1) | -2(1) | 4(1) |
| C1 | 40(1) | 25(1) | 25(1) | 2(1) | -2(1) | 6(1) |
| C2 | 42(1) | 29(1) | 25(1) | 0(1) | 1(1) | 2(1) |
| C3 | 39(1) | 25(1) | 30(1) | 1(1) | 1(1) | 4(1) |
| C4 | 45(1) | 27(1) | 28(1) | 1(1) | -5(1) | 0(1) |
| O2 | 69(3) | 22(1) | 27(1) | 6(1) | 12(2) | -3(2) |
| C5 | 54(4) | 30(1) | 28(1) | 9(1) | 16(2) | 4(2) |
| C6 | 162(6) | 36(2) | 56(2) | 17(2) | 44(4) | 20(3) |
| C7 | 55(2) | 61(5) | 48(2) | 26(2) | -5(2) | -5(3) |
| C8 | 47(3) | 66(3) | 50(3) | 24(2) | 2(2) | -4(2) |
| O2D | 69(3) | 22(1) | 27(1) | 6(1) | 12(2) | -3(2) |
| C5D | 54(4) | 30(1) | 28(1) | 9(1) | 16(2) | 4(2) |
| C6D | 162(6) | 36(2) | 56(2) | 17(2) | 44(4) | 20(3) |
| C7D | 55(2) | 61(5) | 48(2) | 26(2) | -5(2) | -5(3) |
| C8D | 47(3) | 66(3) | 50(3) | 24(2) | 2(2) | -4(2) |
| C9 | 41(1) | 24(1) | 25(1) | 3(1) | -1(1) | -3(1) |
| C10 | 46(1) | 31(1) | 28(1) | -1(1) | -2(1) | 2(1) |
| C11 | 46(1) | 34(1) | 36(1) | 3(1) | -9(1) | 4(1) |
| C12 | 57(1) | 32(1) | 30(1) | 4(1) | -13(1) | -7(1) |
| C13 | 70(2) | 27(1) | 30(1) | -5(1) | -4(1) | -8(1) |
| C14 | 48(1) | 31(1) | 30(1) | -2(1) | -1(1) | 3(1) |
| C15 | 45(1) | 28(1) | 40(1) | 7(1) | -6(1) | -2(1) |
| C16 | 56(1) | 26(1) | 59(2) | 0(1) | -5(1) | 5(1) |
| C17 | 32(1) | 44(1) | 29(1) | 5(1) | 1(1) | -4(1) |
| C18 | 44(1) | 45(1) | 34(1) | -3(1) | 8(1) | -2(1) |
| C19 | 48(2) | 60(2) | 47(1) | -10(1) | 0(1) | -12(1) |
| C20 | 45(1) | 81(2) | 43(1) | 1(1) | -7(1) | -10(1) |
| C21 | 39(1) | 60(2) | 47(1) | 15(1) | -5(1) | -1(1) |
| C22 | 35(1) | 43(1) | 38(1) | 11(1) | 0(1) | -1(1) |
| C23 | 57(2) | 37(1) | 58(2) | -6(1) | 8(1) | -5(1) |
| C24 | 147(4) | 59(2) | 124(3) | -32(2) | -21(3) | 21(2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C25 | 144(3) | 72(2) | 98(3) | 45(2) | 53(2) | 42(2) |
| C26 | 41(1) | 36(1) | 69(2) | 15(1) | -9(1) | -2(1) |
| C27 | 75(2) | 50(2) | 117(3) | 23(2) | 42(2) | 0(2) |
| C28 | 60(2) | 48(2) | 60(2) | 9(1) | 2(1) | -3(1) |

**Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$ x $10^3$)**

| | x | y | z | U |
|---|---|---|---|---|
| H1N | 10141 | 3155 | 5951 | 40 |
| H1 | 8772 | 5223 | 6224 | 36 |
| H6A | 10351 | -188 | 7295 | 127 |
| H6B | 11321 | 510 | 6917 | 127 |
| H6C | 9956 | -161 | 6729 | 127 |
| H7A | 9447 | 2765 | 7601 | 82 |
| H7B | 10995 | 2454 | 7435 | 82 |
| H7C | 10180 | 1569 | 7792 | 82 |
| H8A | 7517 | 1996 | 7172 | 82 |
| H8B | 7830 | 741 | 7431 | 82 |
| H8C | 7636 | 800 | 6853 | 82 |
| H6DA | 10315 | 118 | 6840 | 127 |
| H6DB | 8702 | -101 | 6739 | 127 |
| H6DC | 9321 | -318 | 7272 | 127 |
| H7DA | 9944 | 2746 | 7556 | 82 |
| H7DB | 11068 | 1862 | 7323 | 82 |
| H7DC | 10111 | 1413 | 7762 | 82 |
| H8DA | 7446 | 2459 | 7375 | 82 |
| H8DB | 7410 | 1090 | 7547 | 82 |
| H8DC | 6971 | 1435 | 7003 | 82 |
| H10 | 6884 | 6034 | 5810 | 42 |
| H11 | 5136 | 5856 | 5223 | 46 |
| H13 | 7272 | 3192 | 4570 | 51 |
| H14 | 9020 | 3362 | 5153 | 44 |
| H15A | 10865 | 7342 | 5569 | 45 |
| H15B | 9350 | 6894 | 5421 | 45 |
| H16A | 9171 | 8370 | 6024 | 70 |
| H16B | 10132 | 7602 | 6382 | 70 |
| H16C | 8619 | 7128 | 6241 | 70 |
| H19 | 15898 | 7720 | 6918 | 62 |
| H20 | 16969 | 5955 | 7165 | 67 |
| H21A | 16148 | 4116 | 6905 | 59 |
| H23 | 12672 | 7885 | 6311 | 61 |
| H24A | 13642 | 8877 | 7004 | 165 |
| H24B | 13196 | 9770 | 6576 | 165 |
| H24C | 14794 | 9439 | 6653 | 165 |
| H25A | 13979 | 7705 | 5601 | 157 |
| H25B | 15102 | 8619 | 5815 | 157 |

| | | | | |
|---|---|---|---|---|
| H25C | 13564 | 9072 | 5699 | 157 |
| H26 | 13304 | 3676 | 6068 | 58 |
| H27A | 12665 | 3388 | 6898 | 121 |
| H27B | 14066 | 2652 | 6985 | 121 |
| H27C | 12905 | 2140 | 6624 | 121 |
| H28A | 15517 | 3158 | 5795 | 84 |
| H28B | 14760 | 1980 | 5994 | 84 |
| H28C | 15911 | 2631 | 6319 | 84 |

**Table 6. Torsion angles [°] for 07155.**

| | | | |
|---|---|---|---|
| C4-N1-C1-C9 | -107.4(2) | C4-N1-C1-C2 | 123.8(2) |
| O4-N2-C2-C3 | -113.9(2) | O3-N2-C2-C3 | 65.7(2) |
| O4-N2-C2-C15 | 3.9(3) | O3-N2-C2-C15 | -176.46(19) |
| O4-N2-C2-C1 | 127.2(2) | O3-N2-C2-C1 | -53.1(2) |
| N1-C1-C2-C3 | -47.5(2) | C9-C1-C2-C3 | -176.27(16) |
| N1-C1-C2-C15 | -169.73(16) | C9-C1-C2-C15 | 61.5(2) |
| N1-C1-C2-N2 | 69.13(19) | C9-C1-C2-N2 | -59.7(2) |
| C17-O6-C3-O5 | 3.0(3) | C17-O6-C3-C2 | 178.65(17) |
| C15-C2-C3-O5 | 92.2(2) | N2-C2-C3-O5 | -150.4(2) |
| C1-C2-C3-O5 | -31.9(3) | C15-C2-C3-O6 | -83.5(2) |
| N2-C2-C3-O6 | 34.0(2) | C1-C2-C3-O6 | 152.41(16) |
| C1-N1-C4-O1 | -13.9(3) | C1-N1-C4-O2D | 160.9(3) |
| C1-N1-C4-O2 | -179.8(5) | O1-C4-O2-C5 | 16.5(12) |
| O2D-C4-O2-C5 | -61.4(19) | N1-C4-O2-C5 | -178.5(8) |
| C4-O2-C5-C8 | 60.2(13) | C4-O2-C5-C7 | -60.7(16) |
| C4-O2-C5-C6 | -177.8(11) | O1-C4-O2D-C5D | -12.6(5) |
| N1-C4-O2D-C5D | 172.5(3) | O2-C4-O2D-C5D | 104(2) |
| C4-O2D-C5D-C7D | -61.5(7) | C4-O2D-C5D-C8D | 65.7(5) |
| C4-O2D-C5D-C6D | -176.7(4) | N1-C1-C9-C10 | 133.17(19) |
| C2-C1-C9-C10 | -97.2(2) | N1-C1-C9-C14 | -44.5(3) |
| C2-C1-C9-C14 | 85.1(2) | C14-C9-C10-C11 | 0.7(3) |
| C1-C9-C10-C11 | -177.05(19) | C9-C10-C11-C12 | -0.1(3) |
| C10-C11-C12-C13 | -0.6(3) | C10-C11-C12-Cl1 | 177.49(17) |
| C11-C12-C13-C14 | 0.6(3) | Cl1-C12-C13-C14 | -177.51(17) |
| C12-C13-C14-C9 | 0.1(3) | C10-C9-C14-C13 | -0.7(3) |
| C1-C9-C14-C13 | 177.02(19) | C3-C2-C15-C16 | -60.1(2) |
| N2-C2-C15-C16 | -176.09(18) | C1-C2-C15-C16 | 62.4(2) |
| C3-O6-C17-C22 | 84.9(2) | C3-O6-C17-C18 | -98.2(2) |
| C22-C17-C18-C19 | 0.6(3) | O6-C17-C18-C19 | -176.06(18) |
| C22-C17-C18-C23 | 179.9(2) | O6-C17-C18-C23 | 3.3(3) |
| C17-C18-C19-C20 | -0.4(3) | C23-C18-C19-C20 | -179.8(2) |
| C18-C19-C20-C21 | -0.1(4) | C19-C20-C21-C22 | 0.6(4) |
| C18-C17-C22-C21 | -0.2(3) | O6-C17-C22-C21 | 176.44(18) |
| C18-C17-C22-C26 | 178.8(2) | O6-C17-C22-C26 | -4.6(3) |
| C20-C21-C22-C17 | -0.4(3) | C20-C21-C22-C26 | -179.4(2) |
| C19-C18-C23-C25 | 100.9(3) | C17-C18-C23-C25 | -78.4(3) |
| C19-C18-C23-C24 | -25.8(4) | C17-C18-C23-C24 | 154.9(3) |
| C17-C22-C26-C28 | 126.5(2) | C21-C22-C26-C28 | -54.6(3) |
| C17-C22-C26-C27 | -109.2(3) | C21-C22-C26-C27 | 69.7(3) |