ELECTRONIC MODIFICATION AND DEVELOPMENT OF A MORE REACTIVE CHIRAL PROTON CATALYST FOR THE ENANTIOSELECTIVE AZA-HENRY REACTION AND ITS APPLICATION TO THE SYNTHESIS OF THERAPEUTICS

By

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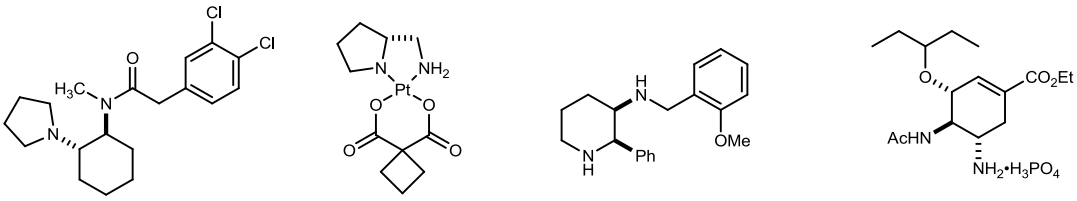
INTRODUCTION

1.1 Approaches to the Stereoselective Synthesis of 1,2-Diamines

Many common structural motifs are found in nature among biologically active compounds. Among these common motifs are 1,2-diamines. The ability to make these

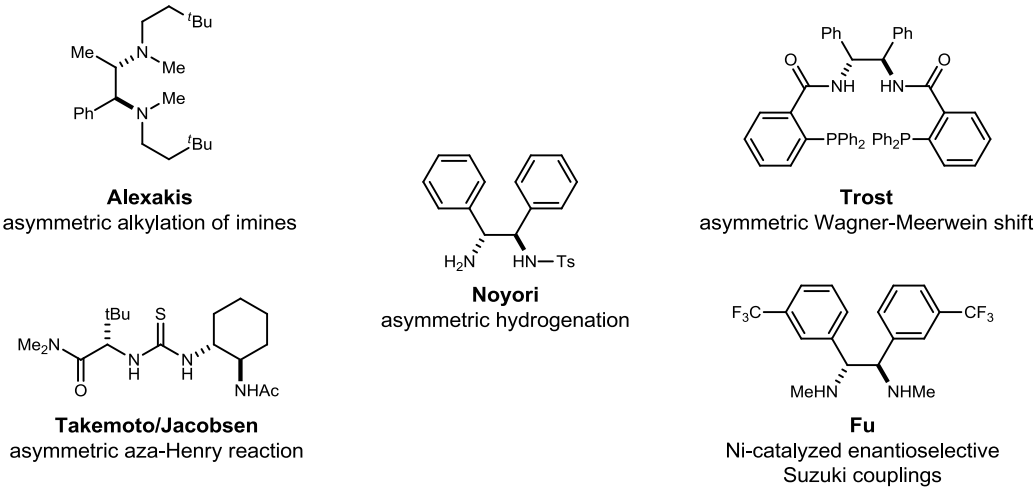
Figure 1. Biologically Active 1,2-Diamines



compounds in a stereoselective fashion is important for making biologically active compounds (Figure 1) as well as asymmetric reagents for synthesis.

Chiral 1,2-diamines are very important backbones of a vast array of asymmetric catalysts (Figure 2). Chiral diamines have been used as chiral ligands in combination with

Figure 2. 1,2-Diamines Used for Asymmetric Catalysis

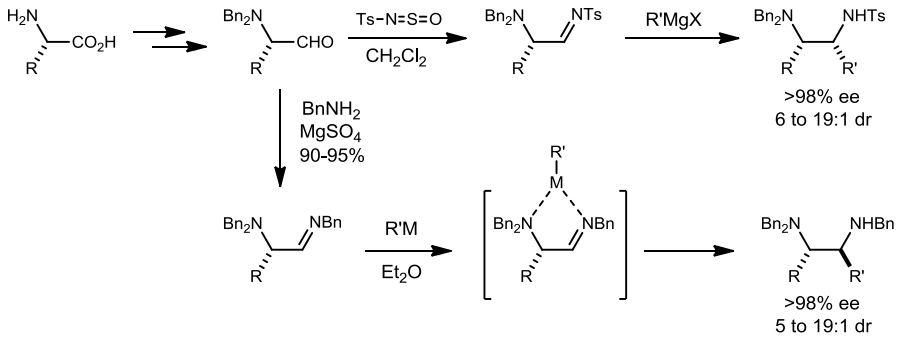


metals and as metal-free chiral organocatalysts.[1,2,3,4,5,6]

Stereochemically enriched 1,2-diamines can be obtained in many different ways. Perhaps the oldest method for this task is resolution using a stoichiometric amount of a chiral resolving agent. This procedure has many drawbacks including the lack of generality towards substrates, as they must be solids for recrystallization-based techniques, and the limited yields that can be obtained by resolution.

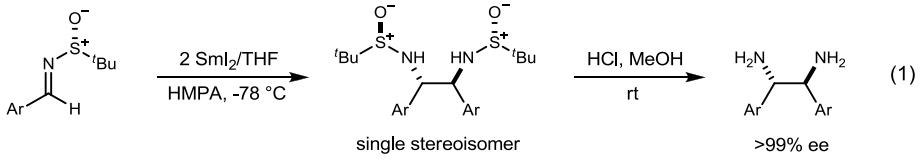
Enantiomerically pure amino acids can be inexpensive starting materials for the synthesis of chiral 1,2-diamines. Reetz demonstrated the use of various *L*-amino acids to

Scheme 1. Reetz' Synthesis of 1,2-Diamines from Amino Acids



obtain both *syn* and *anti*-1,2-diamines (Scheme 1).[7] This solution is ultimately limited by the availability of the amino acid starting material.

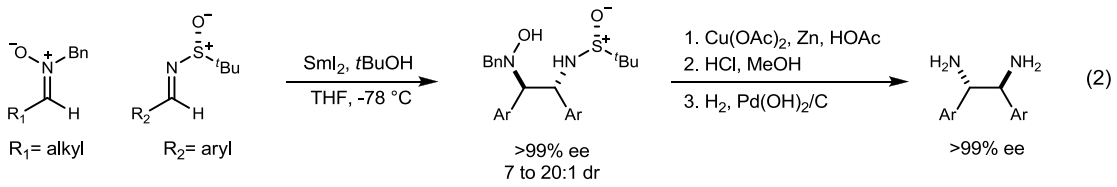
Xu and Lin utilized aryl *N*-sulfinyl imines in a stereoselective samarium mediated



(1)

[1] Perron, Q.; Alexakis, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2503-2506.
[2] Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044-6045.
[3] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102.
[4] Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466-476.
[5] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466-468.
[6] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694-6695.
[7] Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 103-106.

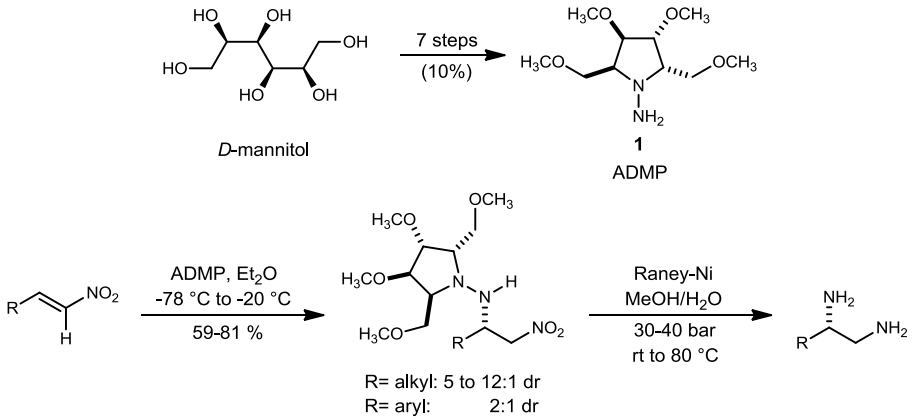
homocoupling (eq 1).[8] This chiral auxiliary approach resulted in the formation of a single stereoisomer which was then reduced to form 1,2-diamines. A cross-coupling reaction between nitrones and imines bearing a chiral auxiliary led to stereoisomerically enriched unsymmetrical 1,2-diamines (eq 2).[9]



(2)

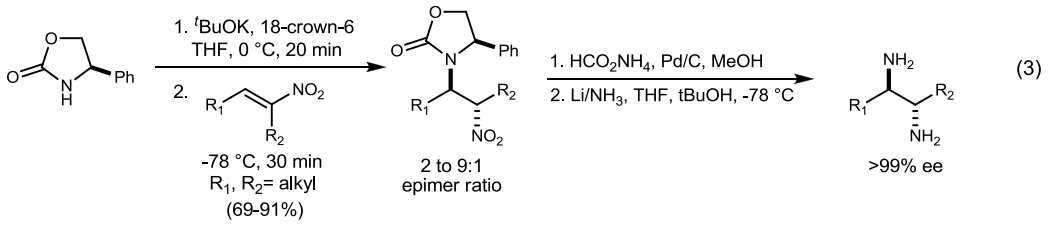
Enders demonstrated the use of diastereoselective Michael additions to nitroalkenes to form 1,2-diamines. A mannitol-derived chiral ammonia equivalent **1** was used as shown in Scheme 2.[10]

Scheme 2. Enders' Diastereoselective Michael Addition to Nitroalkenes

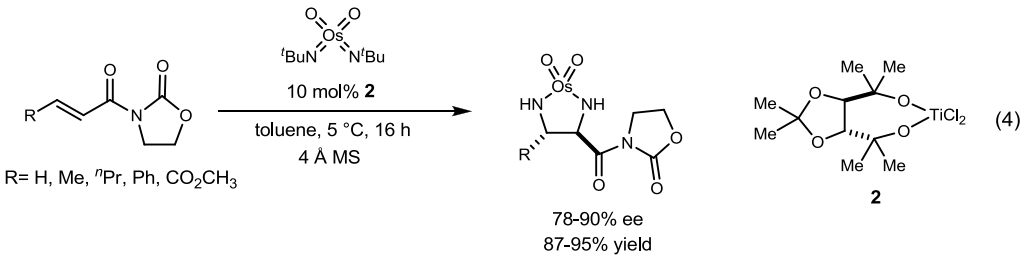


Mioskowski also demonstrated the use of a diastereoselective Michael addition to nitroalkenes (eq 3). An oxazolidinone chiral auxiliary was employed to make 1,2-diamines with high stereoselectivity.

[8] Zhong, Y.; Izumi, K.; Xu, M.; Lin, G. *Org. Lett.* **2004**, *6*, 4747-4750.
[9] Lin, G.; Xu, M.; Zhong, Y.; Sun, X. *Acc. Chem. Res.* **2008**, *41*, 831-840.
[10] Enders, D.; Wiedemann, J. *Synthesis* **1996**, 1443-1450.

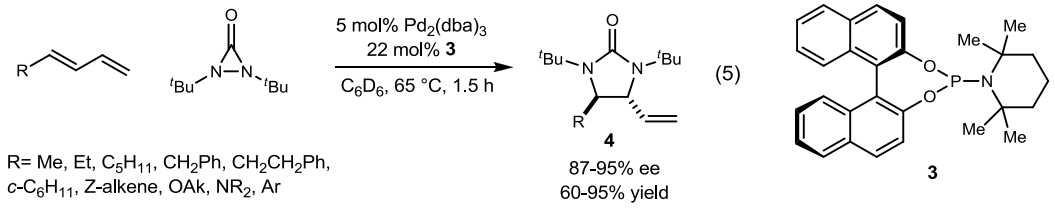


Stereoselective diamination of alkenes has been studied separately by Muniz and



Shi. Muniz was able to diaminate alkenes using osmium and a titanium TADDOL catalyst **2** for absolute stereocontrol, up to 90% ee (eq 4).[11] This method provided reasonable generality. The imide functionality is needed for this reaction to take place, but it can be easily converted to other functionalities like alcohols or carboxylic acids. The osmate imide is readily cleaved by hydride reduction.

Shi was also able to diaminate alkenes stereoselectively.[12] A palladium BINOL derived catalyst was employed to achieve high levels of enantioselectivity (eq 5). This

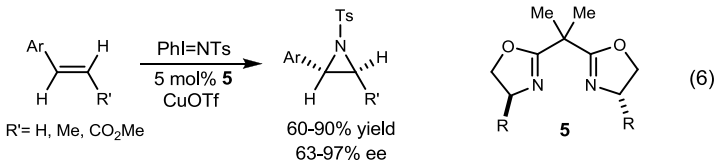


chemistry is limited to the use of dienes as starting materials. The resulting cyclic urea

[11] Almodovar, I.; Hövelmann, C. H.; Streuff, J.; Nieger, M.; Muñiz, K. *Eur. J. Org. Chem.* **2006**, 704-712.
[12] Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688-11689.

product **4** can be easily converted to a 1,2-diamine with a pendant vinyl group or to an 1,2-diamino acid.

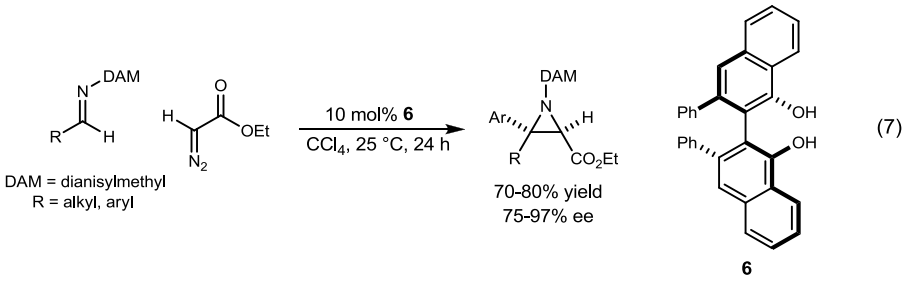
Evans explored the asymmetric aziridination of olefins to accomplish the task of making 1,2-diamines in equation 6.[13] A copper bis-oxazoline catalyst was used to affect



(6)

stereoselectivity. Enantiomerically enriched aziridines could then be opened stereospecifically with a nitrogen nucleophile to yield *anti*-1,2-diamines.

Wulff formed aziridines stereoselectively from *N*-dianisylmethylimines (eq 7).[14] The asymmetric catalyst used was a VANOL-borate system derived from triphenylborate



(7)

and VANOL ligand **6**.

Shibasaki also used aziridines to arrive at 1,2-diamines.[15] By desymmetrizing *meso*-aziridines, a variety of *syn*-1,2-diamines were synthesized (Scheme 3). This procedure was used to make Tamiflu (**7**) in 15 steps from a *meso*-aziridine.

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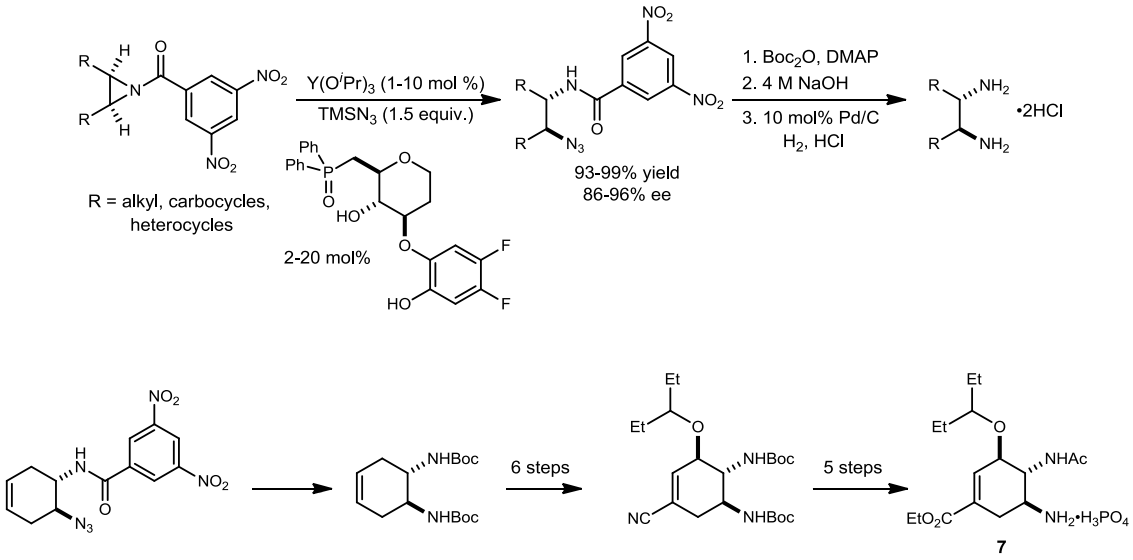
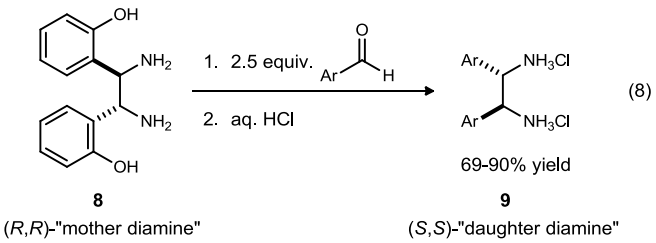
[13] Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328-5329.
[14] Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185-7194.
[15] Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312-6313.

Scheme 3. Shibasaki's Desymmetrization of *meso*-Aziridines and Application to Tamiflu



Chin and coworkers have extensively studied the stereospecific synthesis of C_2-symmetric diamines from the "mother diamine" through the diaza-Cope rearrangement (eq 8).[16] Enantiopurity of the "mother diamine" is maintained as (*R*,*R*) diamine **8** condenses with the aldehyde, undergoes rearrangement, and hydrolyzes to give the (*S*,*S*)-



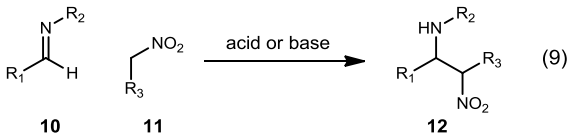
(8)

"daughter diamine" **9**. Electron-rich and electron-deficient aryl groups are tolerated and modest to good yields are seen. Still, this reaction relies on a stoichiometric chiral, non-racemic substrate.

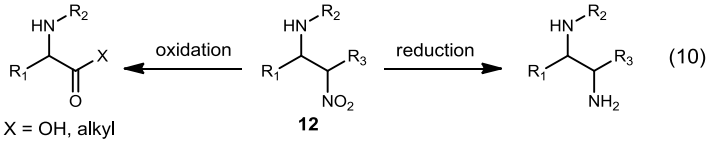
[16] Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184-12191.

1.2 Asymmetric Aza-Henry Reaction

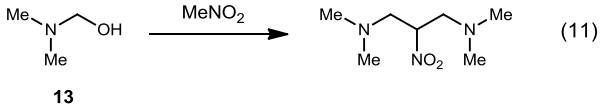
The aza-Henry, or nitro-Mannich, reaction is a C-C bond forming reaction in



which a nitroalkane (**11**) is added to an imine (**10**). This is typically with the aid of an acid or base catalyst. The α-nitro amine products (**12**) of this reaction can be readily transformed into useful products like 1,2-diamines, α-amino acids, or α-amino ketones (eq 10).



The aza-Henry reaction can be traced back to the discovery of nitroalkane additions to aldehydes by Henry in 1896.[17,18] At the same time, Henry outlined a reaction of a nitroalkane with two equivalents of a hemiaminal (eq 11). This reaction could be considered the first example of an aza-Henry reaction. This is simply a traditional Mannich reaction with a nitroalkane as the nucleophile and is also often referred to as a

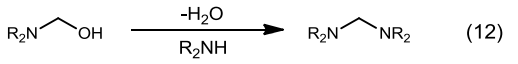


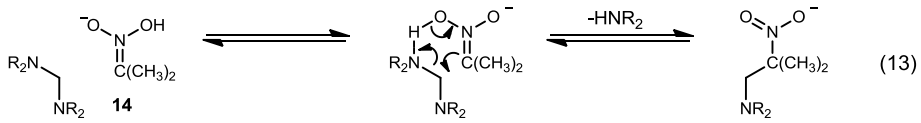
nitro-Mannich reaction. In 1937, Cerf extended the scope of the reaction.[19] Cerf claimed that only two equivalents of **13** will react with nitromethane and only one equivalent of **13** with react with any other nitroalkane. Subsequently, Senkus published work to the

[17] Henry, L. *Bull. Acad. Roy. Belg.* **1896**, *32*, 33.
[18] Henry, L. *Chem. Ber.* **1905**, *38*, 2027.
[19] Cerf de Mauney, C. d. *Bull. Soc. Chim. France* **1937**, *4*, 1451.

contrary in 1946 using primary amines and formaldehyde.[20] At the same time, Johnson used secondary amines to form hemiaminal precursors.[21]

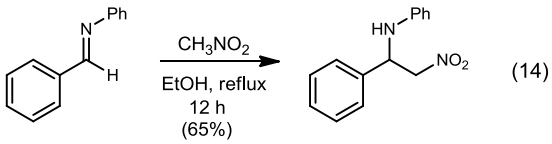
Further developments were not made until the late 1950s when mechanistic studies were performed. Butler proposed that the hemiaminal formed the *gem*-diamine prior to attack from the nitroalkane (eq 12).[22] Then, Fernandez proposed that the *aci*-nitroalkane (**14**, eq 13), analogous to the enol tautomer of a ketone, was the active form





involved in the transition state.[23,24]

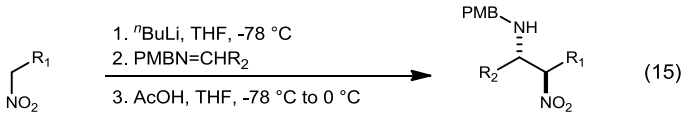
The traditional aza-Henry reaction using an imine (instead of a hemiaminal) and



nitroalkane was not reported until 1950. Hurd and Strong performed a nitromethane addition to *N*-phenylbenzylimine to give the aza-Henry product in 65% yield (eq 14).[25] A similar reaction was also performed with nitroethane in this report, but there was no mention of diastereoselectivity.

[20] Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10-12.
[21] Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12-14.
[22] Butler, G. B. *J. Am. Chem. Soc.* **1956**, *78*, 482-484.
[23] Fernandez, J. E.; Fowler, J. S. *J. Org. Chem.* **1964**, *29*, 402-407.
[24] Fernandez, J. E.; Fowler, J. S.; Glaros, S. J. *J. Org. Chem.* **1965**, *30*, 2787-2791.
[25] Hurd, C. D.; Strong, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4813-4814.

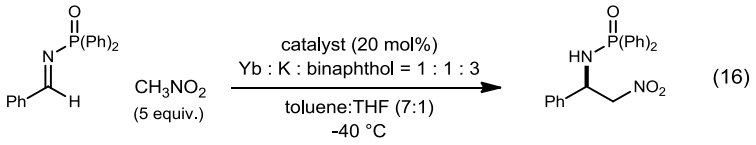
In 1998, Anderson used the aza-Henry reaction as an approach to 1,2-diamines.[26] He added alkyl nitronate anions to *para*-methoxy benzylimines in the presence of a



(15)

Brønsted acid and observed good diastereoselection in a few cases (eq 15). The aza-Henry products were then reduced with SmI_2 and deprotected with ceric ammonium nitrate to give free diamines.

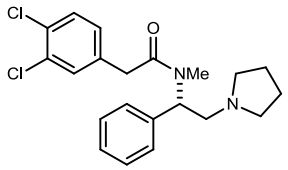
Just one year later, Shibasaki reported a catalytic enantioselective aza-Henry reaction (eq 16). A heterobimetallic complex consisting of $Yb(O^iPr)_3$, KO^tBu, and (*R*)-binaphthol was used to achieve enantioselection up to 91% ee.[27] This catalyst system however failed to catalyze the addition of nitroethane into the phosphonyl imine. An



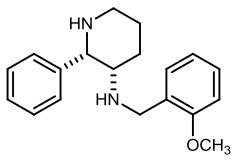
(16)

AlLi[(*R*)-binaphthoxide]$_2$ complex was used to give as high as 83% ee and 7:1 dr with nitroethane additions.[28,29] Shibasaki used this chemistry to synthesize two biologically active compounds, ICI-199441 and CP-99994 (Figure 3).[30] Not only was this a good

Figure 3. Biologically Active 1,2-Diamines Synthesized by Shibasaki



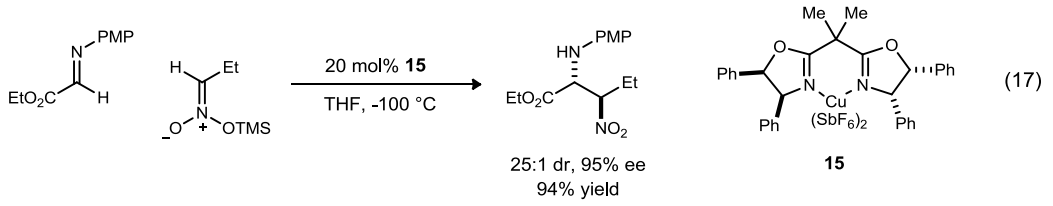
ICI-199441



CP-99994

[26] Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932-9934.
[27] Yamada, K.; Harwood, S. J.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504-3506.
[28] Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980-982.
[29] Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511-524.
[30] Tsuritani, N. Y., K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, *31*, 276.

demonstration of the generality of this catalyst system, but it also showed the advantage of using the asymmetric aza-Henry reaction as a synthetic method. Previously, these compounds were made by functional group transformations starting from an amino acid. The aza-Henry reaction provided a more straightforward route to these compounds.



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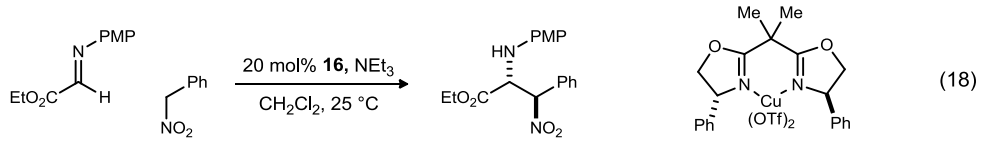
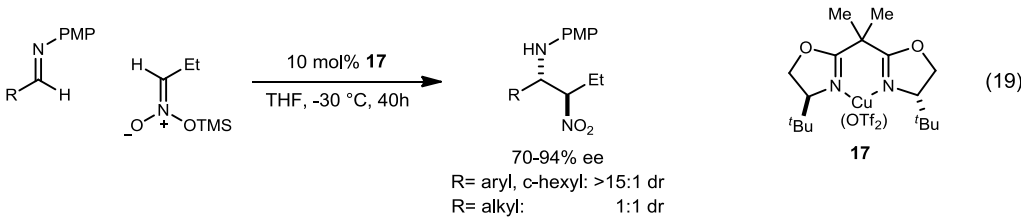


(18)

Shortly after Shibasaki's initial findings, others reported metal-catalyzed enantioselective aza-Henry reactions.[31] In 2001, Jorgensen reported a Cu-Box catalyzed aza-Henry reaction of silyl nitronates to α-imino esters (eq 17).[32] As high as 25:1 dr and 95% ee was achieved with catalyst **15**. Under different conditions, Jorgensen also added

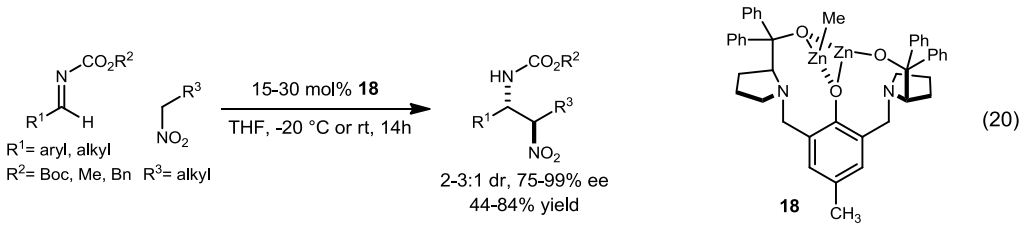


(19)

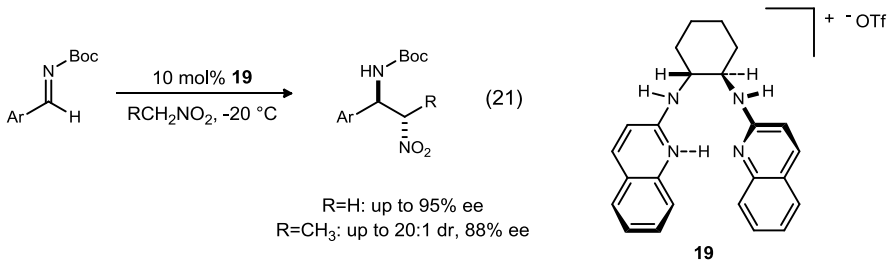
phenylnitromethane to an α-imino ester with low diastereoselection and modest enantioselection (eq 18).[33] In 2005, Anderson also used Cu-Box catalyst **17** for

[31] A review on catalytic enantioselective aza-Henry reactions: Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401-2420.
[32] Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843-5844.
[33] Nishiwaki, N.; Rahbek Knudsen, K.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992-2995.

enantioselective reactions using aryl and alkyl imines (eq 19).[34] More recently, Trost used bimetallic zinc catalyst **18** to achieve good enantioselectivity albeit with low diastereocontrol (eq 20).[35]

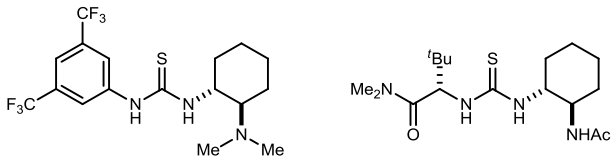


In 2004, Johnston reported organocatalyzed aza-Henry reactions using bisamidine catalyst **19** (eq 21). This work will be discussed in great detail in Chapter 2 of this document.



Much progress has been made recently with metal-free organocatalyzed aza-Henry reactions. In work published near the same time, Takemoto and Jacobsen

Figure 4. Takemoto and Jacobsen's Thiourea Catalysts

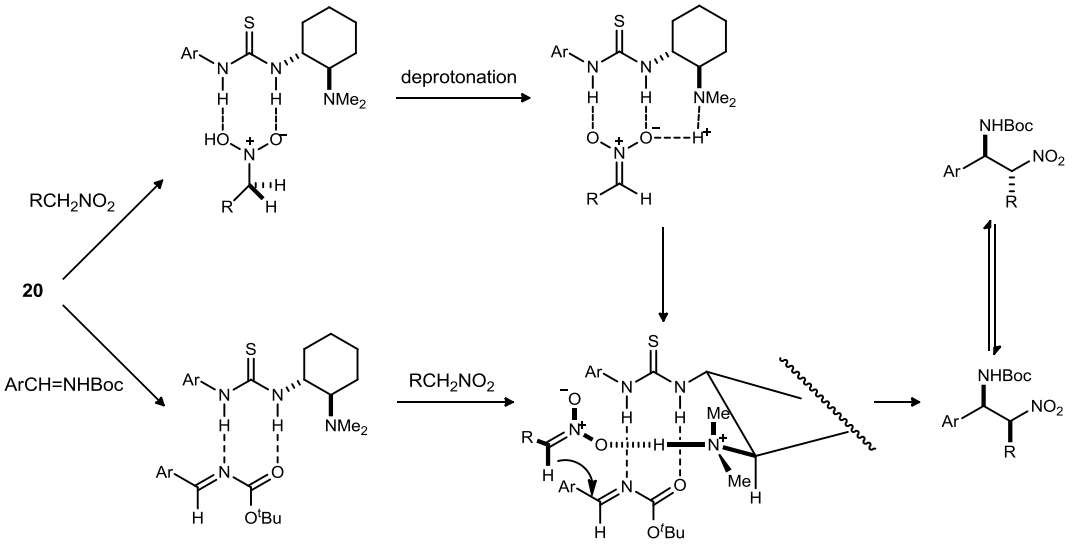


demonstrated aza-Henry reactions promoted by similar thiourea catalysts, **20** and **21** (Figure 4) respectively.[36,37] Takemoto used this asymmetric aza-Henry reaction to make

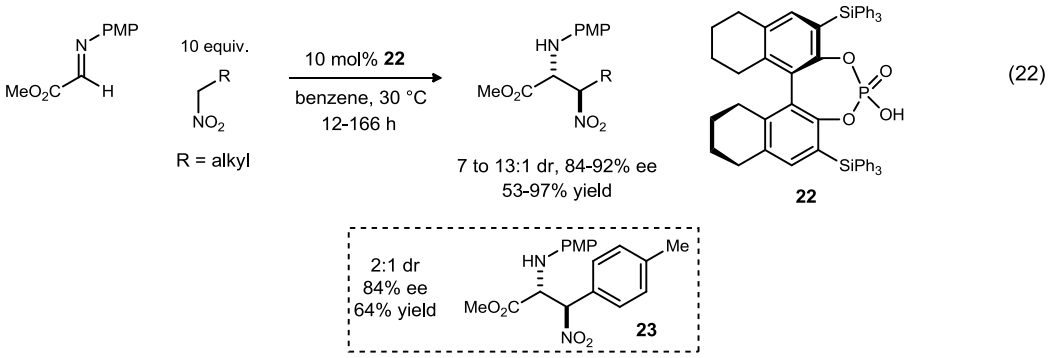
[34] Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665-5670.
[35] Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023-2026.
[36] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625-627.
[37] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466-468.

two biologically active piperidines. Takemoto proposes two different modes of activation that each involve a bifunctional catalyst (Scheme 4).[38] The thiourea N-H protons are crucial for stereochemical induction while the tertiary amine is responsible for deprotonation of the nitroalkane.

Scheme 4. Proposed Reaction Process of Thiourea Catalyzed Aza-Henry Reaction



Rueping demonstrated the use of a chiral BINOL-based phosphoric acid catalyst to promote the asymmetric aza-Henry reaction (eq 22).[39] The addition of aliphatic nitroalkanes to α-imino esters was accomplished with 7-13:1 dr, 84-92% ee and modest to good yield. One example of an aryl nitroalkane addition was given as compound **23**

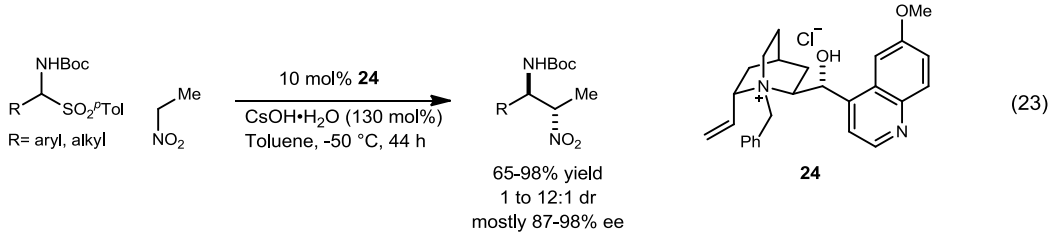


(22)

[38] Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466-476.
[39] Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731-1734.

was synthesized in 2:1 dr and 84% ee.

A phase-transfer catalysis approach to the asymmetric aza-Henry reaction has been demonstrated by Palomo.[40] A cinchona based phase transfer catalyst **24** in combination with exogenous base CsOH is used in equation 23. This reaction starts from the α-amido sulfone, forms the *N*-Boc imine *in situ*, and forms the aza-Henry adduct in one pot. This procedure circumvents some of the practical issues of using pre-formed *N*-Boc imines that typically have a short bench lifetime. Aside from the obvious advantage of eliminating a discreet synthetic step, this allows for use of bench stable solids as starting materials.[41] Also enolizable alkyl *N*-Boc imines are formed *in situ* and used in this reaction. Aryl and alkyl α-amido sulfones were used to produce adducts in consistently high ee and varying dr.



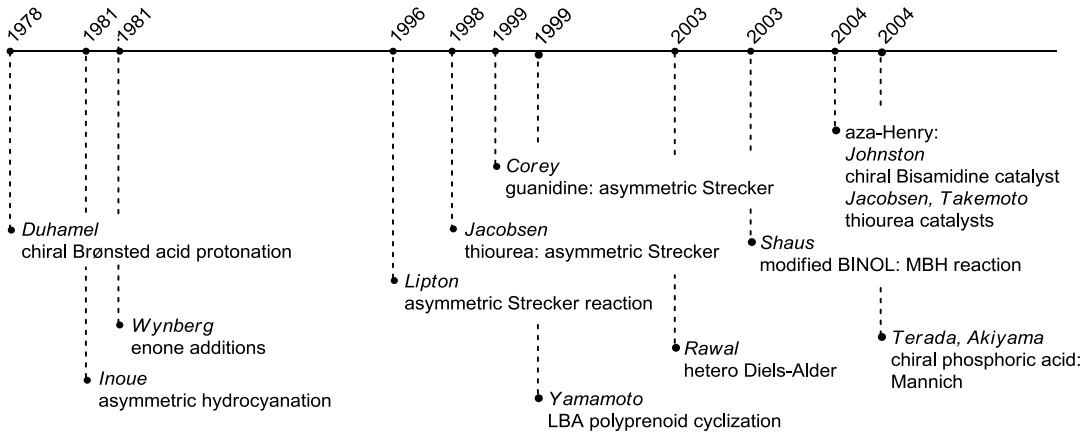
(23)

[40]Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955-7966.
[41] Petrini, M. *Chem. Rev.* **2005**, *105*, 3949-3977.

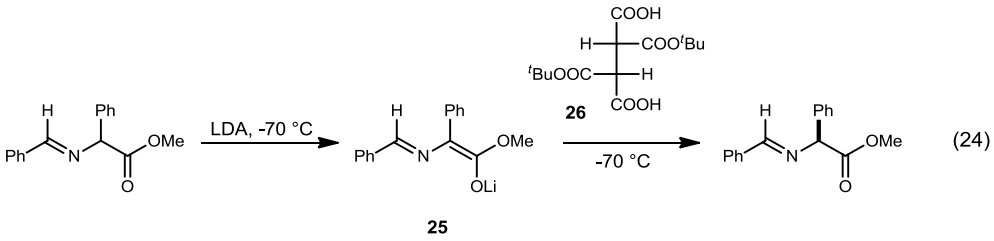
1.3 Asymmetric Brønsted Acid Catalysis

Asymmetric Brønsted acid catalysis is a relatively new area of study by organic chemists. It is essential for chemists to seek ways to enhance reaction rates and make compounds in an efficient and inexpensive manner. Still, much of the driving force for this area is the desire to use "greener" organic materials that do not involve the use of toxic metal-based Lewis acids. Brønsted acid catalysts have been studied since the

Figure 5. Timeline of Asymmetric Brønsted Acid Catalysis



earliest days of organic chemistry, but asymmetric Brønsted acid catalysis has only been the focus of study recently. For the sake of brevity, the discussion will be focused on systems where the primary mode of asymmetric induction is binding noncovalently to a Brønsted acid (not the use of iminium ion or enamine catalysis). This section is organized by catalyst type. For the sake of chronology, a timeline of important accomplishments in asymmetric Brønsted acid catalysis is presented in Figure 5.



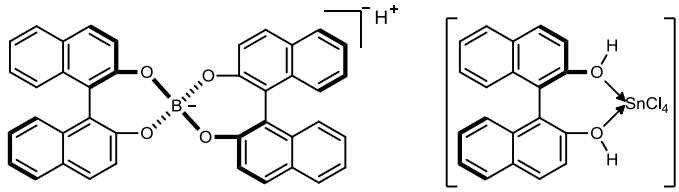
25

(24)

Duhamel's use of a chiral Brønsted acid **26** to enantioselectively protonate a lithium enolate **25** in equation 24 can be viewed as a starting point for asymmetric Brønsted acid catalysis.[42] This is simply an asymmetric protonation which has been demonstrated numerous times.[43] The use of hydrogen bonds to accelerate reactions and to perform reactions enantioselectively will be discussed.

It was ultimately Yamamoto that pioneered the concept of asymmetric Brønsted acid catalysis in the mid 1990s. In earlier work, he used Brønsted acid assisted chiral

Figure 6. Yamamoto's BLA and LBA Catalysts



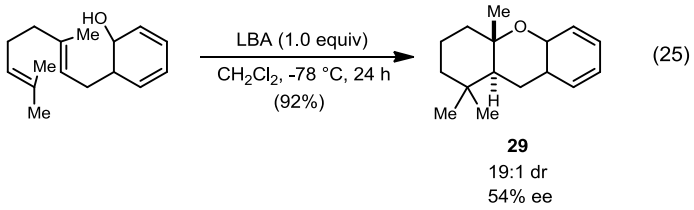
BLA **LBA**

27 **28**

Lewis acids (**27**).[44,45] Although it is not a purely Brønsted acid catalyst, a Lewis acid assisted chiral Brønsted acid (**28**) is different from BLA. A BLA is presumed to both activate and direct a substrate using the chiral Lewis acid center, while the Brønsted acid acts as a secondary control element. In contrast, an LBA activates the substrate through the chiral Brønsted acid, while the Lewis acid serves only as a means by which the Brønsted acid is activated.

[42] Duhamel, L.; Plaquevent, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 7415-7416.
[43] Fehr, C. *Angew. Chem. Int. Ed.* **1996**, *35*, 2566-2587.
[44] Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561-1562.
[45] Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520-10524.

Yamamoto used LBA in a groundbreaking report in 1999 to promote a

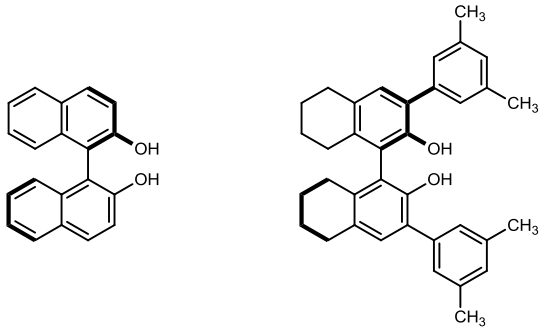


(25)

29
19:1 dr
54% ee

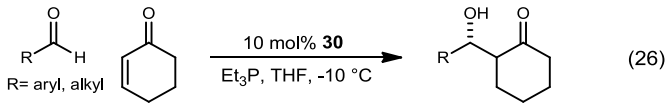
biomimetic polyprenoid cyclization (eq 25).[46] Using LBA as a chiral proton donor, a polycyclic terpenoid **29** was constructed in a single step stereoselectively. This was the first example of an enantioselective biomimetic cyclization of polyprenoids.

Figure 7. Chiral Alcohol Catalysts



(*R*)-BINOL **30**

Many examples of chiral alcohol Brønsted acids emerged beginning in 2003. In that year, Shaus demonstrated an enantioselective Morita-Baylis-Hillman reaction (eq 26)

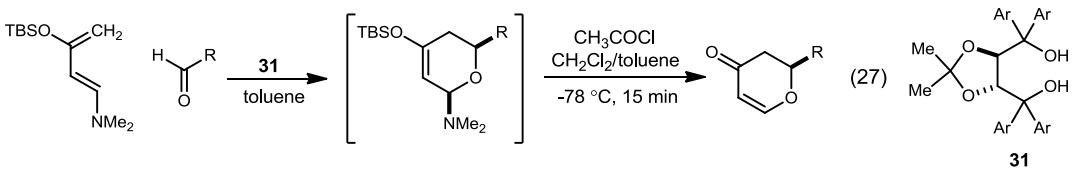


(26)

using a chiral Brønsted acid **27** (Figure 7).[47] Schaus used a modified BINOL framework to achieve as high as 96% ee with aliphatic aldehydes.

[46] Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906-4907.
[47] McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094-12095.

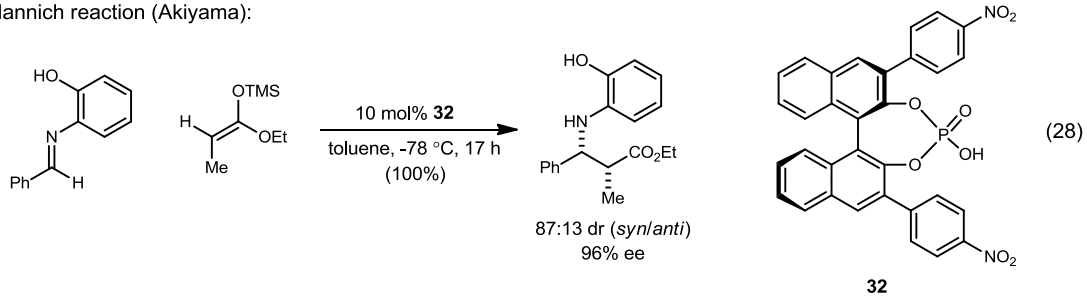
In a report published in *Nature* in 2003, Rawal used a TADDOL chiral diol catalyst **31** to promote hetero Diels-Alder reactions with excellent enantioselectivity (eq 27).[48] Interestingly, Rawal compares this type of catalysis to enzymes, suggesting that



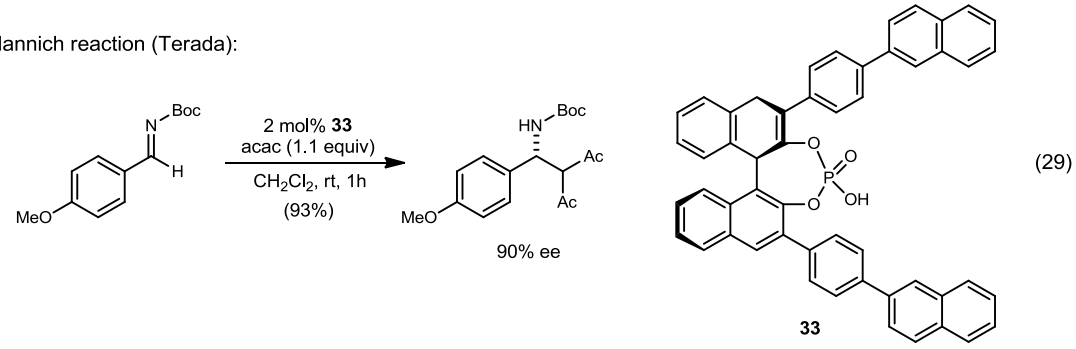
this is a more biomimetic form of traditional Lewis acid catalysis.

Phosphoric acids based on the BINOL framework have become versatile catalysts capable of promoting a variety of reactions.[49] Akiyama (eq 28) and Terada (eq 29) have each demonstrated the utility of these catalysts. Each demonstrated an asymmetric Mannich reaction with their respective catalysts.[50,51]

Mannich reaction (Akiyama):



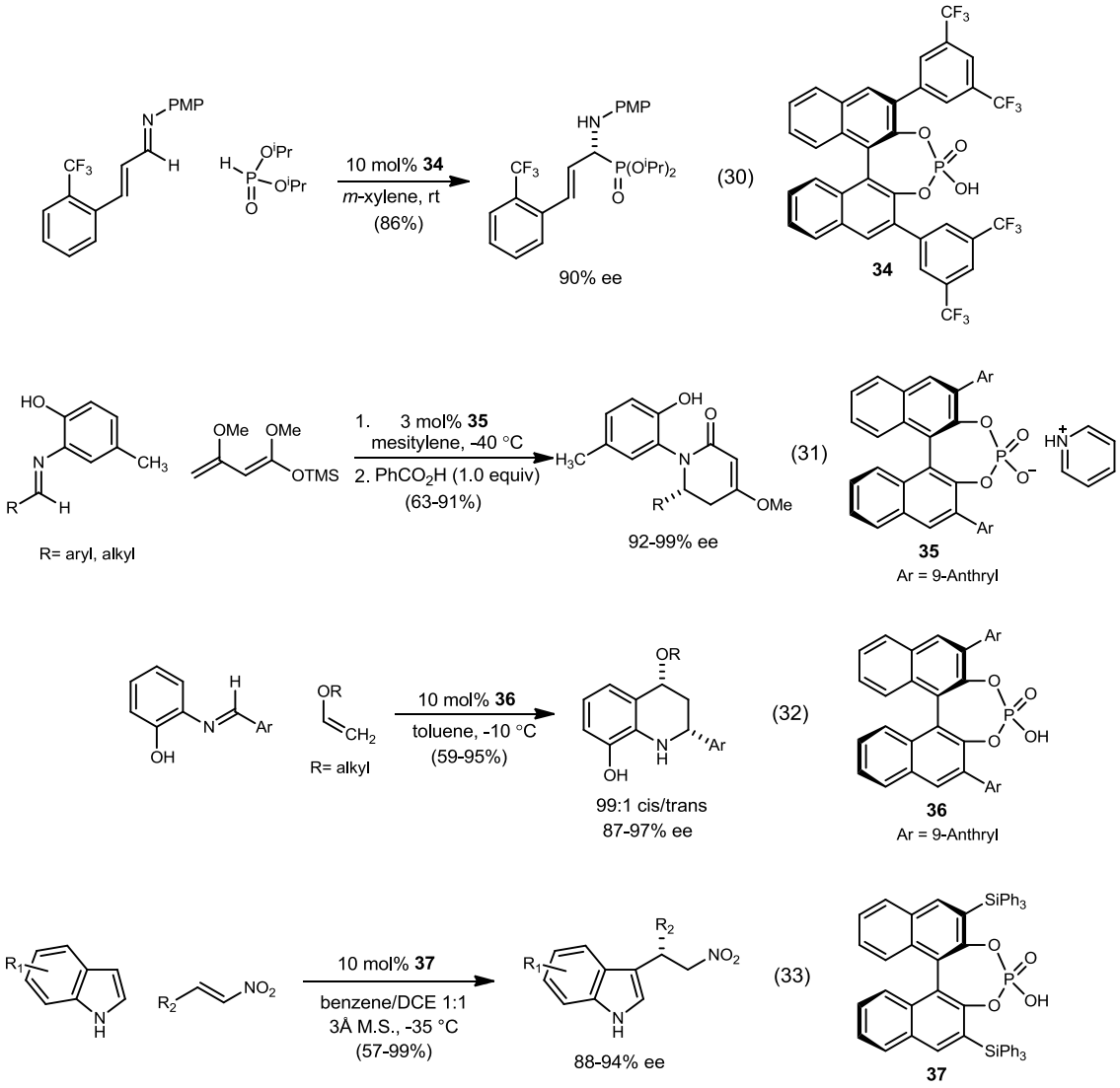
Mannich reaction (Terada):



[48] Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.
[49] Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262-5276.
[50] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566-1568.
[51] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357.

A myriad of reactions catalyzed by these chiral phosphoric acids have since been reported both by Akiyama and Terada. Akiyama was able to use chiral phosphoric acids to perform C-phosphonylation of imines (eq 30)[52], hetero-Diels-Alder reactions (eq 31, 32)[53,54], and Friedel-Crafts alkylations (eq 33).[55]

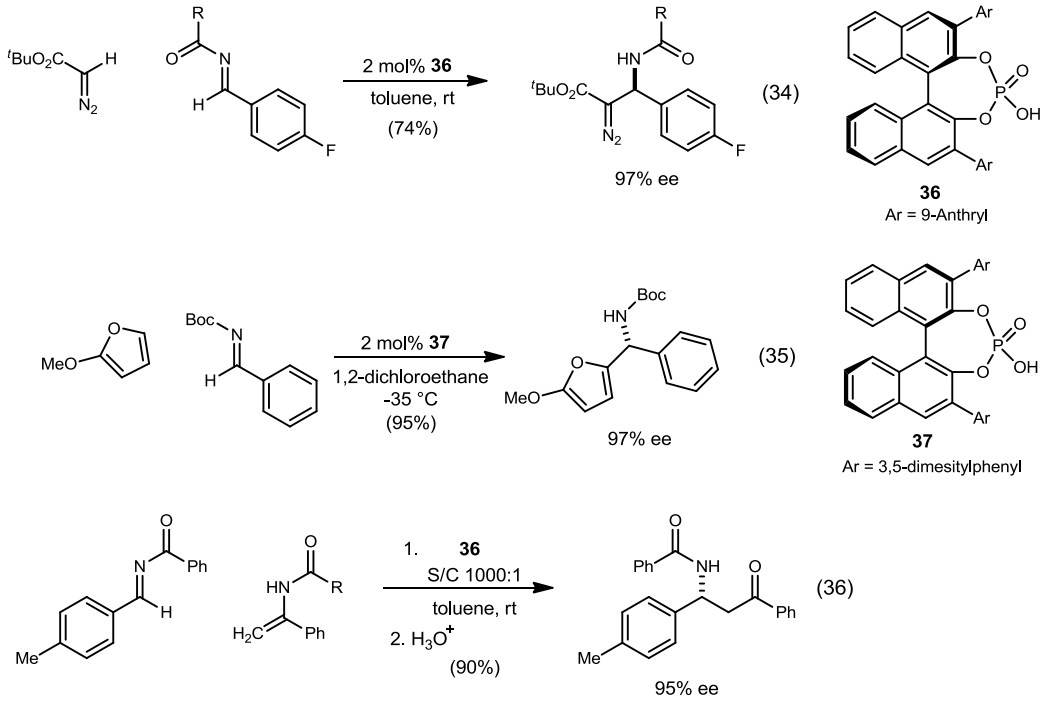
Scheme 5. Chiral Phosphoric Acid Catalyzed Asymmetric Reactions Reported by Akiyama



[52] Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583-2585.
[53] Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796-4798.
[54] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070-13071.
[55] Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016-4018.

Similarly, Terada has used BINOL-derived phosphoric acids to promote asymmetric alkylations of α-diazoesters (eq 34)[56], Friedel-Crafts reactions of furan (eq 35)[57], and aza-ene-type reactions (eq 36).[58]

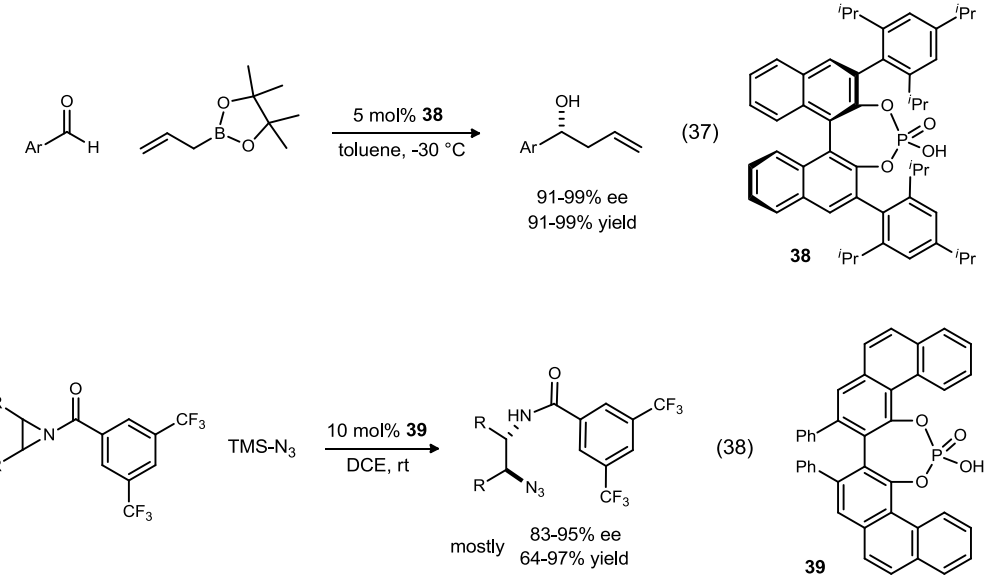
Scheme 6. Chiral Phosphoric Acid Catalyzed Asymmetric Reactions Reported by Terada



A vast majority of the phosphoric acid-catalyzed reactions published involve additions to imines or Friedel-Crafts type additions. More recent reports have displayed work outside of these areas. Antilla has demonstrated the use of chiral phosphoric acids (Scheme 7) in the desymmetrization of *meso*-aziridines[59] (eq 37) and the allylboration of aldehydes[60] (eq 38).

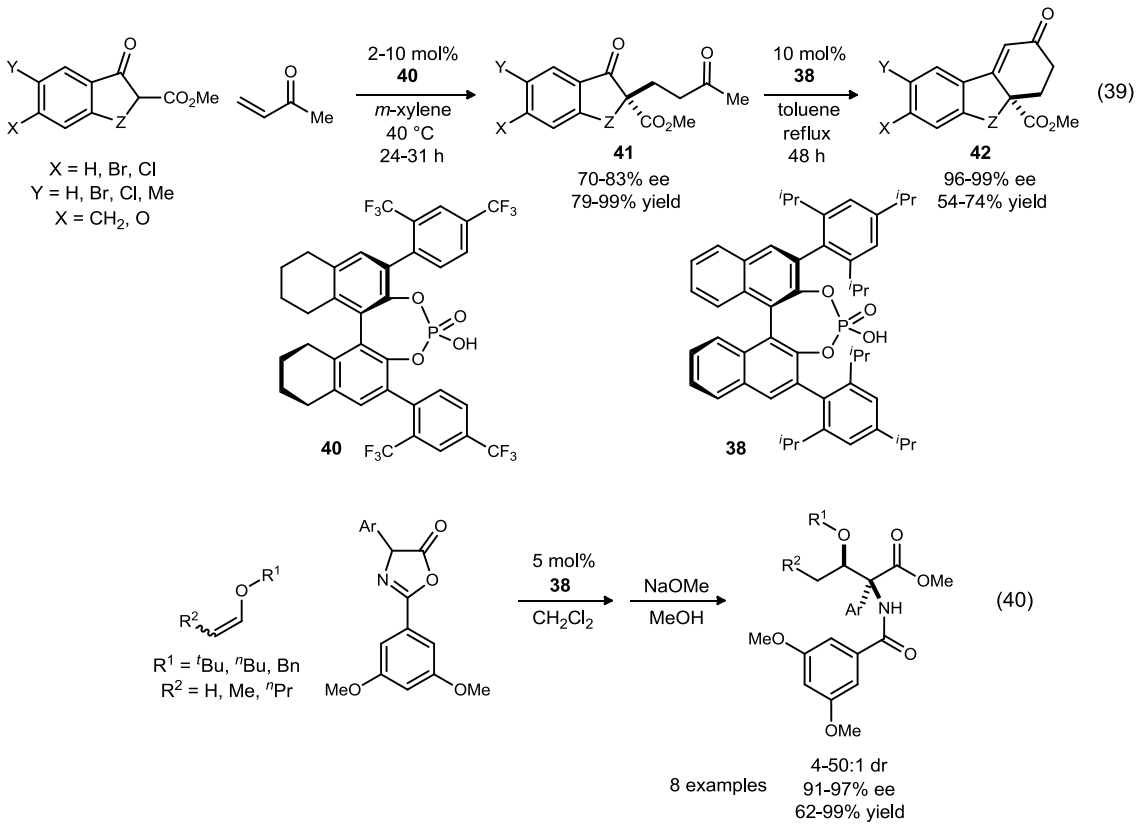
[56] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360-9361.
[57] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804-11805.
[58] Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2254-2257.
[59] Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084-+.
[60] Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884-11886.

Scheme 7. Examples of Chiral Phosphoric Acid-Catalyzed Reactions by Antillla



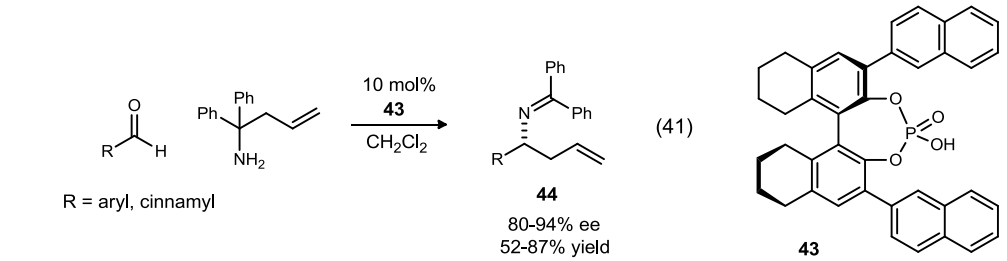
Akiyama has demonstrated chiral Brønsted acid-catalyzed Robinson annulations (eq 39).[61] First, phosphoric acid catalyst **40** promotes the Michael addition to form **41**. Then, a kinetic resolution takes place in the presence of catalyst **38** to preferentially convert one enantiomer of **41** to annulation product **42**. Terada also used catalyst **38** to perform a direct aldol-type reaction of azlactones (eq 40).[62] The vinyl ether is presumably protonated by the acid catalyst to form a hydrogen-bonded ion pair that serves to induce enantioselectivity.

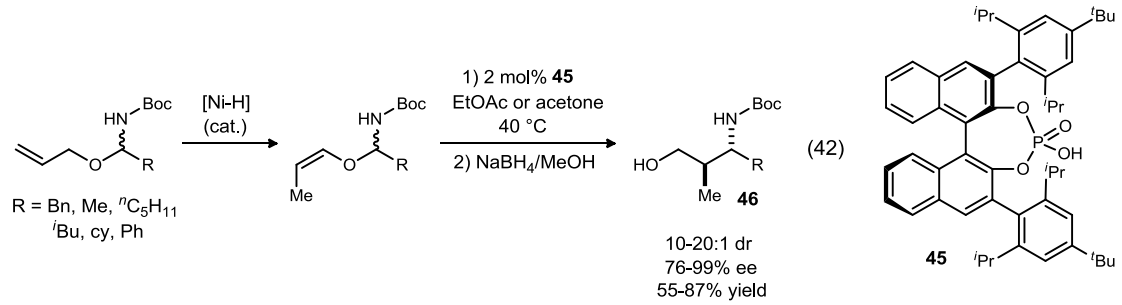
[61] Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4226-4228.
[62] Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430-3431.



Examples of chiral phosphoric acid-catalyzed rearrangements have recently surfaced. Reuping has developed a catalytic, enantioselective aza-Cope rearrangement using catalyst **43** to form homoallylic amine precursor **44** in good enantioselection (eq 41).[63] An enantioselective aza-Petasis-Ferrier rearrangement (eq 42) has been demonstrated by Terada.[64] A Ni-catalyzed olefin isomerization, enantioselective rearrangement catalyzed by **45**, and subsequent aldehyde reduction yielded amino alcohol **46** with good enantio- and diasteroselectivity.

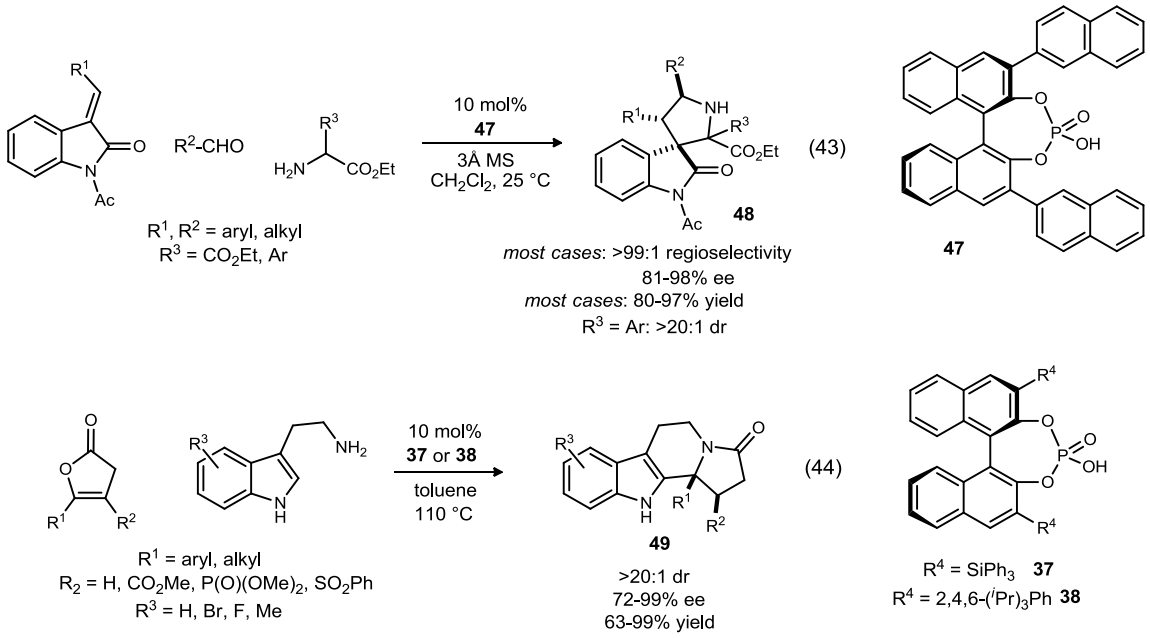
[63] Rueping, M.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 10090-10093.
[64] Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354-6355.





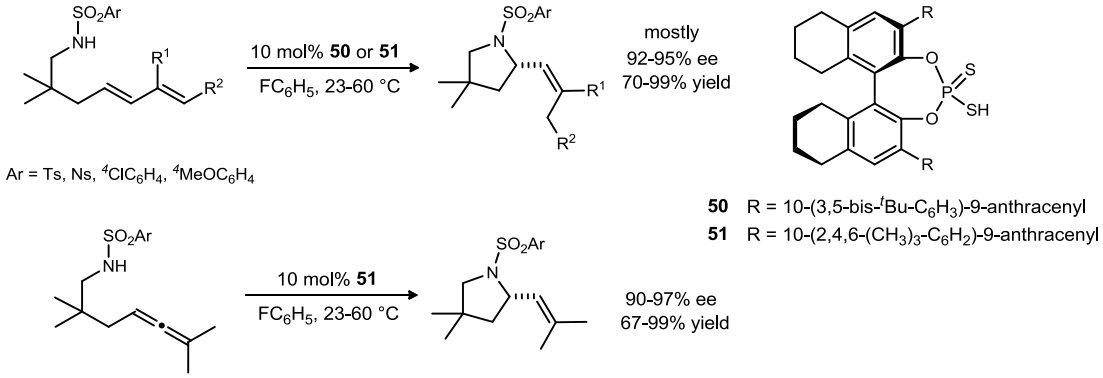
Multi-component and cascade reactions promoted by chiral phosphoric acids have allowed for the enantioselective synthesis of highly complex molecules in a single reaction. Gong has reported a multicomponent asymmetric catalytic three-component 1,3-dipolar cycloaddition (eq 43).[65] Products **48** containing up to two newly formed quaternary stereocenters are obtained in remarkably high regio- and stereoselectivity using catalyst **47**. A Brønsted acid-catalyzed cyclization cascade of *N*-acyliminium ions was demonstrated by Dixon in equation **44**.[66] Phosphoric acids **37** and **38** promoted this reaction to give tetracyclic products **49** with good to excellent stereoselectivity and yield.

[65] Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819-13825.
[66] Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796-10797.



Toste has recently published a report in *Nature* describing asymmetric additions to unactivated alkenes catalyzed by a dithiophosphoric acid (Scheme 8).[67] This intramolecular hydroamination of dienes catalyzed by **50** or **51** or proceeds with excellent enantioselectivity and *E*:*Z* selectivity in most cases. Apart from being a novel transformation, this reaction also is mechanistically distinct from simple hydrogen bond activation. Studies revealed that the phosphoric adds to the diene in an S_N2' fashion then a subsequent S_N2' displacement leads to the product.

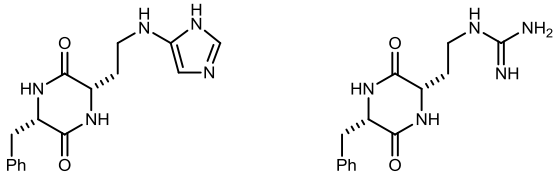
Scheme 8. Toste's Intramolecular Dithiophosphoric Acid-Catalyzed Hydroamination



[67] Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245-249.

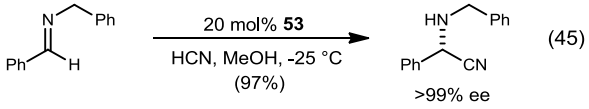
Much success has also been achieved using protonated amines as chiral Brønsted acids. A very early example of this work was demonstrated by Inoue in 1981.[68] He used a dipeptide catalyst **52** to promote an asymmetric hydrocyanation of benzaldehyde that gave >99% ee for some substrates. Still, the reaction suffered from racemization if allowed to go to full conversion.

Figure 8. Inoue and Lipton's Dipeptide Catalysts



52 **53**

Lipton used a strikingly similar catalyst **53** to do asymmetric Strecker reactions (eq 45).[69] This reaction gave products of high enantiopurity and high yields. This reaction did not prove to be general though.

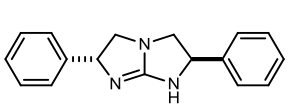


(45)

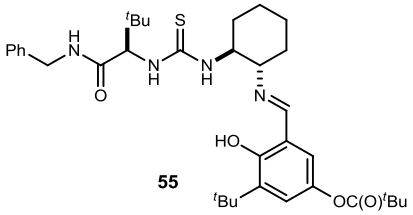
Corey and Jacobsen soon developed novel catalysts for use in the asymmetric Strecker reaction (**54** and **55** respectively).[70,71,72] Both catalysts gave the α-aminonitrile products in high yield and excellent enantioselectivities.

[68] Oku, J. I.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229-230.
[69] Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910-4911.
[70] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157-160.
[71] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.
[72] Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281.

Figure 9. Corey's Guanidine and Jacobsen's Thiourea Catalysts



54

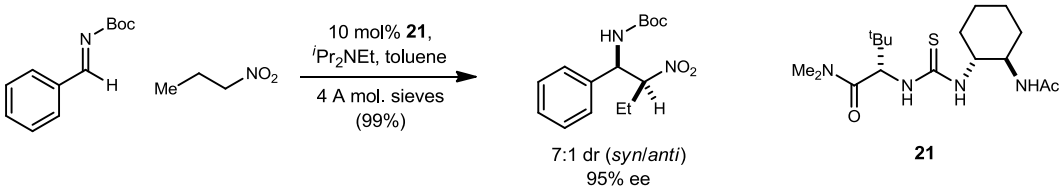


55

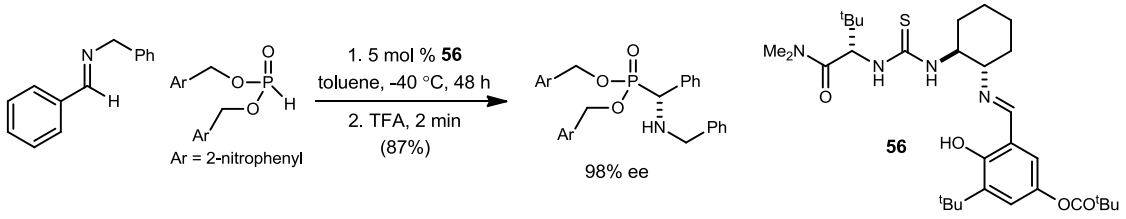
Jacobsen soon expanded the utility of this thiourea type catalyst. With some slight modifications of catalyst **55**, the ability to promote a plethora of asymmetric reactions

Scheme 9. Asymmetric Reactions Catalyzed by Jacobsen's Thiourea Derivatives

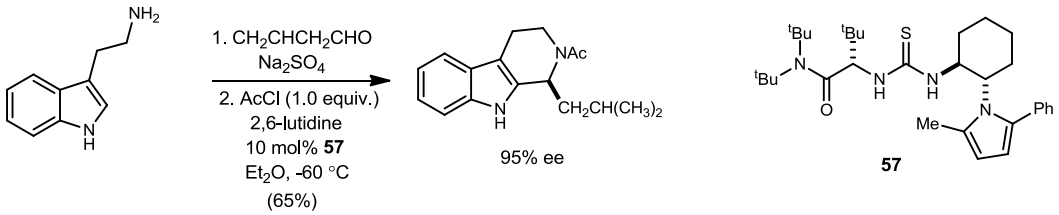
Nitro-Mannich Reaction:



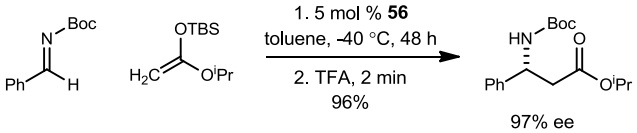
Hydrophosphonylation:



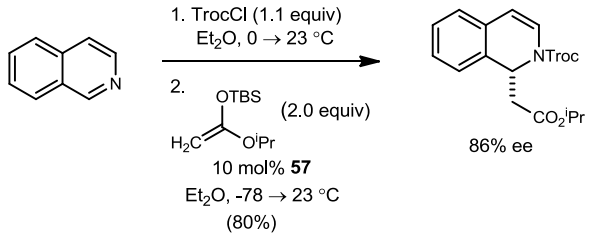
Acyl Pictet-Spengler Reaction:



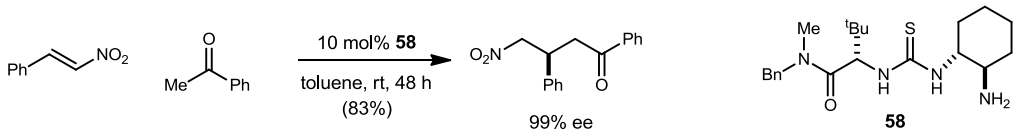
Mannich Reaction:



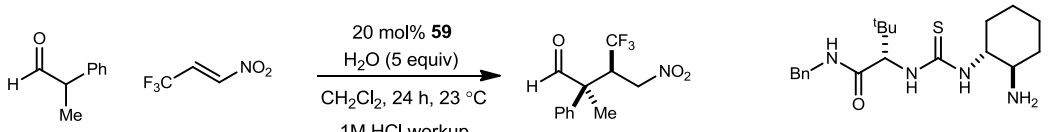
Acyl-Mannich Reaction:



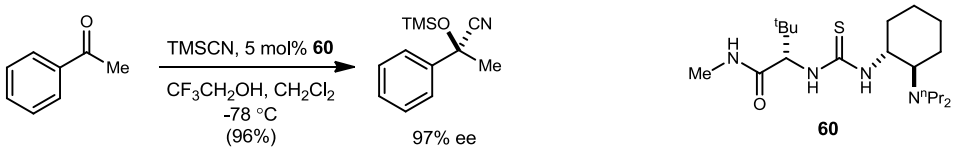
Conjugate Addition of Ketones to Nitroalkenes:



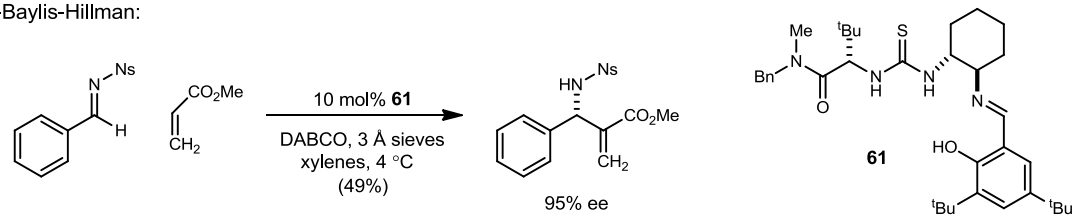
Conjugate Addition of α,α-disubstituted Aldehydes to Nitroalkenes:



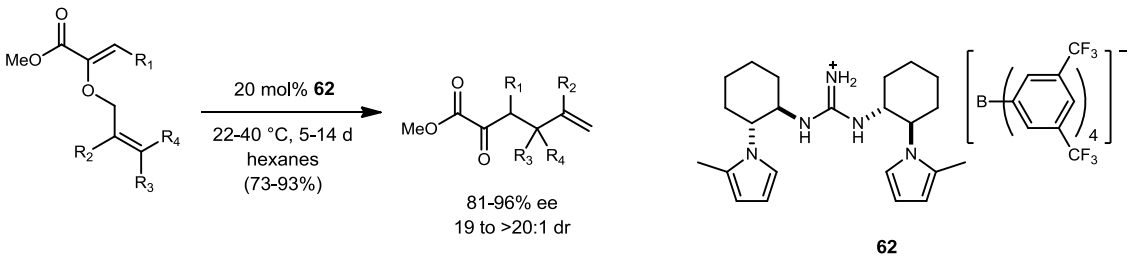
Cyanosilylation of Ketones:



Aza-Baylis-Hillman:



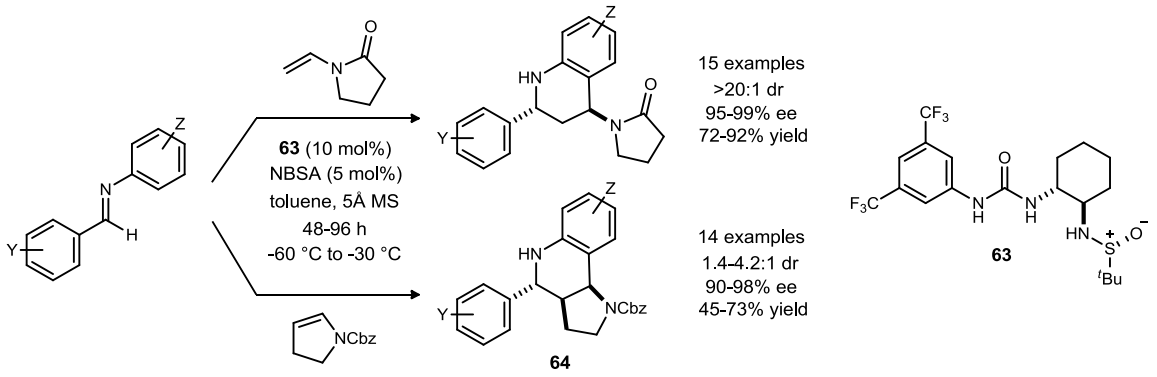
Claisen Rearrangement:



was exhibited. Nitro-Mannich reactions[73], hydrophosphonylations[74], acyl Pictet-Spengler reactions[75], Mannich[76] and acyl-Mannich reactions[77], conjugate additions of ketones and α,α-disubstituted aldehydes to nitroalkenes[78,79], cyanosilylations of ketones[80], aza-Baylis-Hillman reactions[81], and Claisen reaarrangements[82] have all been demonstrated and shown in Scheme 9.

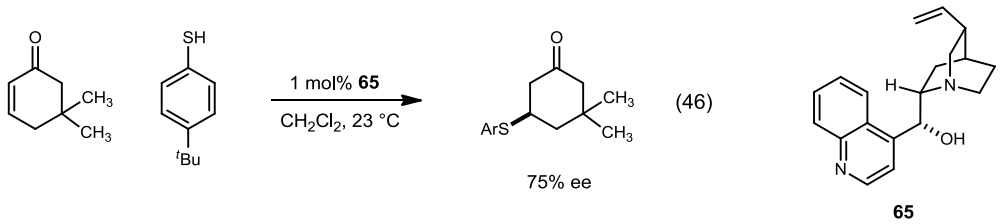
An impressive amount of progress has been made in a very short amount of time by Jacobsen. These thiourea catalysts are shown to be very versatile and useful tools for the synthesis of complex stereoenriched products. This is exemplified in their use in the asymmetric Povarov reaction (Scheme 10).[83] Urea catalyst **63** promotes the formation of two new carbon-carbon bonds and up to three stereocenters (compound **64**) with high stereoselectivity.

Scheme 10. Chiral Urea Catalyzed Povarov Reaction



[73] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466-468.
[74] Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102-4103.
[75] Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558-10559.
[76] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965.
[77] Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700-6704.
[78] Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170-7171.
[79] Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 6366-6370.
[80] Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964-8965.
[81] Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701-1708.
[82] Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228-9229.
[83] Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986-990.

Another catalyst motif that has found much use in asymmetric Brønsted acid catalysis not discussed thus far is the cinchona alkaloids. The pioneering work in this field was done by Wynberg in 1981.[84] He screened a number of cinchona and ephedra alkaloids containing a hydroxyl group and developed enantioselective 1,2- and 1,4-conjugate additions to enones (eq 46). The free hydroxyl group was found to be crucial

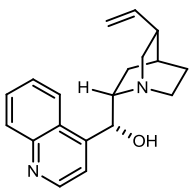


for high levels of enantioselection. Wynberg's work seemed to be well ahead of its time as unfortunately further advances with cinchona alkaloid based asymmetric catalysts were not made until many years later.

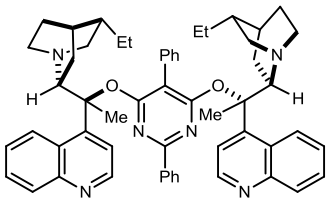
In 2002, Deng published work using an unnatural biscinchona alkaloid **66** to do 1,4-additions with thiols that paralled the work of Wynberg.[85] The mechanism of induction here was shown to be different from that of the natural cinchona alkaloids used by Wynberg. A free hydroxyl was not necessary for enantioselection, and the bisalkaloid derived from the same enantiomer of natural alkaloid gave the opposite enantioselection as the natural alkaloid.

[84] Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417-430.
[85] McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed.* **2002**, *41*, 338-340.

Figure 10. Cinchona Alkaloid Comparison



65



66

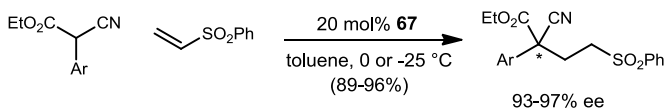
In work published in 2005, Deng used a different cinchona alkaloid to perform conjugate additions to vinyl sulfones (Scheme 8).[86] The 9' –OH group of catalyst **50** was replaced with an aryl ether and a hydroxyl group was added to the quinoline ring to give a catalyst that led to high levels of stereoselection.

Deng also used cinchona alkaloids to perform other asymmetric reactions (Scheme 11). Enone conjugate additions similar to those demonstrated by Wynberg but again with an unnatural alkaloid were performed.[87] Also, Friedel-Crafts reactions between imines and indoles were demonstrated with a cinchona derived-thiourea catalyst.[88] Unnatural alkaloid **70** was used to promote the Diels-Alder reaction between pyrones and α,β-unsaturated esters with good enantio- and diastereoselectivity.[89]

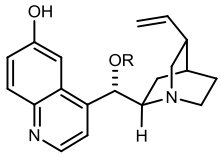
[86] Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948-8949.
[87] Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 947-950.
[88] Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156-8157.
[89] Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364-6365.

Scheme 11. Asymmetric Reactions Catalyzed by Cinchona Alkaloids by Deng

Vinyl Sulfone Conjugate Addition:

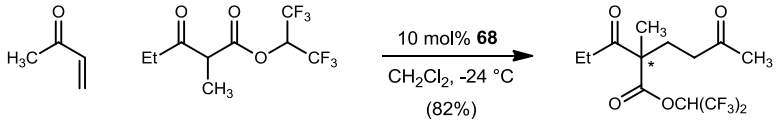


93-97% ee

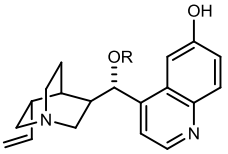


67
R= 9-phenanthryl

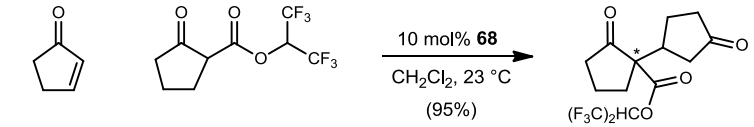
Enone Conjugate Addition:



90% ee

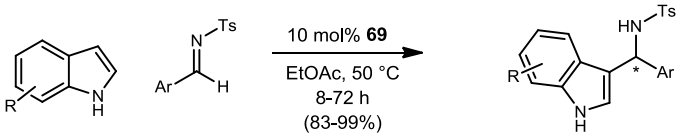


68
R= 9-phenanthryl

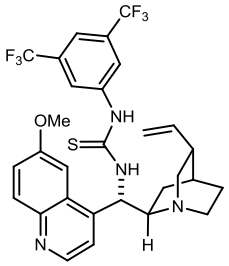


13:1 dr
95% ee

Friedel-Crafts:

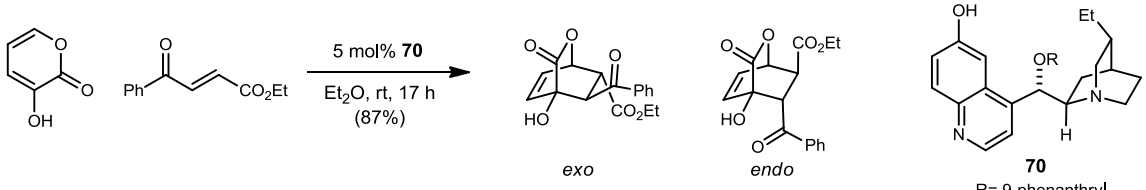


83-97% ee



69
R= 9-phenanthryl

Diels-Alder:

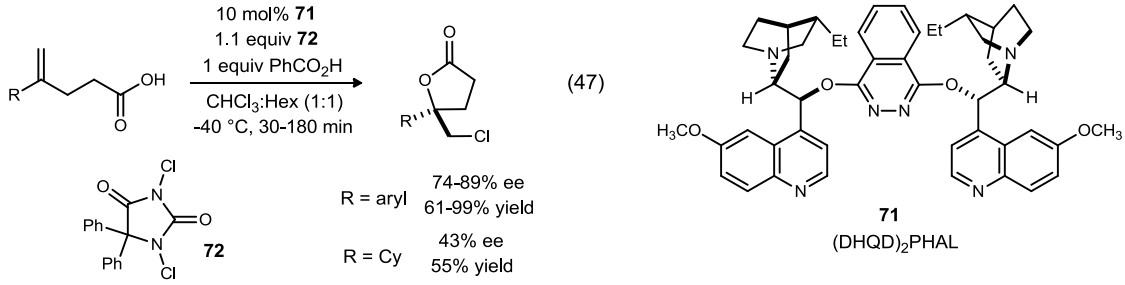


exo *endo*

13:1 dr (*exo*:*endo*)
94% ee

70
R= 9-phenanthryl

A catalytic asymmetric electrophilic halogenation has been accomplished with a cinchona alkaloid catalyst. Borhan has recently described an organocatalytic asymmetric chlorolactonization using $(DHQD)_2PHAL$ (**71**) (eq 47).[90] It seems likely that the protonated chiral amine is promoting enantioselection through hydrogen bonding, but it is also possible that the amine is affecting enantioselection through the covalent formation of a chiral chlorenium source. Nevertheless, this represents a powerful new mode of activation potentially achieved through chiral Brønsted acid catalysis.



(47)

The work described thus far has been focused around three general catalytic motifs: BINOL, chiral urea/thiourea, and cinchona alkaloid. The catalyst discussed henceforth is different from these three motifs, but shares some similar characteristics.

[90] Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298-3300.

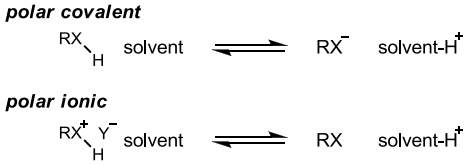
CHAPTER II

CHIRAL PROTON CATALYSIS

2.1 Background

Hydrogen bonding has been heavily exploited by organic chemists over the last several years as seen in the numerous aforementioned reactions. Hydrogen bonds can be characterized as polar covalent or polar ionic (Figure 11). The source of asymmetry in polar covalent hydrogen bond catalysis is the chiral anion. Polar ionic hydrogen bonds on the otherhand contain a neutral chiral ligand for the proton. At the time of the birth of

Figure 11. Comparison of Polar Covalent and Polar Ionic Hydrogen Bond Solvation

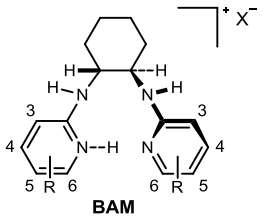


chiral proton catalysis, all of the pre-existing asymmetric hydrogen bond catalysts used polar, covalent hydrogen bonds. One potential advantage to polar ionic hydrogen bond catalysis is the ease with which electrophilicity might be modulated by counterion choice.

2.2 Previous Development

Initially, silyl nitronate additions to imines were performed to gather information about this reaction. The use of silyl nitronate nucleophiles removed the deprotonation

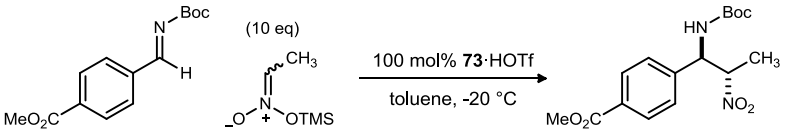
Figure 12. BisAMidine Structure



step. It also simplified the bifunctional catalyst to just a Lewis acid catalyst that solely activated the electrophile.

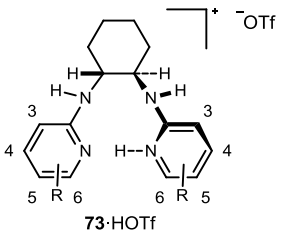
Catalysts of the general structure **73** were envisioned to be chiral Brønsted acids for asymmetric synthesis. Central to this plan was the idea that the acidic proton of the chiral catalyst complex would be an electrophilic "chiral proton". This came to be the

Table 1. Effect of Stereoelectronics of BAM Ligand



entry	R		time (h)	% yield	dr[a] (*anti:syn*)	ee[b] (%)
1	[3]Me	**73a**	88	85	3:1	1
2	[5]Me	**73b**	88	77	8:1	64
3	[6]Me	**73c**	163	56	12:1	70

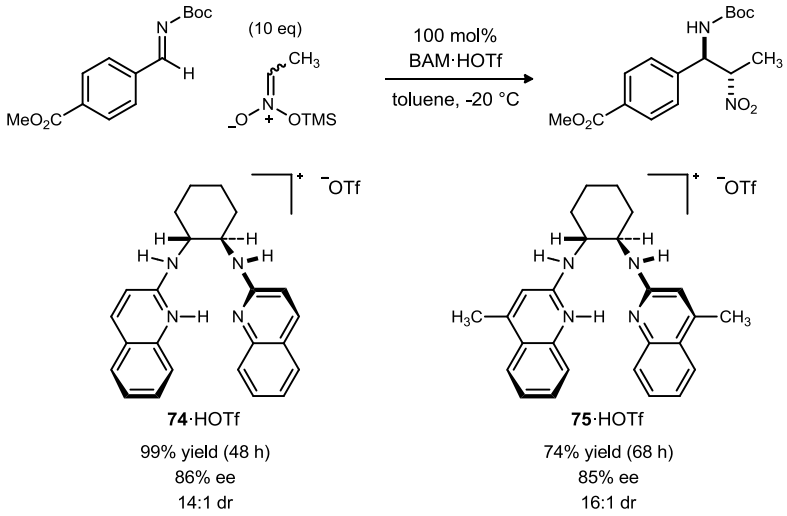
[a]Isolated yields after chromatography. [b]Diastereomer ratios measured by GC. [c]Enantiomer ratios measured by HPLC using chiral stationary phases.



case as catalyst **73** was able to promote asymmetric aza-Henry reactions with good to excellent diastereo- and enantioselectivity. Through much work of optimization of catalyst structure, certain aspects of the catalyst structure were identified as key control elements. Substitution of the pyridine ring directly affects the stereoselection observed

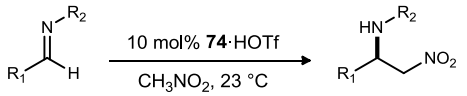
(Table 1). A substituent-free pyridine led to racemic product, as did the catalyst bearing a methyl at the 3- position. However, methyl substitution at the 5- or 6- positions leads to high levels of diastereo- and enantioselection. This led to the use of quinoline in catalyst

Scheme 12. Effect of Stereoelectronics of BAM Ligand



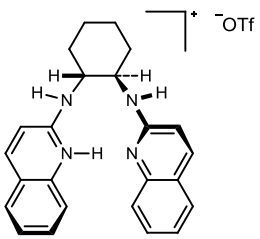
74·HOTf, which gave optimal stereoselection. It is important to note that 4-methyl quinoline or lepidine (**75**·HOTf) exhibited reactivity and stereoselectivity indistinguishable from quinoline (H,QuinBAM·HOTf) shown in Scheme 12. This indicates that substitution by a methyl at the 4- position has little steric or electronic impact on stereoselection.

Table 2. Effect of Electrophile Variation on Stereoselection in the Aza-Henry Reaction



entry	R_1	R_2	time (h)	% conv[a]	ee[b] (%)
1	Ph	^{2}pyridyl	14	95	11
2	$^{p}NO_2Ph$	^{2}pyridyl	36	95	22
3	^{2}pyridyl	DPM	2.5	100	25
4	^{2}pyridyl	CPh_3	no rxn	-	-
5	$^{p}NO_2Ph$	CPh_3	no rxn	-	-
6	^{p}ClPh	CPh_3	no rxn	-	-
7	Ph	Boc	48	25	29
8	^{p}ClPh	Boc	84	50	54
9	Ph	CBz	96	80	14
10	^{p}ClPh	CBz	60	50	48
11	Ph	^{p}OMePh	8	100	11
12	^{2}pyridyl	^{p}OMePh	1	100	11
13	^{2}pyridyl	^{m}OMePh	1	100	4
14	^{2}pyridyl	^{o}OMePh	1	100	6

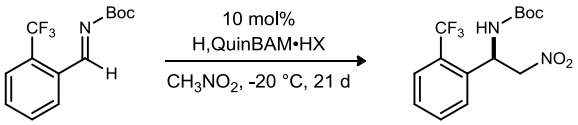
[a]Conversion measured by GC. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.



74·HOTf
H,QuinBAM•HOTf

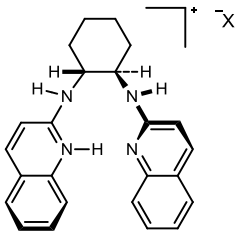
The effect of variation of the electrophile is explored in Table 2. It was important to use an imine with a sufficiently Brønsted basic nitrogen for binding to the chiral proton. Still, the R_2 group must be of correct electronics to provide a sufficiently electrophilic azomethine. Of all R_2 groups used, only the triphenylmethyl exhibited no reactivity. The more electron rich imines (R_2= ^{2}pyridyl, DPM, OMePh) in entries 1-3 and 11-14 exhibited higher reactivity than the carbamate imines (entries 7-11). Although some enantioselectivity was seen with the ^{2}pyridyl and DPM imines as shown in entry 2 and 3, the Cbz and Boc imines performed best in terms of enantioselectivity. In entries 8 and 10, the Boc and Cbz gave product in 54% ee and 48% ee respectively. In terms of utility, Boc and Cbz groups are favorable as they are easily removed to yield the free amines for further manipulation. The Boc and Cbz adducts are also not prone to the retro aza-Henry process like the adducts of more electron rich R_2 groups like DPM.

Table 3. Effect of Counterion on Stereoselection



entry	X	% conv[a]	ee[b] (%)
1	O_2CCH_3	30	31
2	O_3S^pTol	64	53
3	Cl	30	45
4	PF_6	25	20
5	O_3SCF_3	76	75
6	SbF_6	15	70

[a]Conversion measured by GC. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

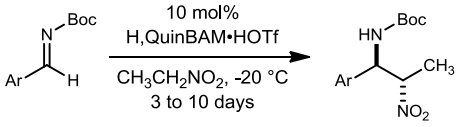


H,QuinBAM•HX

Another important aspect of this catalyst is the role of the counterion. To utilize a polar ionic hydrogen bond, the BAM catalyst must be protonated to make an acid salt. It is presumed that the chiral neutral ligand is responsible for asymmetry, so the counterion should not be involved in this process. It is this logic that suggests that the most loosely associating counterions should be best. H,QuinBAM was protonated with various acids to make different BAM acid salt complexes as shown in Table 3. The weakly associating triflate counterion seems to be best for highest levels of enantioselection. Comparing this to the results given by more strongly associating counterions like acetate leads to the thought that more loosely associating counterions are optimal for this catalyst and reaction.

H,QuinBAM was able to promote the asymmetric aza-Henry reaction and give good enantio- and diastereoselection in most cases. A wide range of aryl *N*-Boc imines in terms of sterics and electronics were tolerated with good generality (Table 4). Reactivity however was poor. It was necessary to run the reactions with the nucleophile as the solvent (56 equivalents) with reaction times of several days.

Table 4. Direct Aza-Henry Reaction Catalyzed by H,QuinBAM·HOTf

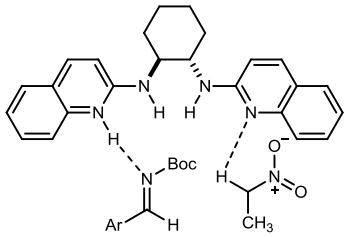


entry	Ar	dr[a]	% ee[b]	% yield
1	2-naphthyl	9:1	44	62
2	1-naphthyl	6:1	56	71
3	C_6H_5	14:1	59	69
4	$^{p}ClC_6H_4$	17:1	82	59
5	$^{p}AcOC_6H_4$	13:1	77	95
6	$^{p}CF_3C_6H_4$	19:1	84	53
7	$^{3,4}F_2C_6H_4$	18:1	86	65
8	$^{p}CF_3C_6H_4$	19:1	84	53
9	$^{m}CF_3C_6H_4$	12:1	69	84
10	$^{o}CF_3C_6H_4$	6:1	83	64
11	$^{p}MeO_2CC_6H_4$	20:1	88	49
12	$^{o}NO_2C_6H_4$	7:1	82	62
13	$^{m}NO_2C_6H_4$	11:1	89	51
14	$^{p}NO_2C_6H_4$	7:1	90	60

[a]Diastereomer ratios measured by GC. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

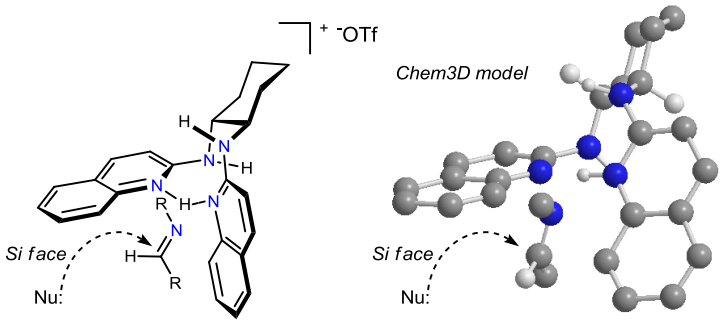
At the time my work began, we were confident that the catalyst was activating the electrophile as a chiral Brønsted acid, due to the observations in the silyl nitronate addition reactions, and activating the nitroalkane by deprotonation. The latter role, however, seemed to affect stereoselection very little since similar diastereo- and enantioselection was observed in both the silyl nitronate and nitroalkane additions. Our hypothesis for this dual activation is depicted in Figure 13. This model uses a single catalyst to bind the azomethine and deprotonate the nitroalkane. Many details of this reaction remained unknown. A series of subsequent experiments revealed crucial information about the mechanism of this reaction.

Figure 13. Mechanistic Picture of Aza-Henry Reaction



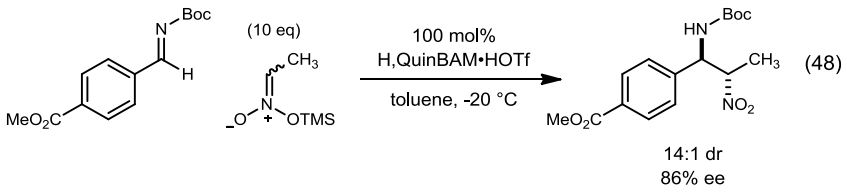
The structure activity relationship studies using silyl nitronate additions were the basis for design of a proposed stereochemical model shown in Figure 14. It is suggested that the proton coordinates to the ligand in a bidentate fashion. With the imine associated

Figure 14. Proposed Catalyst Substrate Complex for the Enantioselective Aza-Henry Reaction



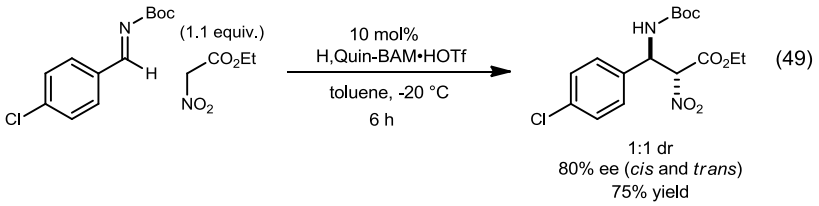
with the catalyst in this fashion, the importance of substitution at the 6-position of pyridine is demonstrated. It is the steric blocking at the 6-position that shields the *Re* face from attack.

The results shown in equation 48 are very similar to that of the parallel reaction of entry 11, Table 4 of 20:1 dr, 88% ee for the direct aza-Henry reaction. Activation in the silyl nitronate addition can only occur through azomethine binding. Therefore, stereocontrol must be achieved through the catalysts' function as a chiral Brønsted/Lewis acid.



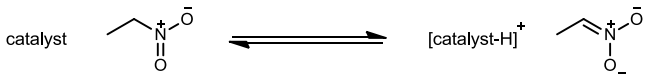
(48)

More mechanistic information was gleaned from the use of a different nitroalkane. α-Nitroesters are significantly more acidic than simple nitroalkanes. These were used in the H,QuinBAM catalyzed aza-Henry reaction, and the results are shown in



(49)

equation 49. With a simple change to a more acidic nucleophile, the reactivity of this system increased dramatically. This allowed for the use of stoichiometric α-nitroester with a shorter reaction time than previously needed with simple nitroalkanes. It is important to consider the simple acid-base equilibrium that exists between catalyst and

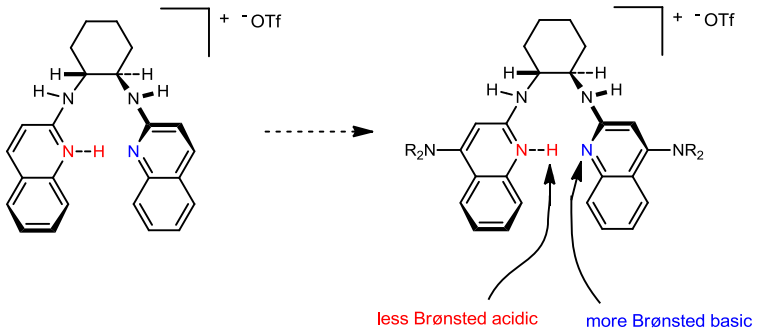


(50)

nitroalkane (eq 50). This result certainly suggests that the more acidic nitroester results in a greater concentration of the nitronate nucleophile, which translates to an enhancement of reaction time. As a result of these findings, we hypothesized that a more Brønsted basic catalyst might increase the reaction rate (Figure 15). This was a somewhat counterintuitive approach to reaction improvement since we had found stereoinduction to be determined by the catalyst's ability to bind the azomethine as a chiral Lewis acid. So an increase in the basicity of the quinoline nitrogen would cause a decrease in the

Brønsted acidity of the conjugate acid of that nitrogen. It would seem that that could be detrimental to the stereoselectivity of the catalyst.

Figure 15. Effect of Catalyst Change on Brønsted Acidity and Basicity

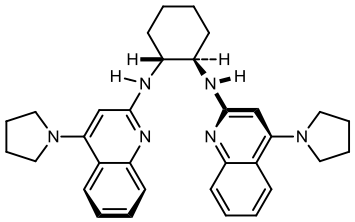


2.3 Catalyst Redesign and Results

Of the numerous positions an additional electron donating group could be placed on the quinoline ring, the 4- position was determined to be optimal. The pK_a measurements of various substituted quinolines have shown that substitution at the 4-position by far has the greatest effect on the pK_a of the quinoline nitrogen. Numerous nitrogen-based electron-donating groups could be installed at the 4-position. Pyrrolidine was chosen owing to its excellent nucleophilicity which should aid in the synthesis of the catalyst. Also, pyrroldine should be an excellent electron donating group based on the enhanced reactivity seen with pyrollidine-based enamines and 4-pyrrolidine substituted pyridines as acylation catalysts.[91] pK_a measurements of 4-substituted pyridines also show 4-pyrrolidinyl pyridine to be the most basic of this series.[92]

[91] Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069-2076.
[92] Kaljurand, I.; Kutt, A.; Soovali, L.; Rodima, T.; Maemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019-1028.

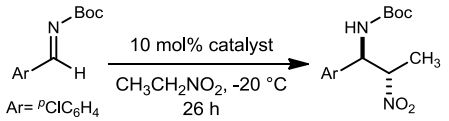
Figure 16. Structure of PBAM



PBAM
76

Initially, PBAM (Figure 16, synthetic details in Chapter 5) was used alongside H,QuinBAM to compare reactivity and stereoselectivity (Table 5). Using 10 mol% catalyst with nitroethane as solvent, a dramatic increase in reactivity was seen with PBAM.[93] Both the free base and the triflic acid salt provided much higher levels of

Table 5. Comparison of the Reactivity of PBAM vs. H,QuinBAM



77

entry	catalyst	conv.[a]	dr[a] (*anti:syn*)	ee[b] (%)
1	H,QuinBAM•HOTf	trace	n/a	n/a
2	PBAM•HOTf	50	6 : 1	76
3	PBAM	74	1 : 1	53

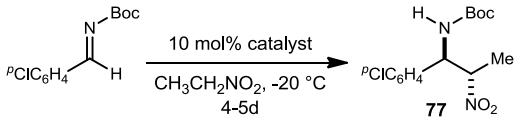
[a]Conversion and diastereomer ratios measured by GC. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

conversion than H,QuinBAM·HOTf. The stereoselection exhibited was slightly lower than what was seen in previous work with H,QuinBAM·HOTf (18:1 dr, 82% ee), but the overall result was still encouraging. Some enantioselection was also seen with the unprotonated catalyst, but was lower than the triflic acid salt. This behavior was unexpected as previous results using the H,QuinBAM free base under the same conditions with nitromethane as the nucleophile lead to little to no enantioselection.

[93] Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880-2882.

The performance of the H,QuinBAM free base turns out to be quite different when using nitroethane rather than nitromethane. Initially (Table 6, entry 1), H,QuinBAM free base provided the aza-Henry product **77** with modest diastereoselection

Table 6. H,QuinBAM and H,QuinBAM·HOTf with Distilled and Undistilled Nitroethane



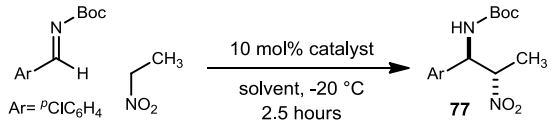
entry	catalyst	conv.[c] (%)	dr[c] *anti*:*syn*	ee[d] (%)
1[a]	H,QuinBAM	49	5:1	73
2[a]	H,QuinBAM•HOTf	24	8:1	87
3[b]	H,QuinBAM	31	5:1	56
4[b]	H,QuinBAM•HOTf	13	15:1	80

[a]Nitroethane used was as supplied by Aldrich. [b]Nitroethane used was distilled from CaH_2 prior to use. [c]Conversion and diastereomer ratios measured by GC. [d]Enantiomer ratios measured by HPLC using chiral stationary phases.

and enantioselection (5:1 dr and 73% ee). To ascertain that this is not an effect of any acidic impurities or stabilizing compounds in the nitroethane, the solvent was distilled over CaH_2 and the same reactions were performed using the distilled nitroethane. It appears that the use of distilled nitroethane had some effect on the reaction as enantioselection dropped from entries 1 and 2 to entries 3 and 4. Still, it is clear that H,QuinBAM free base provides the nitroethane aza-Henry product with significant enantioselection and that the free base of PBAM is not unique among the BAM catalysts with its enantioselectivity in the aza-Henry reaction.

This significant increase in reactivity with the 4-pyrrolidine catalysts led us to attempt this reaction with a stoichiometric amount of nitroethane in solvent. Toluene and 1,2-dichloroethane are solvents that have provided optimal results previously with BAM catalysts, so these solvents were used as shown in Table 7. High levels of conversion were seen in only 2.5 hours with two equivalents of nitroethane at -20 °C. To our delight,

Table 7. PBAM Catalyzed Aza-Henry Optimization



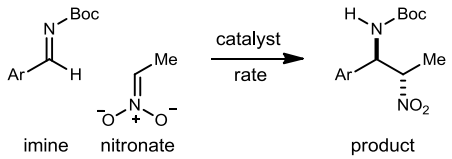
entry	catalyst	solvent	conv.[b]	dr[b] (*anti:syn*)	ee[c] (%)
1	PBAM	DCE	70	1 : 1	60
2	PBAM•HOTf	DCE	73	5 : 1	91
3	PBAM	toluene	40	3 : 1	75
4	PBAM•HOTf	toluene	79	6 : 1	94

[a]Two equivalents of nitroethane were used. Reactions were 1M in toluene and 0.8M in 1,2-dichloroethane . [b]Conversion and diastereomer ratios measured by GC. [c]Enantiomer ratios measured by HPLC using chiral stationary phases.

the enantioselection exhibited with PBAM in solvent was significantly higher than that provided by H,QuinBAM neat in nitroalkane. Diastereoselection was good but did not exceed the diastereoselection provided by H,QuinBAM.

Interestingly, the reaction proved to be faster with stoichiometric amounts of nitroethane in solvent than it was neat in nitroethane (56 equivalents). It did not appear to be an issue of solubility as the PBAM catalysts and the *N*-Boc imine dissolve more easily in nitroethane than toluene. This seems counterintuitive as any increase in concentration of either of the reactants should cause an increase in the rate of the reaction regardless of

Figure 17. Effect of Reactant Concentration on Rate

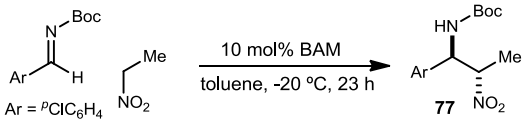


$$\text{rate} = k\,[\text{imine}]^x\,[\text{nitronate}]^x$$

the order with respect to either of the reactants. A simplistic picture of the reaction rate is displayed in Figure 17. Performing the reaction neat in nitroethane should significantly increase the concentration of nitronate thus increasing the rate of the reaction. This does not seem to be the case so it is likely something more complex is going on that explains the significant decrease in reaction time seen in solvent with stoichiometric nitroalkane.

Although it was previously established that PBAM was a more reactive catalyst than H,QuinBAM when used with neat nitroethane, the levels of reactivity seen in Table 5 could be attributed to some combination of optimal solvent, amount of nucleophile, and

Table 8. PBAM/H,QuinBAM Comparison in Toluene



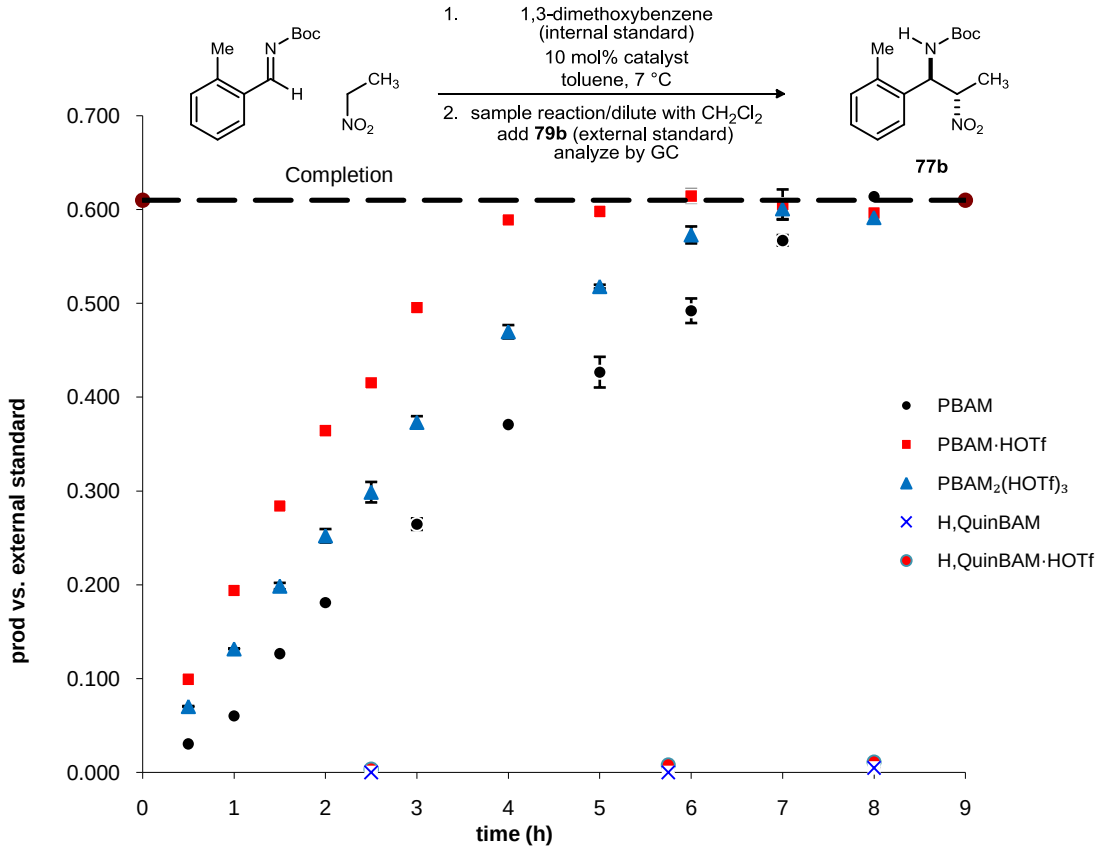
entry	BAM	conversion[b] 3 h (%)	conversion[b] 23 h (%)	dr[c] *anti:syn*	ee[c] (%)	yield[d] (%)
1	PBAM	21	100	1 : 1	71	73
2	PBAM•HOTf	35	100	7 : 1	90	78
3	H,QuinBAM	n/a	1	n/a	n/a	n/a
4	H,QuinBAM•HOTf	n/a	2	n/a	n/a	n/a

[a]All reactions were 1 M in imine with 1.5 equivalents of nitroalkane.
[b]Conversion approximated and diastereomer ratios determined by GC.
[c]Enantiomer ratios measured by HPLC using chiral stationary phases.
[d]Isolated yields..

optimal catalyst. The results in Table 8 specifically show that the reactivity increase with the 4-pyrollidine catalysts plays an crucial role in the success of these optimal reaction conditions. Reactions catalyzed by H,QuinBAM and H,QuinBAM·HOTf (entries 3 and 4, Table 8) were 1% and 2% conversion respectively after 23 hours.

A graphical representation of the reactivity differences of the two catalysts are displayed in Figure 18. Conversion was measured by gas chromatography with the aid of an external standard. This graph clearly shows the increased reactivity of the 4-pyrrolidine catalysts over H,QuinBAM and H,QuinBAM·HOTf. PBAM and the associated salts promoted the reaction to full conversion at 8 hours, as only 1% and 2%

Figure 18. Reactivity Comparsion of H,QuinBAM, PBAM, and their Triflic Acid Salts

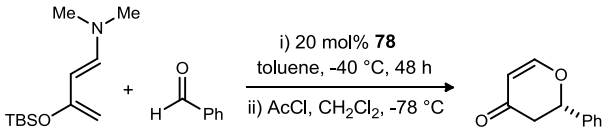


conversion was observed with H,QuinBAM and H,QuinBAM·HOTf, respectively. This figure offers a clear comparison of the reactivity of the three protonation states of PBAM. PBAM·HOTf is the most reactive catalyst, reaching nearly full conversion at 4 hours. $PBAM_2HOTf_3$ is slightly less reactive, reaching full conversion at about 7 hours. The free base of PBAM is the least reactive of the three under these conditions as 8 hours is needed to reach full conversion.

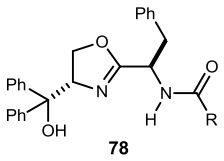
These clear results display the interesting trend of the more Brønsted basic Brønsted acid catalyst PBAM·HOTf providing higher enantioselectivity and diastereoselectivity than H,QuinBAM·HOTf. Although there have been few studies on the effect of catalyst acidity upon the rate and stereoselectivity of an enantioselective

reaction, Sigman has recently published a detailed report on the variation of catalyst pK_a on a hetero-Diels-Alder reaction.[94]

Table 9. Sigman's Oxazoline-Amide Catalyzed Hetero Diels-Alder Reaction



entry	R	ee (%)	yield (%)
1	CF_3	91	67
2	CCl_3	81	61
3	$CHCl_2$	75	53
4	CH_2F	62	17
5	CH_2Cl	52	32



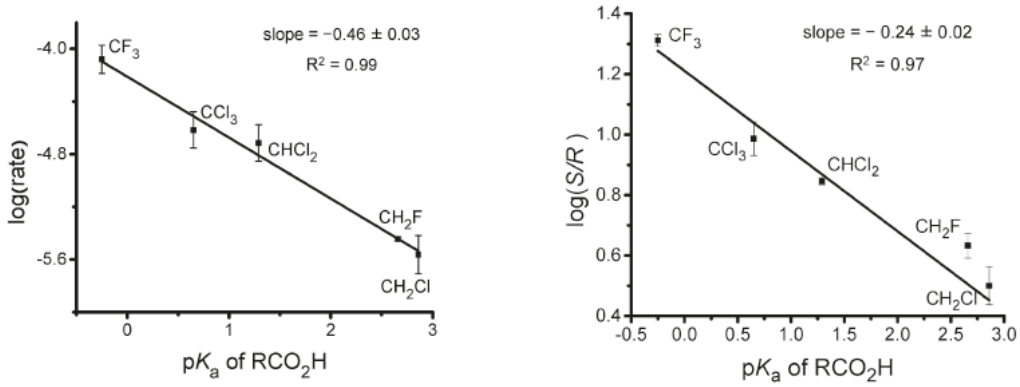
78

Sigman used a catalyst structure (**78**) whose acidity was easily modulated to provide catalysts with a broad range of pK_a values (Table 9) without substantial steric consequence. Through thorough kinetic measurements obtained by *in situ* IR, many details were ascertained about this reaction.[95] This reaction was found to be first order with respect to catalyst, saturation in aldehyde, and first order with respect to diene. The aldehyde is activated by hydrogen bonding with the catalyst to form a catalyst:aldehyde complex, which then reacts with diene. Furthermore, the electronic nature of the aldehyde had a major effect on the saturation kinetics on the catalyst aldehyde complex. This suggested that a stronger hydrogen bond existed between the stronger Brønsted base (more electron-rich aldehyde) and the Brønsted acid (catalyst). Inversely, it was found that the most Brønsted acidic catalyst was the most enantioselective and reactive catalyst. Using the known pK_a values of the corresponding carboxylic acids as an estimate of the pK_a of the catalyst, these values were plotted against log(rate) and log(er) as shown in Figure 19. Both plots showed a linear relationship between pK_a of the catalyst and the

[94] Jensen, K.; Sigman, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4748-4750.
[95] Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194-7201.

rate and enantioselection of the reaction. Simply put, the closer in pK_a the Brønsted acid catalyst and Brønsted basic substrate, the stronger the hydrogen bond between the two, the more rigid the transition state, and the more enantioselective and faster the reaction.

Figure 19. Plots of pK_a vs. Rate and pK_a vs. Enantioselection in Sigman's Enantioselective Hetero-Diels-Alder Reaction

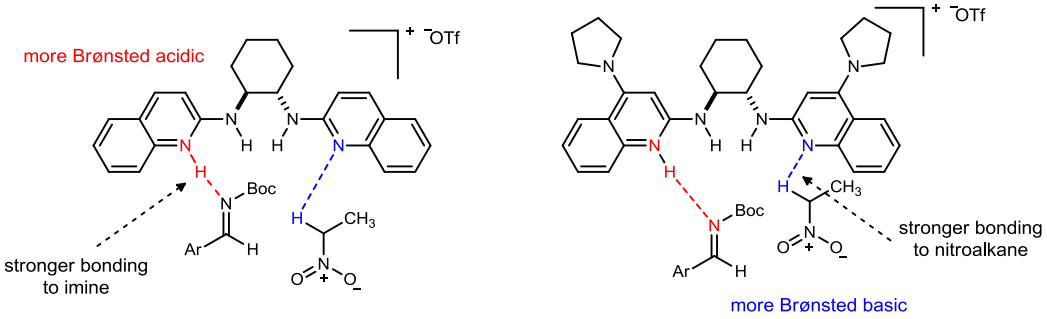


Sigman's system contrasts starkly with our reaction. Kinetic studies of the PBAM-catalyzed aza-Henry were attempted but were inconclusive. Nevertheless, it is clear that our system behaves in the opposite way as the more Brønsted basic catalyst is the most reactive and enantioselective. If our mechanism was the same as Sigman's, our results would make little sense as one would expect the more acidic catalyst to form a stronger hydrogen bond with the imine. This would lead to a faster reaction and higher enantioselectivity assuming there is no steric consequence of the pyrrolidines on the binding pocket.

It seems more likely that the bifunctionality of our catalyst presents a more complicated scenario. The dramatic increase in reactivity of PBAM·HOTf suggests that the catalyst might also bind to the nitroalkane independently before the bond-forming event occurs. Since the catalyst and nitroalkane are closer in pK_a, this binding should be stronger with the more basic catalyst. A visual aid for this rationale is given in Figure 20. This strengthening of the hydrogen bonding with the nitroalkane might atone for the

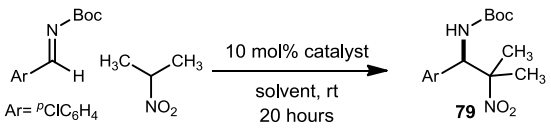
weakening of the hydrogen bonding with imine. Furthermore, the observation of a faster reaction with stoichiometric nitroalkane than with neat nitroalkane suggests a possible saturation of the catalyst with nitroalkane.

Figure 20. Rationale for Increased Stereoselection and Reactivity with More Brønsted Basic Catalysts



Detailed kinetic studies should be performed in the future to give more evidence of the mechanism of this interesting reaction. We have been unable to use *in situ* IR to perform these studies due to precipitation of the product at the concentrations needed to monitor the reaction. Some attempts using gas chromatography to monitor the reaction have been promising, but the data was inconclusive. This method could probably work given a considerable effort. The mechanistic details that can be obtained through kinetic studies is likely to yield very useful information for the future application of this catalyst.

Table 10. Secondary Nitroalkane Additions

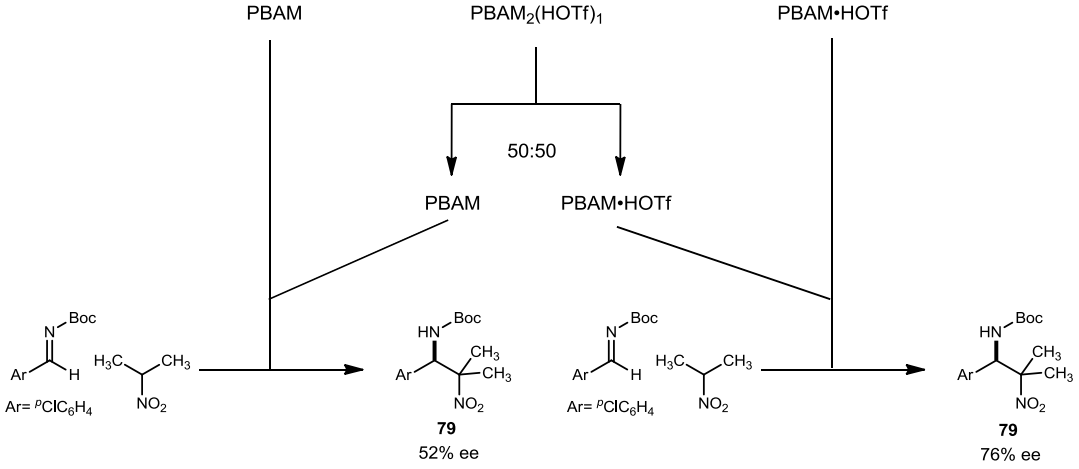


entry	catalyst	conv.[b]	ee[c] (%)
1	PBAM	100	52
2	PBAM•HOTf	100	76
3	$PBAM_2(HOTf)_1$	100	76

[a]1.5 equivalents of 2-nitropropane were used. Reactions were 1M in toluene. [b]Conversion measured by GC. [c]Enantiomer ratios measured by HPLC using chiral stationary phases.

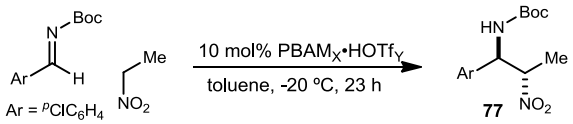
Despite the lack of understanding of mechanism of this reaction, the increased reactivity was evident and applicable to a broader range of substrates. The reactivity of this system was such that a secondary nitroalkane, 2-nitropropane, could be used successfully as the pronucleophile (Table 10). At room temperature for 20 hours, full conversion and enantioselection at the 76% level was measured. Using differing protonation states of PBAM led to interesting results. As has been seen previously in this group, the free base gave lower enantioselection (52% ee). The 1:1 PBAM triflic acid salt gave 76% ee. Curiously, the 2:1 PBAM triflic acid salt gave the same enantioselection as the 1:1 salt. Since the active catalyst in the PBAM free base reactions is the nitronate salt, it is possible that in the case of $PBAM_2(HOTf)_1$ the concentration of PBAM·HOTf is much greater than that of the PBAM nitronate salt *in situ*. This would also explain the enantioselection of $PBAM_2(HOTf)_1$ being equal to that of PBAM·HOTf. Regardless, it

Figure 21. Relationship of Catalyst Protonation State and Enantioselection with 2-Nitropropane to Azomethine



did suggest that further study of protonation state and catalyst performance was warranted.

Table 11. PBAM Catalyst Protonation State Study

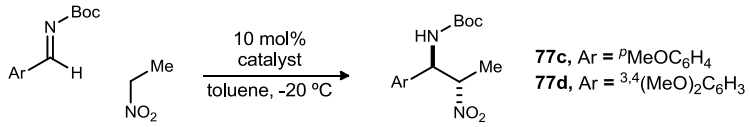


entry		conversion[b] 3 h (%)	conversion[b] 23 h (%)	dr[c] *anti:syn*	ee[c] (%)	yield[d] (%)
1	PBAM	21	100	1 : 1	71	73
2	$PBAM_2(HOTf)$	27	100	4 : 1	91	76
3	PBAM(HOTf)	35	100	7 : 1	90	78
4	$PBAM_4(HOTf)_5$	23	87	13 : 1	92	76
5	$PBAM_2(HOTf)_3$	16	85	15 : 1	90	77
6	$PBAM_2(HOTf)_3$	n/a	96	18 : 1	91	87
7	$PBAM(HOTf)_2$	n/a	12	16 : 1	86	42[e]

[a]All reactions were 1 M in imine. [b]Conversion approximated and diastereomer ratios determined by GC. [c]Enantiomer ratios measured by HPLC using chiral stationary phases. [d]Isolated yields. [e]48 h reaction time.

An array of catalysts was prepared by varying the ratio of ligand to triflic acid., and each was screened in the aza-Henry reaction (Table 11). Again to our delight, a better catalyst emerged. $PBAM_2(HOTf)_3$ gave the same enantioselection as PBAM·HOTf, but the diastereoselection improved from 7:1 to 18:1. Overall, the diastereoselection values increased as the protonation state of the catalyst increased, while enantioselection plateaued at an earlier point. This increase in diastereoselection was at the cost of some reactivity, but this was manageable since the overall reaction times were reasonably short. $PBAM_1(HOTf)_2$ still provided product with high enantio- and diastereoselection. This was unexpected as it was previously observed that the use $H,QuinBAM_1(HOTf)_2$ led to hydrolysis of the imine and no aza-Henry product. It should be stated that use of $PBAM_1(HOTf)_3$ also led to hydrolysis of the imine and no aza-Henry product.

Table 12. PBAM Catalyst Protonation State Study, Part 2



catalyst	Ar	dr[b] (*anti:syn*)	ee[c] (%)	yield[d] (%)	catalyst	Ar	dr[b] (*anti:syn*)	ee[c] (%)	yield[d] (%)
PBAM	$^{p}MeOC_6H_4$	11 : 1	70	91	PBAM	$^{3,4}(MeO)_2C_6H_3$	3 : 1	71	79
$PBAM_2(HOTf)_1$	$^{p}MeOC_6H_4$	19 : 1	88	92	$PBAM_2(HOTf)_1$	$^{3,4}(MeO)_2C_6H_3$	5 : 1	87	88
PBAM•HOTf	$^{p}MeOC_6H_4$	20 : 1	87	76	PBAM•HOTf	$^{3,4}(MeO)_2C_6H_3$	12 : 1	89	80
$PBAM_4(HOTf)_5$	$^{p}MeOC_6H_4$	20 : 1	88	79	$PBAM_4(HOTf)_5$	$^{3,4}(MeO)_2C_6H_3$	15 : 1	89	83
$PBAM_2(HOTf)_3$	$^{p}MeOC_6H_4$	24 : 1	88	84	$PBAM_2(HOTf)_3$	$^{3,4}(MeO)_2C_6H_3$	20 : 1	90	80
$PBAM_1(HOTf)_2$	$^{p}MeOC_6H_4$	23 : 1	90	63					

[a]All reactions were 1 M in imine and quenched at 23 hours. [b]Diastereomer ratios measured by GC. [c]Enantiomer ratios measured by HPLC using chiral stationary phases. [d]Isolated yields.

To ascertain the generality of this trend, the same experiments were performed with different imines. The results in Table 12 exhibit the same trend seen previously. Compounds **77c** and **77d** were formed with increasing diastereoselectivity as the relative amount of triflic acid to catalyst increased. Enantioselectivity plateaued in each case at the 1:1 triflic acid to ligand ratio.

It seemed possible that post-reaction epimerization was affecting the diastereoselectivity observed. A simple experiment was performed to probe this as shown in Table 13. After 7 and 25 hours, essentially the same diastereoselection was seen with both PBAM·HOTf and $PBAM_2(HOTf)_3$. These results indicate that no significant post-reaction epimerization was occuring under these reaction conditions.

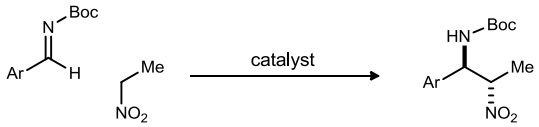
Table 13. Post Reaction Epimerization Study

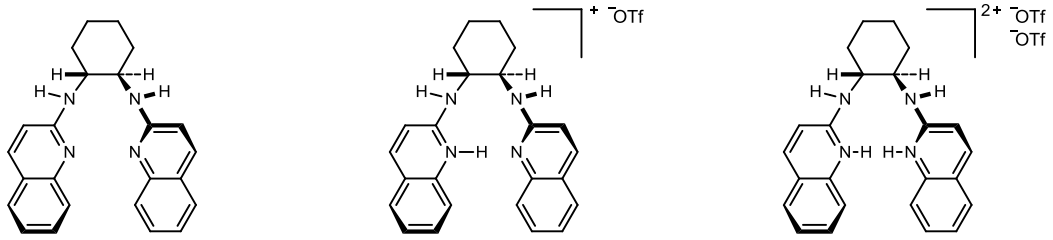
catalyst	dr[b]-7h (*anti:syn*)	dr[b]-25h (*anti:syn*)
PBAM•HOTf	12 : 1	13 : 1
$PBAM_2(HOTf)_3$	21 : 1	20 : 1

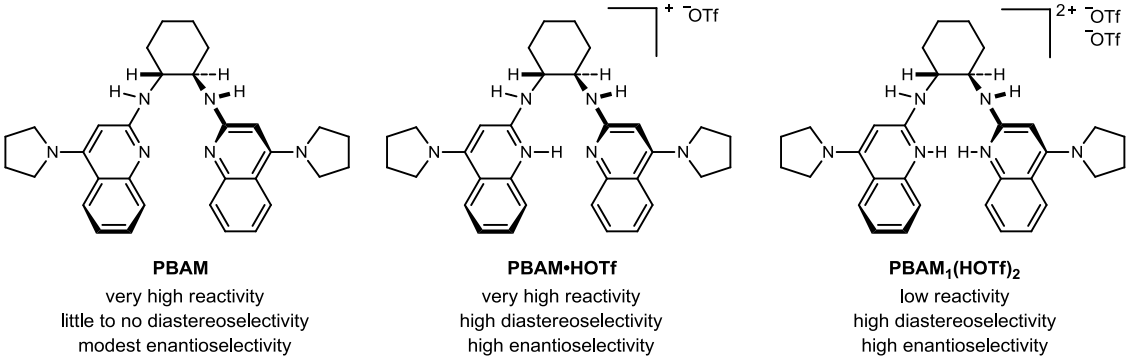
[a]All reactions were 1 M in imine. [b]Diastereomer ratios measured by GC after reaction mixture was filtered cold through silica.

This behavior of PBAM across protonation states is significantly different than the activity exhibited by H,QuinBAM (Figure 22). The free base of PBAM is much more reactive and more selective than the free base of H,QuinBAM. The silyl nitronate additions indicated that the acidity of the catalyst-triflic acid complex was responsible for

Figure 22. Comparison of BAM Catalyst Performance in the Aza-Henry Reaction

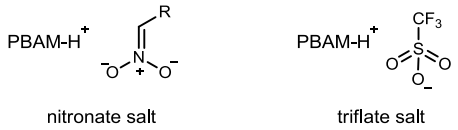






stereoinduction. We therefore suspect that the nitroalkane forms a nitronate salt with PBAM thereby becoming the active catalyst (Figure 23). This nitronate salt of PBAM behaves differently than that of H,QuinBAM. A plausible explanation for this is the

Figure 23. PBAM-Acid Complexes



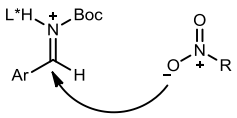
nitronate salt triflate salt

crucial role counterion plays in enantioselection with this reaction. More loosely associated counterions have led to higher levels of enantioselection with H,QuinBAM. It could be the case that the nitronate counterion is more loosely associated with the more basic PBAM catalyst than with the less basic H,QuinBAM catalyst.

The 1:1 triflic acid salt of PBAM is more reactive than and similarly selective as the H,QuinBAM 1:1 triflic acid salt. With the obtained data, it is impossible to determine that the 1:1 triflic acid salt of PBAM is more diastereo- or enantioselective than that of H, QuinBAM. What has been observed thus far is an increase in stereoselection as the reaction was run with stoichiometric nitroalkane and toluene as solvent. The much increased reactivity of PBAM has allowed for these conditions to be used and the increased stereoselection that comes with these optimal conditions. Despite the electronic differences of the catalysts, it is very likely that PBAM·HOTf and H,QuinBAM·HOTf are similarly stereoselective in this aza-Henry reaction.

$PBAM_1(HOTf)_2$ leads to aza-Henry product enantio- and diastereoselectively while $H,QuinBAM_1(HOTf)_2$ leads to hydrolysis of imine. It is possible that

Figure 24. Mechanism of Hydrolysis



H,QuinBAM$_1$(HOTf)$_2$ exceeds the threshhold of Brønsted acidity to access a hydrolysis pathway as shown in Figure 24. A less Brønsted acidic PBAM$_1$(HOTf)$_2$ may not exceed that threshold. The decreased but still significant reactivity seen suggests there still might exist a strong enough Brønsted basic nitrogen with PBAM$_1$(HOTf)$_2$ to deprotonate the

$$2\ \text{PBAM(HOTf)}_2 \rightleftharpoons \text{PBAM•HOTf} + \text{PBAM(HOTf)}_3 \quad (51)$$

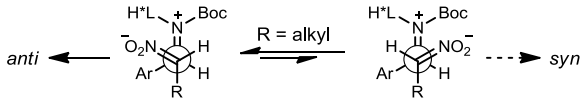
nitroalkane. It is also possible that enough PBAM·HOTf is present to promote the reaction based on the equilibrium displayed in equation 51. This necessary basicity needed to generate the nitronate nucleophile in great enough concentration to compete with hydrolysis might not exist with H,QuinBAM$_1$(HOTf)$_2$.

It seems almost certain that the active Brønsted acid catalyst is different in reactions performed with PBAM$_1$(HOTf)$_2$ than those performed with PBAM·HOTf. This is suggested by observed diastereoselection values and the sheer fact that the catalyst composition is different. It is plausible that PBAM$_1$(HOTf)$_2$ is equally enantioselective and more diastereoselective than PBAM·HOTf when activating an imine in the aza-Henry reaction. This is strange as the binding cavity PBAM$_1$(HOTf)$_2$ should be substantially different from that of PBAM·HOTf due to the lack of a bidentate hydrogen bond in PBAM$_1$(HOTf)$_2$. The similarities in behavior for catalysis by H,QuinBAM and PBAM (dr, ee, same absolute configuration) suggest that a common mechanism for stereoinduction is involved. While this is merely an assumption, there is value in using a single catalyst substrate model to rationalize these observations.

We have formulated a hypothesis for *anti*-selectivity observed in these reactions (Figure 25). In terms of steric consequence of the nitroalkane nucleophile, it seems the alkyl group must be the largest group. The hydrogen must be the smallest group, and the

nitro group fits nicely in between the two. It would seem logical to place the large alkyl group between the aryl group and hydrogen of the imine. The small hydrogen could then be best placed in the area between the bulky ligand and aryl group. This would leave the

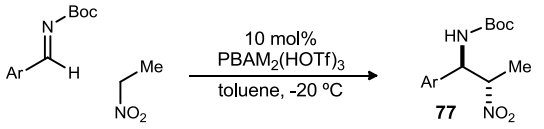
Figure 25. Explanation for Diastereoselectivity



nitro to sit between the hydrogen and the Boc group. This arrangement, however, would lead to *syn*-diastereoselection which is not observed. If the argument is made for a hydrogen bonding interaction between the nitro group and the chiral proton, *anti*-diastereoselection can be explained through the favorable arrangement of atoms of the Newman projection on the left.

The increased reactivity provided by the 4-pyrrolidine catalysts signficantly extended the scope of the aza-Henry reaction both in terms of imine and nitroalkane used. This reaction is very general across a wide variety of aryl imines with the addition of nitroethane (Table 14). Furyl and thiophenyl imines were tolerated. Different functionalities of a methyl ester (entry 9) and an allyloxy group (entry 14) were successfully employed. Diastereoselectivity was exceptionally high (>12:1) in all cases, except for aryl imines substituted at the *ortho* position (11:1 and 8:1 dr, entries 6 and 7).

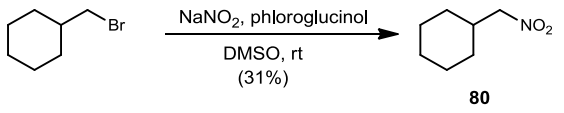
Table 14. Aryl Imine Scope Expansion



entry	Ar		dr[b] (*anti*:*syn*)	ee[b] (%)	yield[c] (%)
1	$^{p}ClC_6H_4$	**77**	18:1	91	87
2	$^{p}MeOC_6H_4$	**c**	24:1	88	84
3	$^{3,4}(MeO)_2C_6H_3$	**d**	20:1	90	80
4	^{2}Np	**e**	16:1	82	84
5	$^{p}MeC_6H_4$	**f**	28:1	89	100
6	$^{o}MeC_6H_4$	**b**	11:1	90	66
7	^{1}Np	**g**	8:1	87	97
8	$^{p}FC_6H_4$	**h**	26:1	93	66
9	$^{p}MeO_2CC_6H_4$	**i**	12:1	91	63
10	$^{2}C_4H_3O$	**j**	19:1	87	90
11	$^{2}C_4H_3S$	**k**	20:1	95	100
12	$^{3}C_4H_3S$	**l**	35:1	91	92
13	$^{p}PhSC_6H_4$	**m**	20:1[d]	89	80
14	$^{p}AllylOC_6H_4$	**n**	28:1	89	91

[a]All reactions were 1 M in imine with 1.5 equivalents of nitroalkane and quenched at 24 hours. Absolute and relative configuration of **77** assigned by chemical correlation/X-ray. The remaining stereochemical assignments are made by analogy. [b]Diastereomer ratios measured by GC unless otherwise noted. Enantiomer ratios measured by HPLC using a chiral stationary phase. [c]Isolated yields. [e]Approximated by ^{1}H NMR.

The ability to use stoichiometric amounts of nitroalkane allowed us to easily demonstrate the use of different nitroalkanes. Nitroalkanes can be synthesized from the corresponding alkyl bromides and sodium nitrite as reported by Kornblum.[96] Nitromethyl cyclohexane (**80**) was prepared according to this procedure (31% yield) in equation 52.

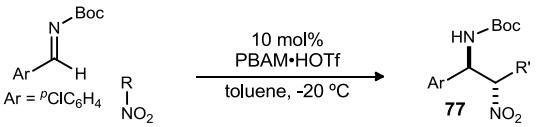


(52)

This reaction exhibited generality with different nitroalkanes (Table 15). Although diastereoselectivity was lessened to 7-13:1 dr when using branched nitroalkanes (entries 3 and 4), enantioselectivity was good and consistent across the scope.

[96] Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497-1501.

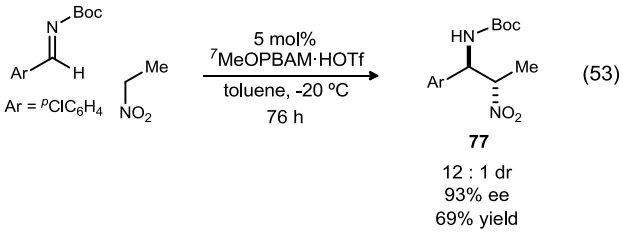
Table 15. Nitroalkane Scope Expansion



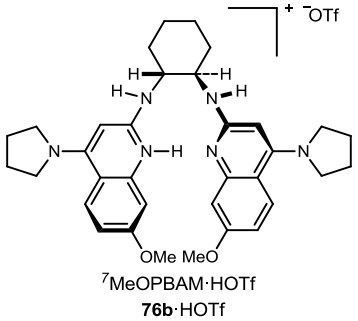
entry	R		dr (*anti:syn*)	ee[b] (%)	yield[c] (%)
1	^{n}Pr	**o**	20:1[d]	91	86
2	^{n}Bu	**p**	23:1[d]	89	89
3	^{i}Bu	**q**	7:1[e]	88	61
4	$CH_2C_6H_{11}$	**r**	13:1[e]	89	85

[a]All reactions were 1 M in imine with 1.5 equivalents of nitroalkane and quenched at 24 hours. The stereochemical assignments are made by analogy. [b]Enantiomer ratios measured by HPLC using a chiral stationary phase. [c]Isolated yields. [d]Measured by HPLC. [e]Measured by ^{1}H NMR.

It was not until the conclusion of the study of the addition of aliphatic nitroalkanes that a library of substituted PBAM catalysts were made. To this point, a broader screen of catalysts was not applied to this reaction. One new PBAM derivative, ^{7}MeOPBAM·HOTf (**76b**·HOTf), was used in the nitroethane addition (eq 53) similar to

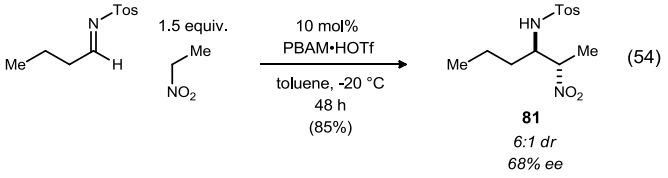


(53)



the reaction in Table 14 with the exception that 5 mol% catalyst was used. **77** was produced with slightly higher enantioselectivity (93% ee vs 91% ee - Table 14, entry 1) than $PBAM_2(HOTf)_3$. It seems possible that the use of the different PBAM derivatives discussed later in the document could result in higher enantioselectivities in the aza-Henry addition of simple nitroalkanes.

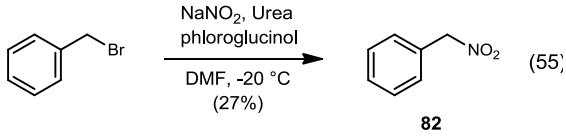
The ability to use aliphatic imines as substrates would drastically broaden the scope and applicability of the BAM-catalyzed aza-Henry reaction. To this point, aliphatic imines have been unstable to our reaction conditions. PBAM has given us the reactivity to approach this challenge. Some success has been achieved using aliphatic *N*-tosyl imines as electrophiles using PBAM as a catalyst. Fair enantio- and diastereoselection was exhibited as the best result obtained was 6:1 dr and 68% ee (eq 54).



(54)

2.4 Synthesis of Aryl Nitroalkanes

1,2-Diaryl-1,2-diamines are a very useful class of compounds that can be approached by the addition of aryl nitromethanes to aryl imines and subsequent reduction. Phenylnitromethane **82** can be made from benzyl bromide and sodium nitrite



(55)

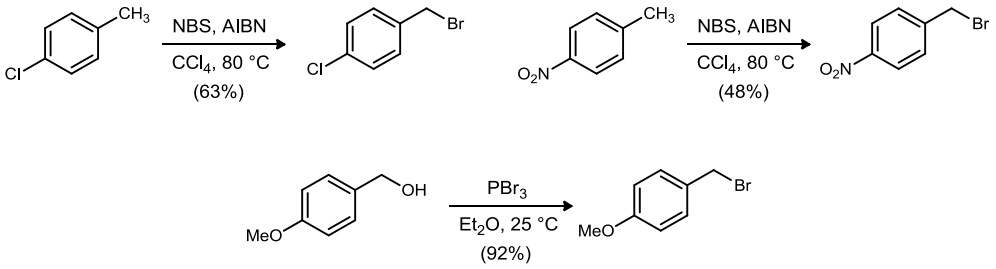
as initially described by Nathan Kornblum of Purdue University (eq 55).[97] Our other attempts to make this compound from various oxidations of benzaldoxime were unsuccessful.[98]

Benzyl halides are good starting materials since many are commercially available. A few of these compounds were synthesized in one step (Scheme 13). The *p*-chloro and *p*-nitro benzyl bromides were made by free-radical halogenation from the corresponding

[97] Kornblum, N.; Weaver, W. M. *J. Am. Chem. Soc.* **1958**, *80*, 4333-4337.
[98] Base, D. S.; Vanajatha, G. *Synth. Comm.* **1998**, *28*, 4531 - 4535.

toluene compounds. *p*-Methoxy benzyl bromide was made from the treatment of the benzyl alcohol with PBr_3.

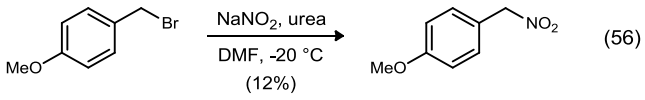
Scheme 13. Synthesis of Subsituted Benzyl Bromides



As it is with the synthesis of other nitroalkanes with the corresponding alkyl bromide and metal nitrites, formation of the alkyl nitrite is a competitive process. In this case, benzyl nitrite formation not only lowers the yield directly, but it can also react further with the desired phenylnitromethane as noted by Kornblum. Furthermore, we have found that benzyl nitrite converts to benzaldehyde on silica during column chromatography. Adding to the problem, benzaldehyde and phenylnitromethane are difficult to separate using flash chromatography. In this reaction, phloroglucinol is used to convert benzyl nitrite to benzyl alcohol to avoid the destructive pathway and ease purification. The yield is quite low as the reaction did not go to completion and has not been optimized. Still, a high yield of this reaction cannot be expected as phenylnitromethane is formed in a 60:40 ratio to benzyl nitrite. Even though nitro formation is generally favored slightly, this nitrite nitrogen versus oxygen nucleophilicity issue is an inherent problem in making nitroalkanes in this way. In the over 50 years since Kornblum's studies, no solution to this problem of O versus N nucleophilicity has been reported. It seems most effective way to make phenylnitromethane specifically is through nitrite addition, even though there have been other methods reported.[99,100]

[99] Kurz, M. E.; Chen, T. R. *J. Org. Chem.* **1978**, *43*, 239-242.

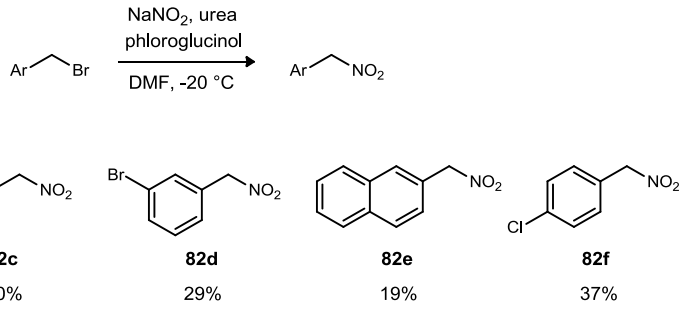
The importance of phloroglucinol as an alkyl nitrite scavenger was confirmed



(56)

with our attempt to synthesize *p*-methoxy phenylnitromethane (eq 56). After 3 hours, the reaction was quenched and found to be a mixture of desired product, alkyl nitrite, and alcohol (2.6 : 1 : 2.2). An attempt to isolate the nitro compound by column chromatography failed as *p*-methoxybenzaldehyde coeluted with the desired compound. This formation of aldehyde is a result of decomposition of the alkyl nitrite on the column. When phloroglucinol is in the reaction mixture, it reacts with the alkyl nitrite to form the benzyl alcohol which is easily separated from the nitro compound by column chromatography. Nevertheless, 520 mg was isolated after two columns and an additional 500 mg was isolated after vacuum distillation followed by column chromatography to give the desired product in 12% yield. Undoubtedly, some desired material was not isolated as indicated by the crude NMR.

Scheme 14. Arylnitroalkane Syntheses from Corresponding Benzyl Bromide

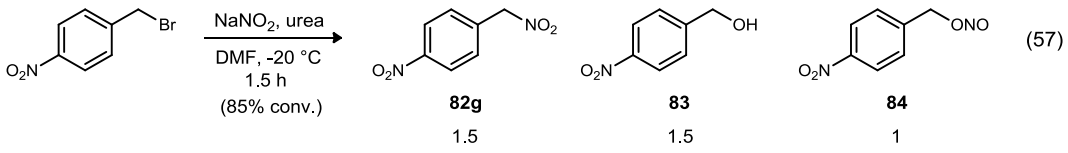


This method was found to be useful in making several different aryl nitroalkanes from the corresponding benzyl bromides (Scheme 14). We erred on the side of stopping the reactions somewhat early, as allowing the reaction to continue past full conversion

[100] Kurz, M. E.; Ngoviwatchai, P.; Tantrarant, T. *J. Org. Chem.* **1981**, *46*, 4668-4672Kurz, M. E.; Chen, T. R. *J. Org. Chem.* **1978**, *43*, 239-242.

results in the destruction of product. All reactions were performed at -20 °C for 4 to 6 hours. All aryl nitroalkanes were purified by column chromatography. The yields shown are low mainly because of the formation of alcohol and other compounds resulting from attack through the oxygen of the nitrite. To a lesser extent, low yields are due to reactions not being run to full completion and the inability to completely isolate the nitroalkane formed. The latter problems could easily be addressed with some optimization, but the amounts of product isolated were sufficient for exploratory work. Halogenated benzyl bromides proved to be good substrates for this reaction. The *o*-dichlorophenylnitromethane **82b** was formed in relatively excellent yield of 57%. The *o*-Br (**82c**) and *m*-Br (**82d**) nitroalkanes were formed in 30% and 29% yield respectively. *p*-Chlorobenzyl bromide was smoothly nitrated to give **82f** in 37% yield. 2-Nitromethylnaphthalene (**82e**) was also formed from the corresponding bromide in lower yield (19%).

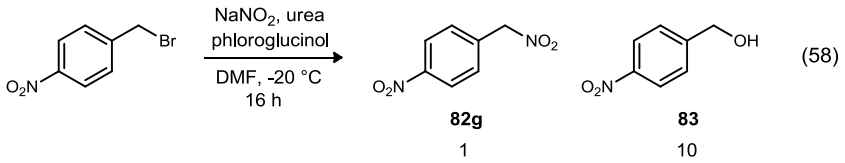
Other procedures had to be employed for certain substrates. The reaction of sodium nitrite with *p*-nitrobenzyl bromide in the absence of phloroglucinol proceeds in a



(57)

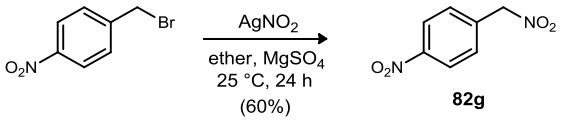
similar fashion to other benzyl bromides. After column chromatography, the desired nitroalkane (**82g**) was unable to be separated from unidentified byproducts presumably from the decomposition of alkyl nitrite **84** on silica. Unfortunately, the employment of phloroglucinol to convert the alkyl nitrite **84** to alcohol **83** was not successful as analysis of the crude reaction showed a 10:1 ratio of alcohol to nitro (eq 58). In retrospect, this

product distribution might have more to do with decomposition of product owing to the unduly long reaction time of 16 hours.



(58)

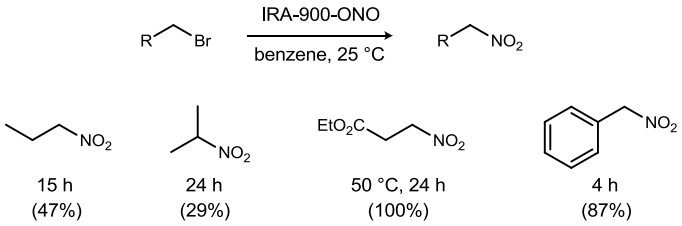
Nevertheless, we sought to use better conditions for this particular reaction. Kornblum also used silver nitrite to nitrate alkyl and benzyl halides.[101] Although we were unable to reproduce the yield reported by Kornblum (75%), we were able to isolate **82g** in 60% yield after column chromatography (eq 59) which was sufficient.



(59)

More recent work by Gelbard indicated a better way to make aryl nitroalkanes.[102] He used a nitrite resin to nitrate aryl and alkyl halides. This resin is made by simply

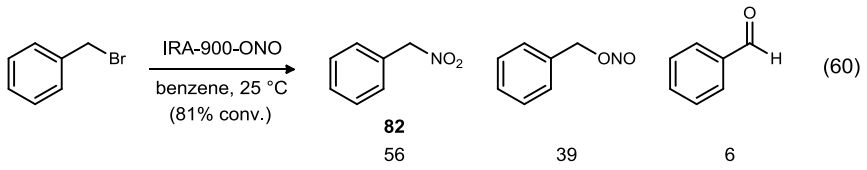
Scheme 15. Gelbard's Nitrating Resin



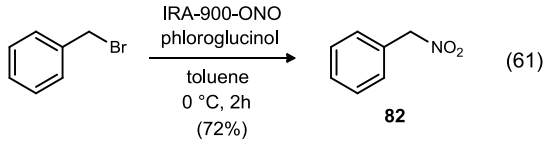
washing commercially available Amberlite IRA-900(Cl^-) resin with aqueous $NaNO_2$ solution. This reaction has the obvious advantage of the use of polymer-supported reagents, which is simple workup. The resin can be filtered off and presumably retreated and reused. Gelbard reacted the corresponding bromides with the resin in benzene at 25-50 °C (Scheme 15). Less valuable nitroalkanes 1-nitropropane and 2-nitropropane were

[101] Kornblum, N.; Smiley, R. A.; Blackwood, R. K.; Iffland, D. C. *J. Am. Chem. Soc.* **1955**, *77*, 6269-6280.
[102] Gelbard, G. *Synthesis* **1977**, 113-116.

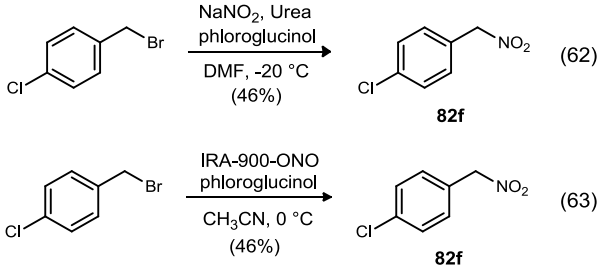
formed in low yield (47% and 29% respectively). A β-nitro ester was formed in reportedly quantitative yield. Phenylnitromethane was formed from benzyl bromide in excellent isolated yield of 87%. Intrigued by this result, work was done in this lab by Anand Singh to reproduce this exceptional result for this valuable compound.[103]



Under the exact conditions described by Gelbard, full conversion was not achieved. Also, a considerable amount of the alkyl nitrite and a small amount of benzaldehyde was seen by crude NMR (eq 60). Ultimately, results more akin to Gelbard's result were achieved by change of solvent to toluene, the change of



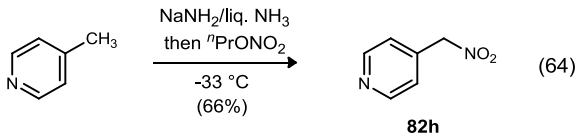
temperature to 0 °C, and the addition of phloroglucinol to the reaction. The optimal result of 72% isolated yield is displayed in equation 61. The O vs. N selectivity seen from reaction to reaction with this system is prone to significant amount of variability, but overall better N selectivity is seen using this resin than with sodium nitrite.



[103] Johnston, J. N.; Singh. A. *Unpublished results*.

As *p*-chloro phenylnitromethane became a very important substrate for us, our desire to obtain a higher yielding procedure to make it increased. Some time was spent using the IRA-900-ONO resin to improve the yield of **82f**. Despite screening a variety of conditions and solvents, we could never reach the yield of 72% achieved with phenylnitromethane for compound **82f**. Essentially no increase in yield of nitroalkane over the Kornblum conditions is seen. **82f** can be obtained in 46% isolated yield using the IRA-900-ONO resin (eq 63). Our best result with the Kornblum conditions was 46% yield on a relatively large scale of 170 mmol (13.1 grams isolated, eq 62). With either reaction (resin or $NaNO_2$ as the nitrite source), the benzyl alcohol is the major product and could be recovered, converted to the corresponding benzyl bromide, and resubmitted to the nitration conditions.

Perhaps the most direct route imaginable for the synthesis of aryl nitroalkanes is the C-H activation of the corresponding toluene leading directly to the nitro compound

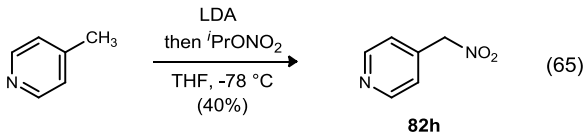


82h (64)

without the intermediacy of a benzyl halide. In work once again originating from the undoubted (former) capital of nitro chemistry, Purdue University, Henry Feuer reported the nitration of alkyl substituted heterocyclic compounds in 1972.[104] Sodium or potassium amide was used to deprotonate a variety of heterocyclic compounds before quenching with *n*-propyl nitrate to form the desired nitro compounds. A representative reaction is shown in equation 64. 4-Picoline was converted to 4-nitromethylpyridine **82h** in 66% yield. Most yields for this reaction are between 50 and 70%, and some substrates

[104] Feuer, H.; Lawrence, J. P. *J. Org. Chem.* **1972**, *37*, 3662-3670.

fail to form the desired nitroalkane at all. Nevertheless, this is a great way to make heteroaryl nitromethane compounds.



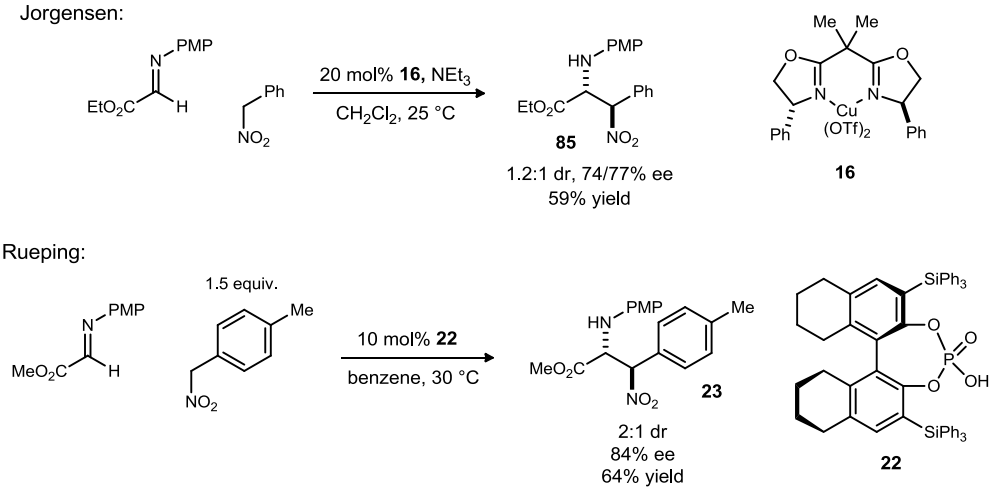
82h (65)

We emulated the Feuer work in the design of the reaction in equation 65. LDA was used as a substitute for $NaNH_2$, and isopropyl nitrate was used in place of *n*-propyl nitrate simply due to its commercial availability. In unoptimized results, **82h** was formed in appreciable yield of 40% using LDA in THF at -78 °C. This method has the promise of being a quick way to access heteroaryl nitroalkanes from robust starting materials.

2.5 BAM Catalyzed Additions of Aryl Nitroalkanes to Azomethine

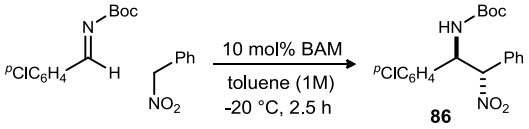
The use of arylnitroalkanes as substrates for the asymmetric aza-Henry reaction is rare. Only two examples exist in the literature (Scheme 16). Jorgensen produced adduct **85** in 1.2:1 dr and 74/77% ee (major/minor).[33] Reuping performed a similar addition to an α-imino ester with 2:1 dr and 84% ee.[39] Aryl nitroalkanes are a relevant substrate, as this reaction produces precursors to valuable chiral, non-racemic substituted 1,2-diamines. The scarcity of aryl nitroalkane additions reported in the literature could be an indication of the poor performance of this substrate in the aza-Henry reaction with other catalyst systems.

Scheme 16. Examples of Aryl Nitroalkane aza-Henry Additions



In comparison to a simple alkyl nitroalkane like nitroethane (pK_a = 16.7 in DMSO)[105], phenylnitromethane is considerably more acidic (pK_a = 12.2 in DMSO).[106]

Table 16. Phenylnitromethane Additions at -20 °C



entry	BAM	conv.[a] (%)	dr[a] (*anti:syn*)
1	PBAM	100	>20:1
2	PBAM•HOTf	100	>20:1
3	$PBAM_2(HOTf)_3$	100	>20:1

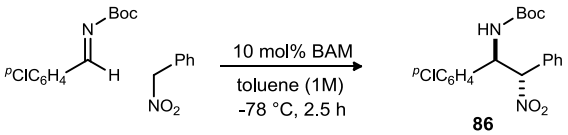
[a]Conversion and diastereomer ratios measured by ^{1}H NMR.

Since phenylnitromethane is more easily deprotonated than other nitroalkanes, it should be expected that the aza-Henry reaction should be faster with phenylnitromethane. Performing the reaction under similar conditions as previously used with aliphatic nitroalkane additions, we indeed found that the addition of phenylnitromethane was much faster than those of simple aliphatic nitroalkanes. With PBAM catalysts of three different protonation states, full conversion was achieved after just 2.5 hours (Table 16). Each

[105] Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006-7014.
[106] Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321-325.

catalyst gave aza-Henry product **86** in greater than 20:1 dr. By comparison, a full day was needed to achieve full conversion with nitroethane under these conditions.

Table 17. Phenylnitromethane Additions at -78 °C

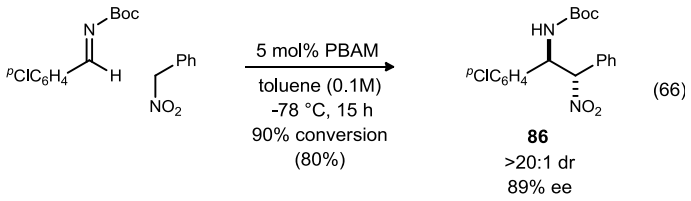


86

entry	BAM	conv.[a] (%)	dr[a] (*anti*:*syn*)	ee[b] (%)
1	PBAM	100	>20:1	78
2	PBAM•HOTf	100	>20:1	76
3	PBAM$_2$(HOTf)$_3$	100	>20:1	76

[a]Conversion and diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

With such a reactive system in hand, the reaction was performed at -78 °C. The results are displayed in Table 17. Even at -78 °C, reactions performed with all three catalysts were complete after only 2.5 hours. The most remarkable result of this series of reactions is the fact that unprotonated PBAM was equally enantioselective as its protonated counterparts. Never before in the use of BAM catalysts in any reaction has the free base provided enantioselection equal to that of the protonated catalysts. Enantioselection in these reactions was high but not at the level seen with aliphatic nitroalkanes as displayed previously.



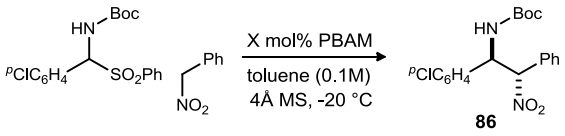
(66)

Unexpectedly, a notable increase in enantioselection was observed when the reaction was run under more dilute conditions (eq 66). Of course, this was at the expense of longer reaction time, but time to completion remained reasonable at less than one day. This time with just 5 mol% catalyst aza-Henry product **86** was obtained in greater than

20:1 and 89% ee with 80% yield. We speculate that solubility issues contribute to the slight drop in ee at higher concentrations.

The ability of unprotonated PBAM to promote the aza-Henry reaction of phenylnitromethane with high enantio- and diastereoselectivity gave us the confidence to try the elimination of the α-amido sulfone to the imine and subsequent aza-Henry reaction in one pot. As discussed previously with the work of Palomo in Chapter 1, there are many advantages to doing these two reactions in one pot. Initial attempts using just

Table 18. One-Pot Elimination/Aza-Henry with PBAM



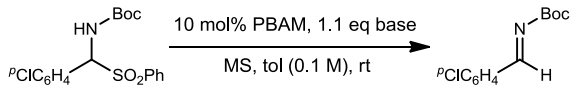
86

entry	X	conv. (%)	dr[a] (*anti:syn*)	ee[b] (%)
1	20	39	>20:1	n/a
2	50	89	>20:1	74

[a]Conversion and diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

catalytic amounts of PBAM did not go to completion as shown in Table 18. Still, this was encouraging as significant conversion to aza-Henry product was observed with high diastereoselectivity and moderate enantioselectivity. The conversion of these reactions consistently correlated with the catalyst loadings. For example a catalyst loading of 20 mol% would cause the reaction to occur, but conversion would reach 40% and go no further as shown in entry 1, Table 18. We speculated that was due to catalyst diprotonation during the reaction, rendering it inactive as it is no longer sufficiently basic to promote the elimination of sulfinic acid.

Table 19. One-Pot Elimination/Aza-Henry with PBAM



entry	base	2h conv.(%)[a]	26h conv.(%)[a]
1	NEt_3	11	12
2	DMAP	25	27
3	imidazole	n/a[b]	n/a[b]
4	pyridine	15	17

[a]Conversion measured by ^{1}H NMR. [b]Full consumption of α-amido sulfone, but imine was not formed.

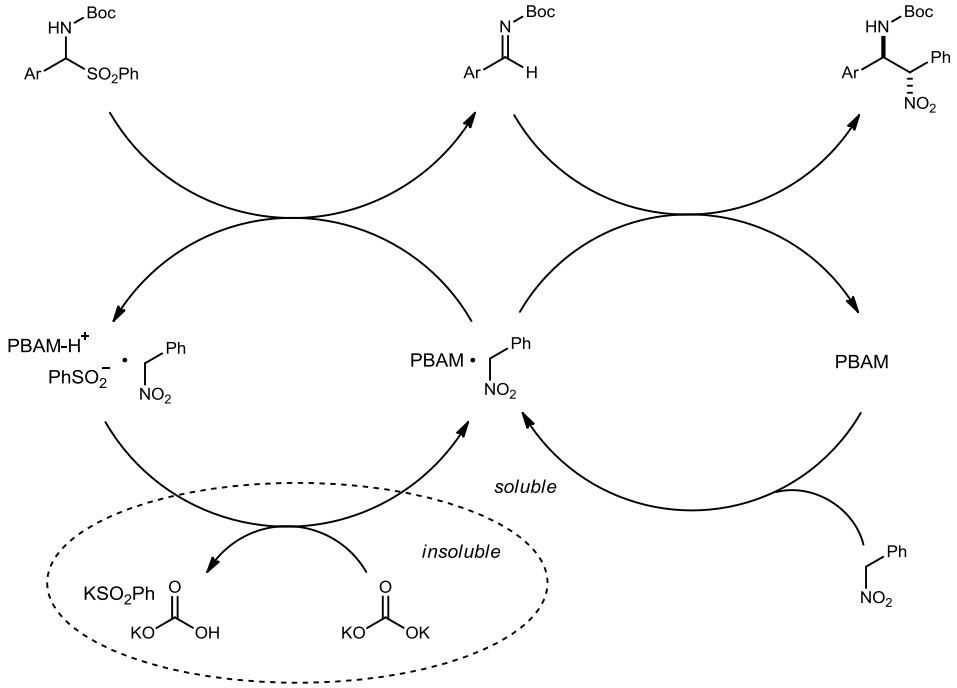
This suggested that an exogenous stoichiometric base should be employed to aid in the elimination. Initially, a wide range of stoichiometric organic bases were used to aid in the process as shown in Table 19. Four organic amine bases of varying pK_a values were chosen, but none of these bases led to a notable increase in conversion to imine.

Although, the addition of a stoichiometric organic base did not appear to promote the one pot elimination/aza-Henry, potassium carbonate remained a candidate for the one-pot process, as it is the base used to perform the elimination of the α-amido sulfones to make the imines. When potassium carbonate was used in conjunction with PBAM in the one-pot reaction, a remarkably fast conversion was observed by comparison to the reaction times needed for the carbonate elimination of sulfones to imines. Oddly, the K_2CO_3 elimination, when performed separately, is quite sluggish at room temperature as several days are typically needed to reach full conversion. The slow step in this process has to be the elimination based on the previously displayed work. This large increase in the rate of elimination in this system indicates that the PBAM/K_2CO_3/phenylnitromethane reagent combination is much more efficient at promoting the elimination than K_2CO_3 alone. This is something that Palomo also observed when using CsOH in combination with cinchona alkaloids and nitroalkanes to perform aza-Henry reactions starting from the α-amido sulfones. The diastereoselection

was low presumably due to the high temperature of this reaction and the possibility of post-reaction epimerization at this temperature. Enantioselection was good for this temperature. There seems to be little influence of the heterogeneous base (K_2CO_3) on enantioselection of this reaction.

A proposed mechanism of this one-pot reaction is given in Scheme 17. The basicity of the combination of PBAM and phenylnitromethane is responsible for the elimination step. The elimination is much slower using PBAM and K_2CO_3 without phenylnitromethane. Therefore, the most active base species is likely the *in situ* formed nitronate of phenylnitromethane. The organic base must be recycled to get full

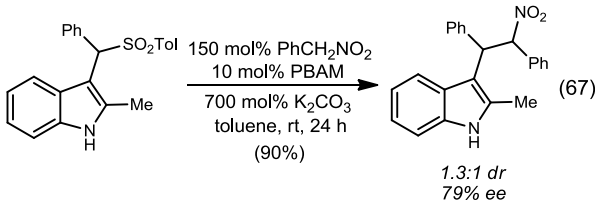
Scheme 17. Proposed Mechanism of One-Pot Elimination Addition



conversion of the sulfone to imine, so K_2CO_3 deprotonates the conjugate acid of the base species. The reformed PBAM·phenylnitromethane is then able to eliminate more sulfone to imine. The K_2CO_3 does not participate in the aza-Henry reaction, and

PBAM·phenylnitromethane is responsible for forming aza-Henry product stereoselectively.

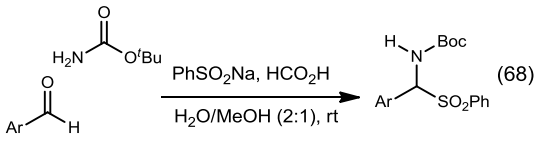
This one-pot elimination of sulfones and subsequent addition has been utilized in a 1,4-addition to indoles.[107] Good enantioselection with low diastereoselection was



(67)

observed in preliminary studies shown in equation 67. This is a good example of the utility of this one-pot reaction as the vinylogous imine intermediate to this point has proven to be difficult to isolate, yet the addition product to the vinylogous imine (formed *in situ*) has been isolated in excellent yield (90%).

These α-amido sulfones are made via a simple process from the corresponding aldehyde, phenylsulfinic acid sodium salt, *tert*-butyl carbamate, and formic acid in a water/methanol mixture (eq 68). The resulting sulfones are simply filtered and are sufficiently pure without further manipulation. The formic acid and sulfinate salt

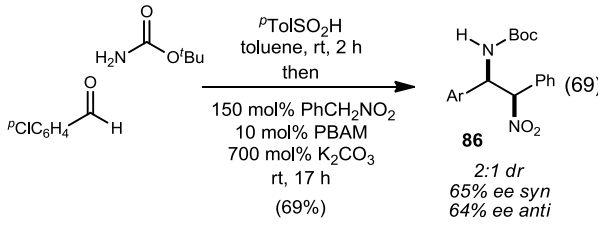


(68)

presumably react to make phenylsulfiinic acid *in situ*, so this reaction takes place by merely stirring the sulfinic acid, aldehyde, and carbamate.

It seemed possible that this three step process from aldehyde, to sulfone, to imine, and finally to aza-Henry product could be accomplished in one reaction. Sulfinic acid

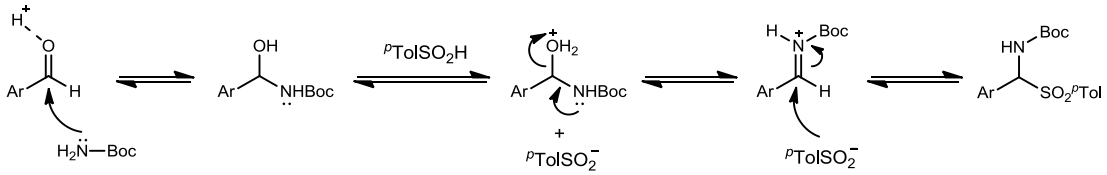
[107] Dobish, M. C.; Johnston, J. N. *Org. Lett.* **2010**, *12*, 5744-5747.



was made prior to the reaction for the purpose of simplification. Remarkably, the reaction resulted in 69% yield still with significant enantioselection (eq 69). Possibly due to post-reaction epimerization, 2:1 dr favoring the *syn* diastereomer was observed.

This result also placed focus on the mechanism of α-amido sulfone synthesis. The most likely scenario is outlined in Scheme 18. If the imine or iminium is being formed and subsequently trapped by the sulfinate, it would seem possible that that imine or iminium could be trapped by a different nucleophile. The use of stoichiometric amounts of sulfinic acid may not be necessary.

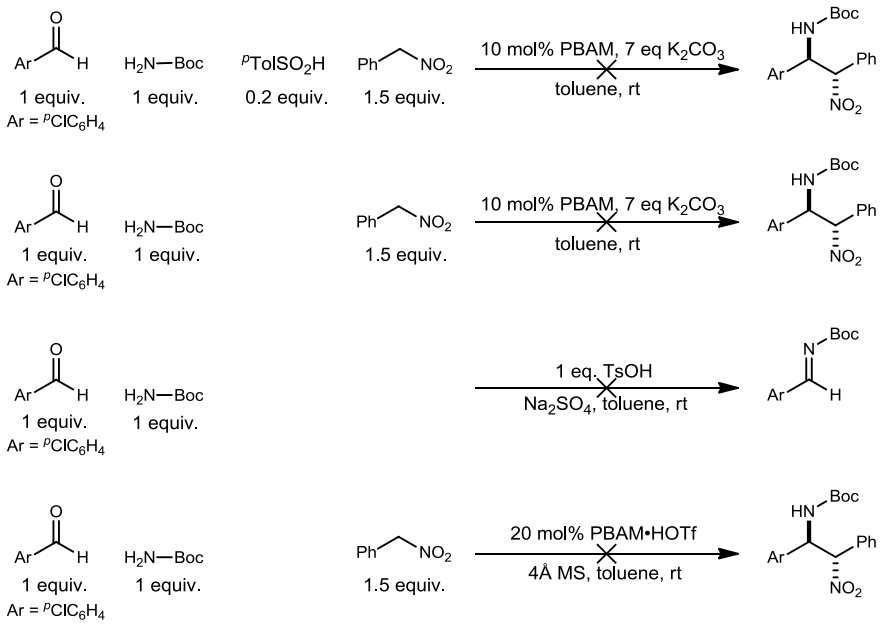
Scheme 18. Proposed Mechanism of Sulfone Formation



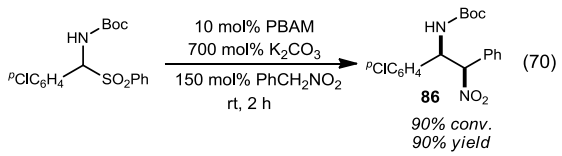
A series of reactions was performed that affirmed some necessary aspects of this sulfone formation (Scheme 19). Using a catalytic amount of sulfinic acid and combining all reagents at once resulted in no reaction. The same result occurred when using no sulfinic acid and when combining the rest of the reagents at once. At this point, it seemed that an equivalent of acid was needed to promote iminium formation. Combining carbamate, aldehyde, and an equivalent of tosic acid led to no reaction. Finally, a catalytic amount of PBAM·HOTf was used with aldehyde, carbamate, and phenylnitromethane. Since PBAM·HOTf can act as both an acid and a base, it was

thought that its acidity could help promote imine formation. The basicity of the catalyst could help form the nitronate, and imine could be trapped by the nitronate in a stereoselective fashion. This strategy also resulted in no reaction. All of the reactions in Scheme 19 resulted in only recovered starting materials.

Scheme 19. Probing the Mechanism of Sulfone Formation

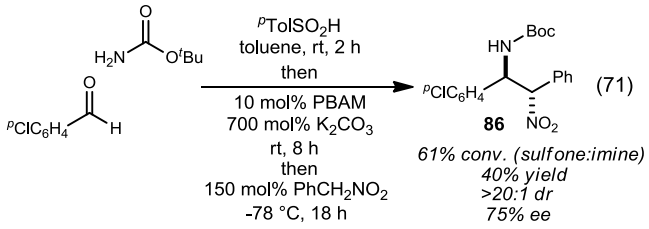


Nevertheless, we had a remarkable process in hand that went through two isolable intermediates to form a product with two stereocenters with good stereoselection. Enantioselection and diastereoselection were still short of the levels previously exhibited with nitroalkane additions to imines. It seemed the lowering of the reaction temperature could help us achieve these higher levels. The sulfone formation and elimination to imine could be performed at room temperature. The third step of the process could then be done at -20 °C or -78 °C to favor higher enantio- and diastereoselection. After the imine was formed, the reaction could be cooled before the addition of phenylnitromethane. This did not turn out to be successful as the elimination to the imine was very sluggish in the absence of phenylnitromethane.



(70)

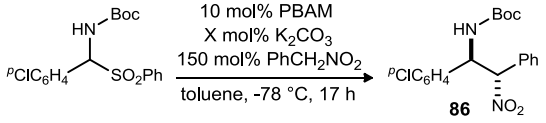
In equation 70, the elimination and aza-Henry reaction occurred to the level of 90% conversion in 2 hours at room temperature. The product **86** was formed in 1:1 dr, 74% ee *anti* and 53% ee *syn*. In contrast, the reaction in equation 71 was allowed to stir for 8 hours at room temperature. Still, this longer time did not allow for full conversion of the sulfone to imine. This suggests that phenylnitromethane plays a role in the



(71)

elimination step. It seems phenylnitromethane is essential for rapid sulfone elimination to imine, so optimal reaction conditions must involve the imine formation and aza-Henry reaction occurring simultaneously.

Table 20. One-Pot Elimination/Aza-Henry Reaction at -78 °C

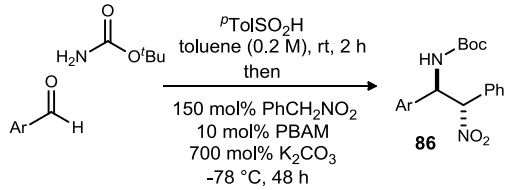


entry	concentration (M)	K_2CO_3 (mol%)	conv.[a] (%)	dr[a] (*anti:syn*)
1	0.1	200	30	>20:1
2	0.1	700	46	>20:1
3	0.2	700	64	>20:1[b]
4	0.5	700	63	>20:1

[a]Conversion and diastereomer ratios measured by ^{1}H NMR. [b]48% isolated yield, 79% ee measured by HPLC using chiral stationary phases.

The elimination and addition steps of this process were isolated to examine the viability of performing these steps at -78 °C as shown in Table 20. Significant levels of conversion were seen after 17 hours further highlighting the enhanced ability this system has of eliminating the sulfone to imine. Concentrating the reaction and increasing the equivalents of K_2CO_3 appeared to have some positive effect on the conversion of this reaction; while this favored higher conversion, stereoselection is lowered slightly (*vide supra*). The product **86** of entry 3 was isolated (48% yield) and found to be 79% ee. Diastereoselection was found to be >20:1 with all reactions.

Table 21. Aldehyde Scope of One-Pot Elimination/Aza-Henry Reaction at -78 °C



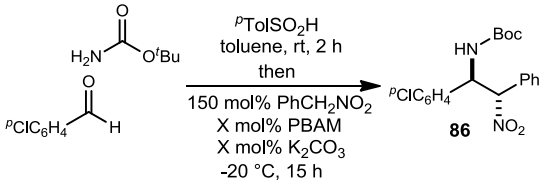
entry	Ar		conv.[a] (%)	dr[a] (*anti:syn*)	ee[b] (%)	yield (%)
1	^{p}ClC$_6$H$_4$	**86**	39	>20:1	82	27
2	^{o}MeOC$_6$H$_4$	**b**	60	>20:1	85	58
3	^{2}naphthyl	**c**	49	>20:1	78	35
4	^{2}thiophene	**d**	54	>20:1	58	31

[a]Conversion and diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

This was performed with different aldehydes to show the scope of the reaction (Table 21). A 48 hour reaction time and a concentration of 0.2 M were chosen as optimal conditions for reactivity. The results were disappointing in that all reactions did not go to full conversion despite the longer reaction times. It was encouraging that similar levels of enantio- and diastereoselection were observed with different aldehydes. Since full conversion has not been achieved at -78 °C, it seemed like the reaction would need to be run at a warmer temperature. It also seemed likely that decreasing the concentration of these reactions would be beneficial as the reaction mixtures were always very thick and it was difficult to achieve sufficient stirring throughout the reaction.

Table 22 displays the results of varying base and catalyst equivalents at a more dilute concentration of 0.09 M and warmer temperature of -20 °C. Entry 2 represents a good result of 72% yield after 15 hours reaction time and a lower base and catalyst loading. Diastereoselection was still exceptional under these conditions, but enantioselection was only at the level of 74% ee.

Table 22. Further Optimization of One-Pot Reaction

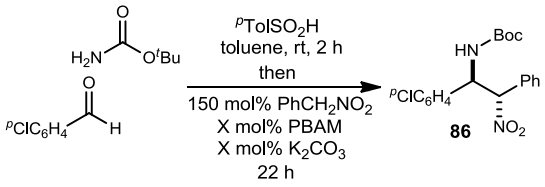


entry	PBAM (mol%)	K_2CO_3 (mol%)	conv.[a] (%)	dr[a] (*anti:syn*)	ee[b] (%)	yield (%)
1	5	700	59	17:1	68	69
2	5	300	75	>20:1	74	72
3	2	700	46	>20:1	n/a	n/a
4	2	300	41	>20:1	n/a	n/a

[a]Conversion and diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

Further experiments in Table 23 indicate the equivalents of K_2CO_3 can be lowered without the loss of reactivity. All three reactions were performed at different temperatures and catalyst loading to find an optimal reaction protocol. It seems that -20 °C is the temperature needed to obtain high reactivity and yields without the sacrifice of diastereoselection observed at room temperature. Still, enantioselectivity is only moderate at 73% ee. The 83% yield in entry 2 is the best yield we have obtained in this reaction and notable considering the complexity of the process.

Table 23. Further Optimization of One-Pot Reaction

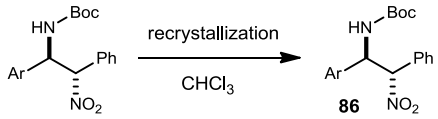


entry	PBAM (mol%)	K_2CO_3 (mol%)	°C	conv.[a] (%)	dr[a] (*anti:syn*)	ee[b] (%)	yield (%)
1	10	700	-78	36	>20:1	n/a	n/a
2	10	300	-20	85	>20:1	73	83
3	5	300	-78	56	>20:1	n/a	n/a

[a]Conversion and diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

Although it was clear that diastereoselection was excellent in this process, the absolute configuration of the products had to be determined. A series of recrystallizations was performed to stereochemically enrich the previously synthesized aza-Henry products (Table 24). Entries 3 through 6 all exhibited enrichment in the crystals obtained. Crystalline material of exceptionally high ee and dr were obtained for the substrate in entry 4 (**86g**). An X-ray crystal structure was obtained from this material.[108] The *anti* stereochemistry assigned to all *N*-Boc imine phenylnitromethane addition products in this document is by analogy to this experimental assignment. This enrichment by recrystallization was reproducible as shown in entry 5.

Table 24. Recrystallization of Phenylnitromethane Addition Products



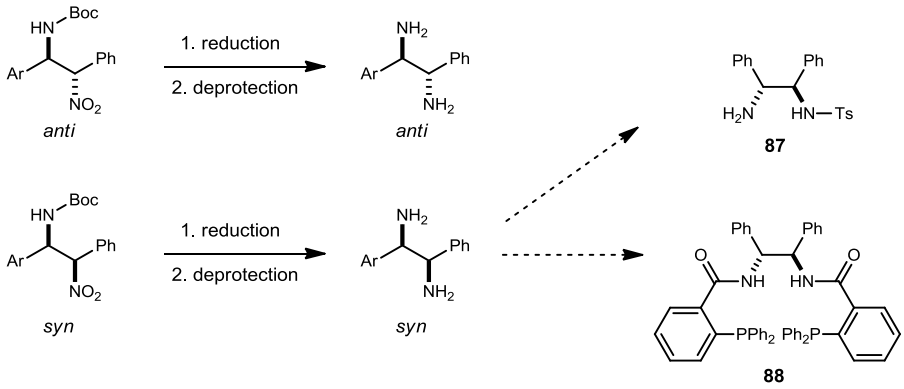
entry	Ar		dr[a] (*anti:syn*)	ee[a] (%)	dr[a] (*anti:syn*)	ee[a] (%)
1	$^pClC_6H_4$	**86**	4 : 1	76	n/c	n/c
2	$^2C_4H_3S$	**d**	4 : 1	77	7 : 1	73
3	$^3C_4H_3S$	**e**	10 : 1	84	10 : 1	90
4	$^pPhSC_6H_4$	**f**	7 : 1	82	31 : 1	97
5	$^pPhSC_6H_4$	**f**	7 : 1	82	32 : 1	95
6	$^pMeO^mBrC_6H_3$	**g**	8 : 1	73	13 : 1	82

[a]Diastereomer and enantiomer ratios measured by HPLC using chiral stationary phases.

[108] See Experimental Section for data.

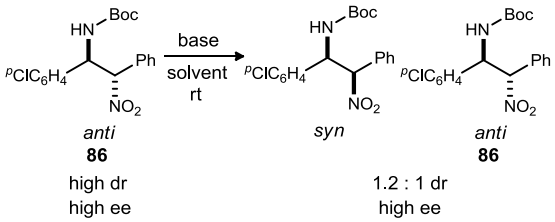
The diastereomer obtained in these reactions is the *anti* diasteromer. The *syn* diastereomer is more often employed in applications of asymmetric catalysis. The *syn* diastereomer could easily be converted to the *syn*-1,2-diaryl-1,2-diamine by reduction and deprotection (Scheme 21) That diamine could be used as the chiral backbone for many asymmetric catalysts like Noyori's ligand (**87**) and Trost's ligand (**88**).

Scheme 21. 1,2-Diaryl-1,2-Diamine *Anti* and *Syn* diastereomers



Fortunately, the diastereomer obtained from these aza-Henry reactions is the kinetic diastereomer. Allowing these reactions to warm up and stir with either PBAM or

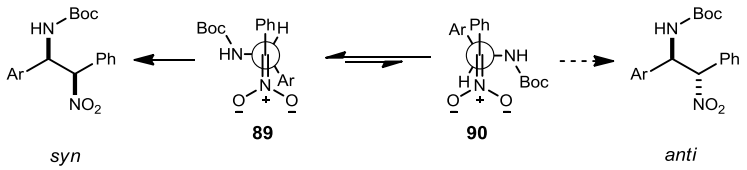
Scheme 20. Epimerization of Aza-Henry Products



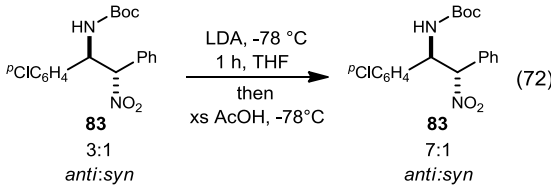
an achiral base can lead to epimerization. We experimentally determined that at equilibrium a 1.2:1 mixture of diastereomers favoring the *syn* diastereomer is obtained (Scheme 20).

Another potential approach to epimerization as a means to generate high *syn* β-amino-nitroalkane would be to diastereoselectively protonate one face of the nitronate

Figure 26. Model for Kinetic Protonation of Phenylnitromethane Addition Products



under kinetic conditions (excess acid, low temperature). A model for this kinetic protonation of the nitronate is shown in Figure 26. A Felkin-Anh type model could suggest that **89** represents a lower energy transition state than **90** due to steric interactions of the -Ar and -Ph groups in **90**. Protonation from the right side of **89** would lead to *syn* product. In equation 72, the aza-Henry adduct was deprotonated with lithium



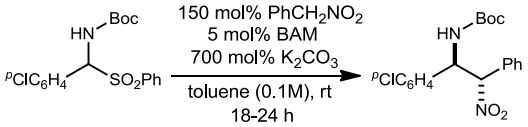
(72)

diisopropylamide to form the lithium nitronate salt. The nitronate salt was then protonated with acetic acid. Unfortunately, the selectivity exhibited was for the face of the nitronate leading to the *anti* product.

A final approach to the *syn* diastereomer that was investigated was the search of our catalyst collection for one that might provide kinetic *syn*-selectivity. Table 24 shows the effect of variation at the 4-position of the quinoline has on stereoselection in the one-pot phenylnitromethane addition reaction. For simplicity this reaction was performed at room temperature. At room temperature diastereoselection is uniformly low across all catalysts, and only *anti*-selectivity is observed. Less Brønsted basic catalysts in entries 1

and 2 performed poorly in terms of enantioselection. Increasing the Brønsted basicity in entries 3 through 5 had a positive effect on enantioselection. It is likely that the less reactive, less Brønsted basic catalysts did not promote the reaction to the extent to compete with a probable background rate.

Table 25. One-Pot Aza-Henry BAM Catalyst Screen

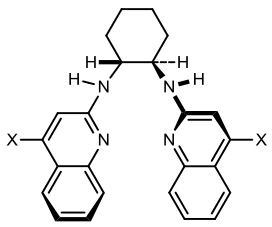


86

entry	X		dr[a] *anti:syn*	ee (%)[b] *anti*	ee (%)[b] *syn*
1	CF_3	**91**	3:1	5	3
2	Cl	**92**	3:1	13	9
3	H	**74**	2:1	31	25
4	Me	**75**	4:1	59	44
5	OMe	**93**	4:1	49	44
6	morpholine	**94a**	3:1	33	53
7	piperidine	**94b**	2:1	31	51
8	1-methylpiperizine	**94c**	4:1	48	51
9	*N*-methylaniline	**94d**	4:1	65	64
10	butylamine	**94e**	1:1	46	47
11	dibutylamine	**94f**	4:1	19	30
12	diethylamine	**94g**	5:1	22	47
13	homo-piperidine	**94h**	1:1	60	35
14	pyrrolidine	**76**	1:1	79	56

[a]Diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.

BAM



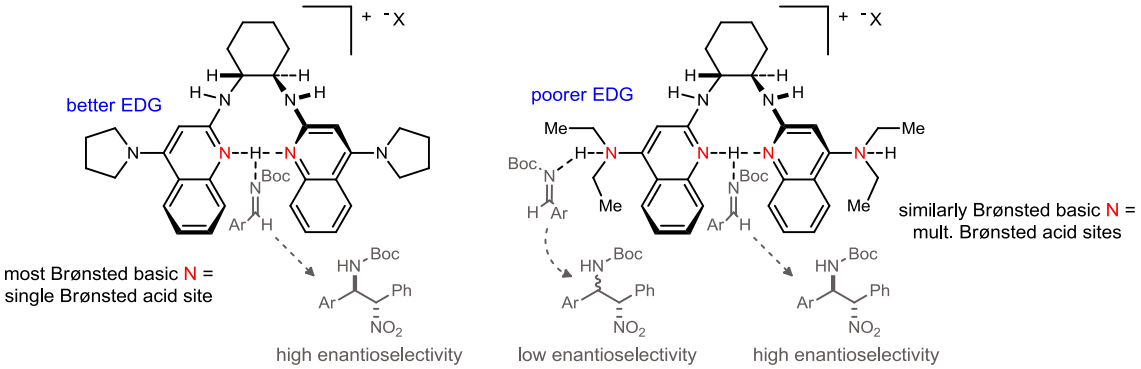
Despite the lack of *syn*-selectivity observed in all reactions in Table 25, other useful information could be gathered from these results. A variety of different electron-rich amines were coupled to make the catalysts in entries 6 through 15. The cyclic secondary amines (morpholine, piperidine, *N*-methylpiperazine, and homopiperidine) should be similar electronically to pyrrolidine based on nucleophilicity measurements.[109] Interestingly, the pyrrolidine based catalyst remained the best catalyst in terms of enantioselection by far. It seems unlikely that the slight steric differences with the different amines plays a factor in this as these changes are relatively far away from the binding pocket. Although we do not have the pK_a measurements to definitely suggest

[109] Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679-3688.

this, it seems that the pyrollidine catalyst is likely the most basic catalyst as the only noticeable trend seen in this table is that the enantioselectivity of this transformation increases with the Brønsted basicity of the catalyst. Of the non-pyrollidine catalysts, the catalyst derived from *N*-methylaniline in entry 9 provided the highest enantioselectivity.

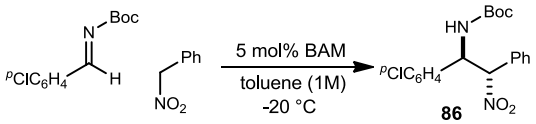
The results in Table 25 seem to follow a trend of increased Brønsted basicity of the quinoline nitrogen leading to increased enantioselection. Specifically, the highest enantioselectivity with the 4-pyrrolidine substituted catalyst should be expected based on the increased electon donating ability of the pyrrolidine in this system. To this point, all our evidence points to this increased Brønsted basicity of the quinoline nitrogen being the reason for this increase in enantioselection. An explanation for the observed decrease in enantioselectivity seen with other 4-amino substituted catalysts is given in Figure 27. The excellent electron-donating abilities of pyrrolidine increases the basicity of the quinoline nitrogen ensuring that the imine associates with a proton bound to the quinoline nitrogen. The introduction of less electron-donating amines at the 4-position opens up the possibility of an undesired protonation site becoming competitive with the quinoline nitrogen. If the imine is activated by a proton bound to the 4-amino nitrogen, a less enantioselective pathway could be accessed leading to lower enantioselection.

Figure 27. Rationale for Decreased Enantioselectivity with other Amines at the 4-position



A series of catalysts were screened to ascertain the optimal ligand for the phenylnitromethane addition to the preformed *N*-Boc imine. The results are shown in Table 26. The use of less Brønsted basic catalyst **93** resulted in essentially the same enantioselection as PBAM. Substitution at the 7- and 8- positions of the quinoline in the catalyst **95** resulted in no enantioselection but still high diastereoselection. This seems to suggest that steric bulk in the 8-position of the catalyst completely disallows the typical binding leading to no facial bias. Unsymmetrical catalyst **96,** used previously in this group in the addition of α-nitro esters to aryl imines to provide product with generally higher diastereo- and enantioselection than H,QuinBAM·HOTf (**74**·HOTf), resulted in similar enantioselection and diastereoselection values as PBAM. As seen in previous work in this group with nitroalkane additions, the triflic acid salt of unsymmetrical catalyst **97** led to exceptional diastereoselection. Enantioselection of the opposite enantiomer but of similar magnitude to PBAM was exhibited with this catalyst. Unprotonated **97** gave essentially no enantioselection but still high diastereoselection. This was strange as it was the first time with phenylnitromethane additions that a significant difference in enantioselection was observed between the triflic acid salt and free base of a particular catalyst.

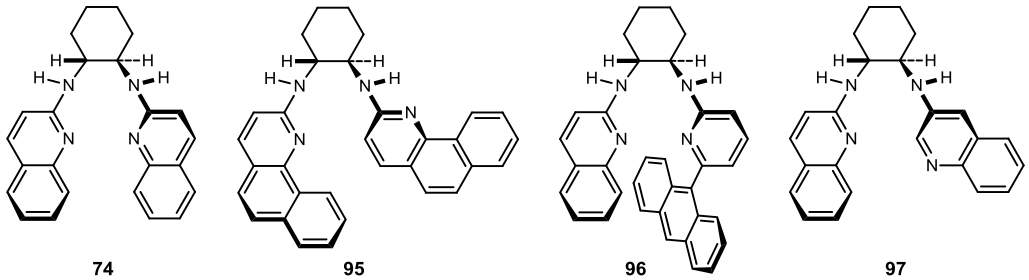
Table 26. Phenylnitromethane Aza-Henry Catalyst Screen



86

entry	BAM	dr[a] *anti:syn*	ee (%)[b] *anti*
1	**74**	>20:1	67
2	**74**•HOTf	>20:1	66
3	**95**	>20:1	0
4	**95**•HOTf	>20:1	0
5	**96**	>20:1	53
6	**96**•HOTf	13:1	72
7	**97**	>20:1	-3
8	**97**•HOTf	>20:1	-72
9	PBAM	>20:1	70
10	PBAM•HOTf	>20:1	70
11	PBAM$_2$(HOTf)$_3$	>20:1	70

[a]Diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.



74 H,Quin-BAM

95 H,^{2}(^{7,8}benzoQuin)-BAM

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

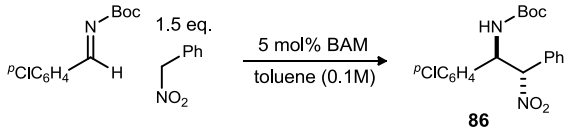
97 H,^{2}Quin(^{3}Quin)-BAM

The stereoselectivity provided by catalysts **96** and **97** (Table 26) as well as the success of the use of unsymmetrical catalysts in nitroacetate additions[110,111] led us to explore more Brønsted basic derivatives of these catalysts (Table 27). It was hoped that these catalysts would provide the increased reactivity observed with the ^{4}pyrrolidine catalysts and the increased stereoselectivity observed with catalysts such as **96**. The synthesis of these compounds is explained in Chapter 5. These catalysts were used with the optimized conditions for phenylnitromethane additions. Catalysts **98** and **99** did appear to offer similar but slightly reduced reactivity compared to PBAM as 49-70% conversion was observed after 20-44 hours (entries 2-5, Table 27). Enantioselection was

[110] Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466-3467.
[111] Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866-5867.

signficantly lower while diastereoselection was equally high with this series of catalysts. As seen with PBAM, the triflic acid salts generally provided similar enantioselection values to the free bases. **98** and structurally similar **99** provided comparable stereoselection values (>20:1 dr, 63-77% ee). The ^{2}quin^{3}quin catalyst (**99** and **99**·HOTf) provided the lowest enantioselection of the series (27% and 32% ee respectively).

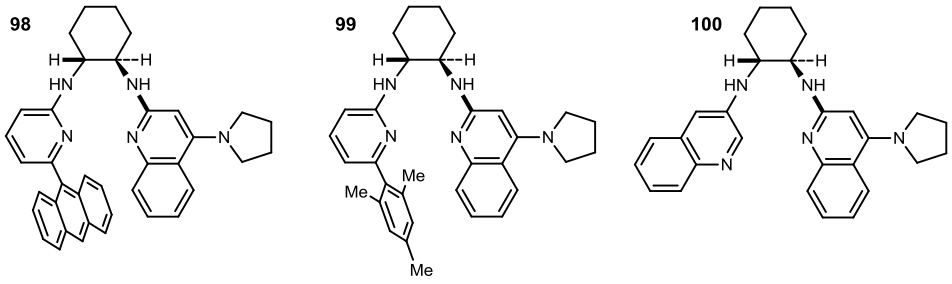
Table 27. Performance of non-C_2-symmetric PBAM Catalysts



86

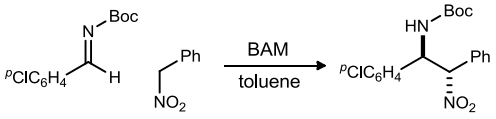
entry	BAM	time (h)	conv. (%)[a]	dr[a] *anti:syn*	ee (%)[b] *anti*
1	PBAM	15	90	>20:1	89
2	**98**	20	66	>20:1	63
3	**98**•HOTf	44	49	>20:1	68
4	**99**	20	61	>20:1	64
5	**99**•HOTf	44	70	>20:1	77
6	**100**	20	68	10:1	27
7	**100**•HOTf	44	70	>20:1	32

[a]Conversion and diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.



Throughout the broad screen of catalysts, it was interesting to find that catalyst **92c** performed significantly better than **92** (Table 28). A clear trend has already been established in that stereoselectivity increases as Brønsted basicity of the catalyst increases. Methyl substitution at the 5- and 7- positions seemingly had a positive effect on stereoselection. This could be an electronic effect, a steric effect, or a combination of the two. It seemed logical to extend this design to the 4-pyrrolidine catalysts seeking a similar increase in stereoselection.

Table 28. Phenylnitromethane Aza-Henry Catalyst Screen of ^{4}Cl BAM Catalysts



86

entry	BAM		temp. (°C)	dr[c] *anti:syn*	ee (%)[d] *anti*
1[a]	^{4}Cl	**92**	rt	8:1	22
2[a]	^{4}Cl^{5,7}Me	**92c**	rt	12:1	40
3[b]	^{4}Cl	**92**	-20	10:1	30
4[b]	^{4}Cl^{5,7}Me	**92c**	-20	14:1	64

[a]Reactions were 0.1 M in imine using 10 mol% catalyst. [b]Reactions were 1M in imine using 5 mol% catalyst. [c]Diastereomer ratios measured by ^{1}H NMR. [d]Enantiomer ratios measured by HPLC using chiral stationary phases.

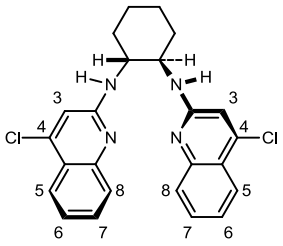
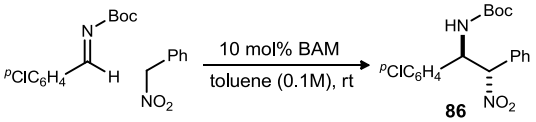


Table 29 exhibited the reactivity of 4-pyrrolidine catalysts with substitution at the 5-,6-, and 7- positions. Catalyst **76c** substituted at the 5- and 7- positions exhibited lower enantioselectivity than PBAM. This was somewhat expected as any substitution at the 5-position would force the pyrrolidine ring to twist out of the plane of the quinoline

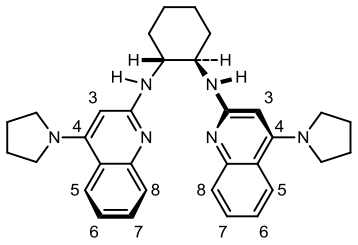
Table 29. Phenylnitromethane Aza-Henry Catalyst Screen of ^{4}Pyrrolidine Catalysts



86

entry	BAM		dr[a] *anti:syn*	ee (%)[b] *anti*	ee (%)[b] *syn*
1	^{4}Pyrr	**76**	1:1	88	50
2	^{4}Pyrr^{5,7}Me	**76c**	1:3	46	26
3	^{4}Pyrr^{6,7}Me	**76d**	1:1	95	39
4	^{4}Pyrr^{7}OMe	**76b**	1:1	91	43

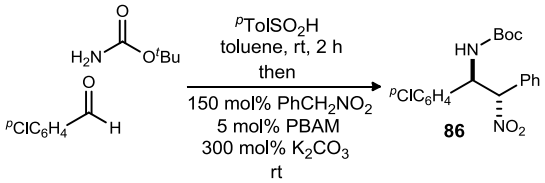
[a]Diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.



rendering it unable to donate into the quinoline system. Catalysts **76d** and **76b** preliminarily appeared to be more enantioselective than PBAM. Extending this study to the one-pot elimination addition reaction, a similar result was seen. Again, the PBAM catalysts with substitution at the 6- and 7- positions gave significantly higher

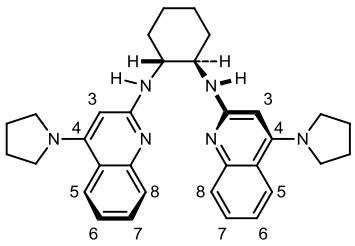
enantioselection for the *anti* diastereomer. These results are shown in Table 30. Diastereoselection was low as usual at ambient temperature.

Table 30. Phenylnitromethane Aza-Henry Catalyst Screen of [4]Pyrrolidine Catalysts in One-Pot Reaction



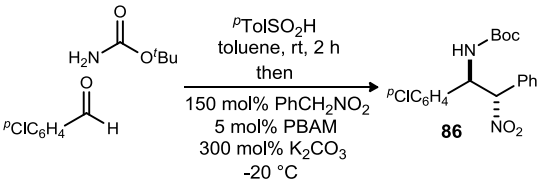
entry	BAM		dr[a] *anti:syn*	ee (%)[b] *anti*	ee (%)[b] *syn*
1	[4]Pyrr	**76**	1:1	79	56
2	[4]Pyrr[6,7]Me	**76d**	1:1	88	31
3	[4]Pyrr[7]OMe	**76b**	1:1	90	41

[a]Diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.



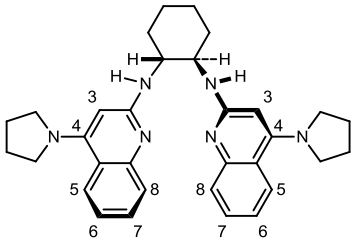
Using optimal conditions for the one-pot elimination addition reaction these substituted [4]pyrrolidine catalysts were not found to perform as well as PBAM (Table 31). At -20 °C, catalyst **76d** provided product **86** with 11:1 dr and 74% ee. Catalyst **76b** was also similar to PBAM in that it provided product in 7:1 dr and 71% ee. Unfortunately it appears that enantioselection of the *anti* diastereomer for all [4]pyrrolidine catalysts decreases at lower temperatures in the one-pot elimination/addition procedure.

Table 31. Phenylnitromethane Aza-Henry Catalyst Screen of [4]Pyrrolidine Catalysts in One-Pot Reaction



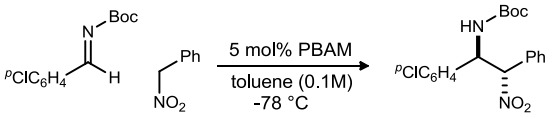
entry	BAM		dr[a] *anti:syn*	ee (%)[b] *anti*
1	[4]Pyrr	**76**	>20:1	74
2	[4]Pyrr[6,7]Me	**76d**	11:1	70
3	[4]Pyrr[7]OMe	**76b**	7:1	71

[a]Diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.



These catalysts were also employed in the direct addition of phenylnitromethane to imines under optimum conditions for stereoselection in Table 32. Almost identical enantioselection and diastereoselection to PBAM was exhibited by catalysts 7**6d** and **76b**.

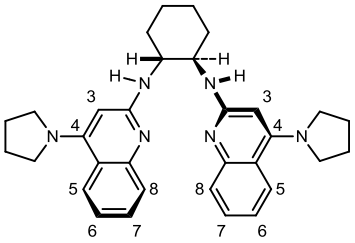
Table 32. Phenylnitromethane Aza-Henry Catalyst Screen of ^{4}Pyrrolidine Catalysts at -78 °C



86

entry	BAM		dr[a] *anti:syn*	ee (%)[b] *anti*
1	^{4}Pyrr	**76**	>20:1	89
2	^{4}Pyrr^{6,7}Me	**76d**	>20:1	85
3	^{4}Pyrr^{7}OMe	**76b**	>20:1	90

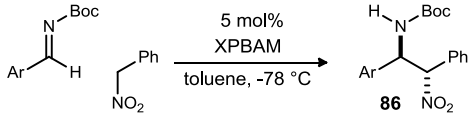
[a]Diastereomer ratios measured by ^{1}H NMR. [b]Enantiomer ratios measured by HPLC using chiral stationary phases.



To this point, it seems inconclusive that substitution of ^{4}pyrrolidine catalysts at the 6- and 7- positions positively affects stereoselection.

With optimal conditions established for the enantioselective aza-Henry addition of phenylnitromethane to azomethine, the substrate scope for this reaction was explored. This reaction was found to be very general as tolerance of a broad range of aryl *N*-Boc

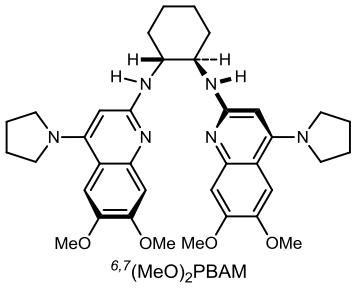
Table 33. Aryl Imine Variation in Aryl Nitroalkane Addition Reaction



86

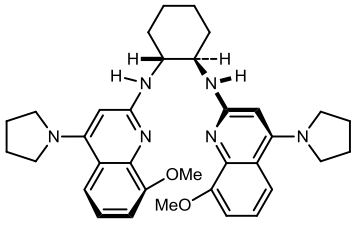
entry	Ar	XPBAM	# cat. screened		dr[b] (*anti:syn*)	ee[b] (%)	yield[c] (%)
1	^{p}ClC$_6$H$_4$	^{8}MeO	>10	**86**	13:1	91	97
2	^{2}C$_4$H$_3$S	^{8}MeO	6	**86d**	21:1	87	90
3[e]	^{p}MeO^{m}BrC$_6$H$_3$	^{8}MeO	3	**86g**	33:1	75	78
4[e]	^{o}MeC$_6$H$_4$	^{8}MeO	2	**86h**	50:1	87	88
5	^{o}CF$_3$C$_6$H$_4$	^{8}MeO	2	**86i**	20:1	77	87
6[e]	^{p}Oallyl	^{6,7}(MeO)$_2$	2	**86j**	101:1	84	79
7[d]	^{p}MeC$_6$H$_4$	^{6,7}(MeO)$_2$	1	**86k**	38:1	91	93
8[e]	^{m}MeC$_6$H$_4$	^{8}MeO	2	**86l**	28:1	81	90
9[d]	^{p}FC$_6$H$_4$	^{6,7}(MeO)$_2$	2	**86m**	15:1	87	97
10[d]	^{3}pyridyl	^{6,7}(MeO)$_2$	1	**86n**	28:1	60	82
11[d]	^{3}C$_4$H$_3$S	^{6,7}(MeO)$_2$	1	**86e**	30:1	82	85
12[d]	^{2}C$_4$H$_3$O	^{6,7}(MeO)$_2$	4	**86o**	18:1	68	85
13[e]	^{p}MeOC$_6$H$_4$	^{6,7}(MeO)$_2$	2	**86p**	81:1	85	83
14[d]	^{p}CF$_3$C$_6$H$_4$	^{6,7}(MeO)$_2$	4	**86q**	14:1	84	99
15	^{p}PhOC$_6$H$_4$	^{6,7}(MeO)$_2$	2	**86r**	25:1	83	97
16[d]	^{p}PhC$_6$H$_4$	^{6,7}(MeO)$_2$	1	**86s**	44:1	93	99
17[d]	^{2}Naphth	^{6,7}(MeO)$_2$	1	**86c**	25:1	91	99
18[e]	^{p}MeSC$_6$H$_4$	^{6,7}(MeO)$_2$	1	**86t**	69:1	93	94
19[e]	^{m}MeOC$_6$H$_4$	^{6,7}(MeO)$_2$	2	**86u**	38:1	89	88
20[e]	^{m}ClC$_6$H$_4$	^{6,7}(MeO)$_2$	2	**86v**	17:1	74	79

[a]All reactions were run using 1.1 equiv of nitroalkane in toluene (0.1 M) and 18-26 h reaction time unless otherwise noted. Configuration assigned by analogy to an adduct whose absolute and relative configuration was assigned by X-ray crystallography. [b]Ee, er, and dr were determined by HPLC. [c]Isolated yield after column chromatography. [d]1.2 equiv of imine used. [e]Warmed to -20 °C for 1h before workup.



^{6,7}(MeO)$_2$PBAM

76e



^{8}MeOPBAM

76f

imines was shown. Diastereoselection (13:1 dr or greater) and yields (78-99%) were unanimously high across all substrates and with all [4]pyrrolidine bisamidine catalysts used. Some less reactive imines required warming to -20 °C to reach full conversion and high yield. For most of the twenty entries in Table 33, multiple catalysts were screened to find the optimal catalyst for enantioselection. In all cases where multiple catalysts were used, the [8]MeOPBAM (**76f**) or [6,7](MeO)$_2$PBAM (**76e**) catalysts were found to be the most enantioselective. Both electron-rich aryl imines (entries 6, 13, 15, 18, and 19) and electron-poor aryl imines (entries 1, 5, 9, 12, and 20) were tolerated.

Good results were obtained with imines having substitution at the ortho, meta, and para positions. Ortho substituted imines (entries 4 and 5) performed well, with lower enantioselection of 77% ee seen with the *o*-CF_3 imine. Good enantioselection was also seen with the examples of meta substituted imines (entries 8, 19) while only modest enantioselection was seen with the *m*-Cl imine (entry 20, 74% ee). The use of vast array of para-substituted imines led to good enantioselection (entries 1, 6, 7, 9, 13-16, and 18).

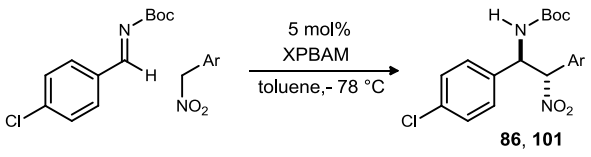
Varying levels of enantioselection were seen when using heteroaromatic *N*-Boc imines. The best example was 21:1 dr and 87% ee with the 2-thiophene imine (entry 2). The 3-thiophene imine (entry 11) led to lower, but still good enantioselection (82% ee). Other examples suffered from lower enantioselection. The 3-pyridyl (entry 10, 60% ee) and 2-furyl imines (entry 12, 68% ee) unfortunately gave only modest enantioselection despite being screened with a number of chiral proton catalysts.

Some functionality was tolerated as halogens and an alkene were brought in as a part of the aryl *N*-Boc imine. An aryl fluoride, chloride, and bromide were all tolerated (entries 1, 3, 9, and 20) with mostly good enantioselection. An alkene was also

incorporated successfully as the *p*-Oallyl imine (entry 6) gave good enantioselection of 84% ee.

With the imine scope thoroughly explored, we sought to also use different aryl nitroalkanes to further demonstrate the generality of this transformation. The results are

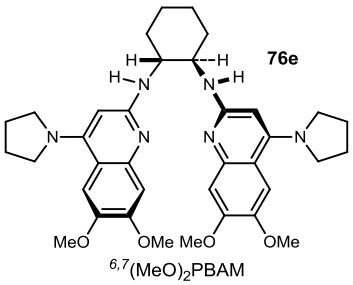
Table 34. Aryl Nitroalkane Variation in Enantioselective Addition



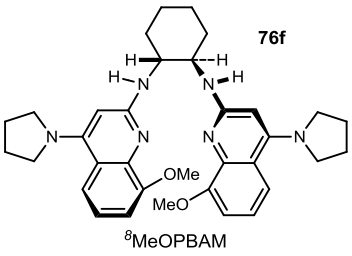
86, **101**

entry	Ar		XPBAM	# cat. screened	dr[b] (*anti:syn*)	ee[b] (%)	yield[c] (%)
1	$^{o}BrC_6H_4$	**101b**	$^{6,7}(MeO)_2$	3	4 : 1	76	91
2	$^{m}BrC_6H_4$	**101c**	$^{6,7}(MeO)_2$	5	13 : 1	89	91
3	^{2}Np	**101d**	$^{6,7}(MeO)_2$	3	10 : 1	80	99
4	$^{p}NO_2C_6H_4$	**101e**	$^{6,7}(MeO)_2$	3	2 : 1	76	99
5[d]	$^{p}MeOC_6H_4$	**101f**	$^{6,7}(MeO)_2$	3	17 : 1	86	90
6	C_6H_5	**86**	^{8}MeO	>10	13 : 1	91	97
7	^{4}pyridyl	**101g**	$^{6,7}(MeO)_2$	8	1.4 : 1	71/67	57
8	$^{p}ClC_6H_4$	**101**	^{8}MeO	>10	9 : 1	95	95

[a]All reactions were run using 1.1 equiv of nitroalkane in toluene (0.1 M) and 18-26 h reaction time unless otherwise noted. Configuration assigned by analogy to an adduct whose absolute and relative configuration was assigned by X-ray crystallography. [b]Ee, er, and dr were determined by HPLC. [c]Isolated yield after column chromatography. [d]Warmed to -20 °C for 1h before workup.



$^{6,7}(MeO)_2$PBAM

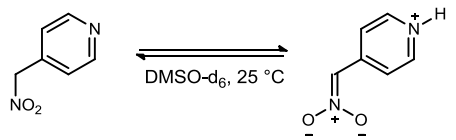


^{8}MeOPBAM

shown in Table 34. Once again, excellent yields were seen with most cases. Tolerance of substitution at the ortho, meta, and para positions was demonstrated. Substitution at the ortho position was problematic as lower enantio- and diastereoselection (4:1 dr, 76% ee) was seen with the *o*-Br phenylnitromethane (entry 1). The *m*-Br nucleophile (entry 2) fared much better leading to 13:1 dr and 91% ee. The previously displayed results using the *p*-Cl phenylnitromethane (entry 8) demonstrate good diastereoselection and excellent enantioselection with a para- substituted nucleophile. Both electron-poor (entry 4) and electron-rich (entry 5) phenylnitromethanes were employed. The *p*-NO2 nucleophile gave low dr (2:1) but modest ee (76%). The low diastereoselection was not unexpected for this substrate as post-reaction epimerization is more likely due to the increased acidity of this

product. The electron-rich *p*-methoxy phenylnitromethane gave excellent diastereoselection (17:1 dr) and good enantioselection (86% ee).

A heteroaromatic substrate, 4-nitromethylpyridine (entry 7), was also successfully used in this reaction, although with essentially no diastereoselection and only modest enantioselection (71% and 67% ee) and yield (57%). Once again, the low diastereoselection could be expected as the inherent basicity of that aza-Henry product could promote post-reaction epimerization, a process that must be controlled with this reaction. This 4-nitromethylpyridine (**82h**, eq 73) substrate is a challenging nucleophile



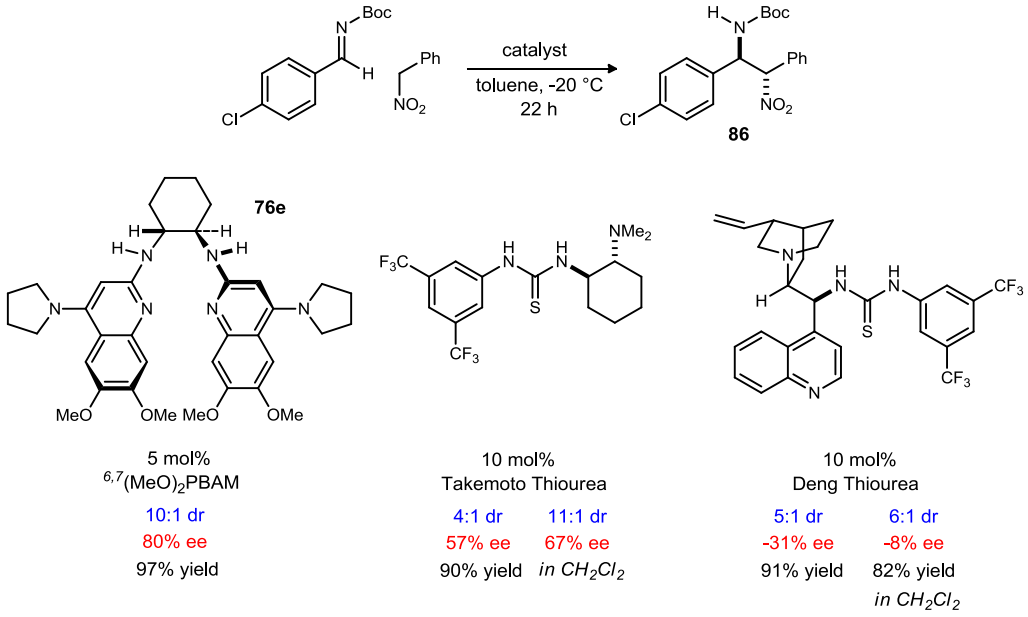
82h **82h-**tautomer (73)

for this reaction in that itself is appreciably Brønsted basic and could potentially form an appreciably Brønsted acidic nitronate salt *in situ*. A ^{1}H NMR spectrum of 4-nitromethylpyrdine in DMSO-d_6 actually shows that an equilibrium exists in solution between the neutral species and the zwitterionic pyridinium nitronate species. This tautomer could act as a non-selective catalyst promoting formation of racemic product. The modest enantioselectivity here at least indicates that our enantioselective catalyst is outcompeting any aforementioned unselective Brønsted acid species that could be formed with this substrate. This furthers the case for this system offering broad applicability.

Despite the plethora of examples of enantioselective aza-Henry reactions in the literature, only two examples of the addition of aryl nitroalkanes currently exist as discussed earlier (Scheme 16). The absence of aryl nitroalkane examples in the literature could be due to the lack of commercial availability of these compounds, the fact that

these compounds perform poorly with the reported system, or simply because the substrate was not considered for whatever reason. In order to compare the performance of our catalysts to others in the field, we used two other common catalysts with our conditions for the aryl nitroalkane aza-Henry reaction (Scheme 22).

Scheme 22. Catalyst Comparison with Aryl Nitroalkane Additions



The thioureas popularized by Takemoto and Deng did promote the aza-Henry reaction to form product **86**. The reaction temperature of -20 °C was chosen to ensure sufficient conversion to product. 10 mol% of the Takemoto thiourea promoted this reaction to yield **86** in 4:1 dr and 57% ee in our optimal solvent for this reaction, toluene. This catalyst was also used with Takemoto's optimal solvent, CH_2Cl_2, to give **86** in higher diastereo- and enantioselection (11:1 dr, 67% ee). The Deng thiourea offered lower enantioselection as 31% ee of the opposite enantiomer was yielded in toluene. Essentially no enantioselection was observed in CH_2Cl_2 (61% ee, -8% ee). Under the same conditions, 5 mol% $^{6,7}(MeO)_2$PBAM (**76e**) gave 10:1 dr and 80% ee. Although it is unfair to make the assumption that thiourea-based catalysts are inferior catalysts for this

transformation, this data suggests that the use of aryl nitroalkanes as nucleophiles in this reaction cannot be viewed as a simple substrate change. A catalyst proven to promote the aza-Henry reaction with aryl *N*-Boc imines and simple alkyl nitroalkanes with exceptional stereoselectivity (4-14:1 dr, 92-99% ee) fails to do the same under similar conditions with aryl nitroalkanes.

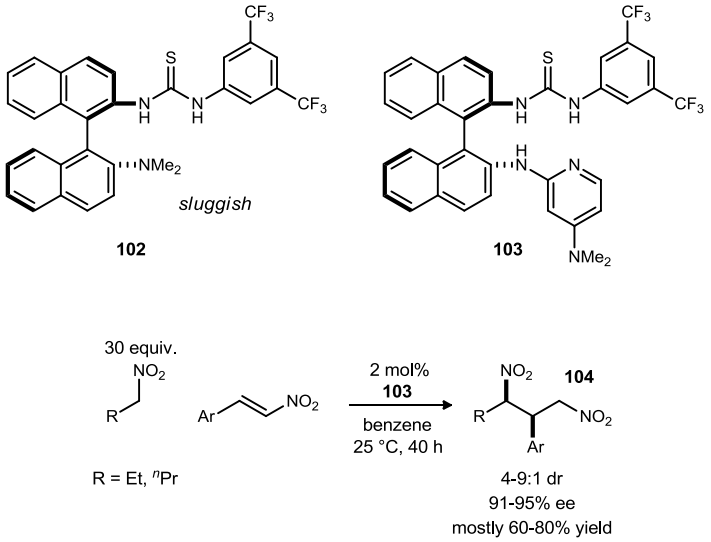
2.6 Michael Additions to Nitroalkenes

With the unique reactivity that PBAM exhibits, it seems likely that this catalyst could be applicable to a broader range of reactions dependent on pronucleophile deprotonation. To explore the utility of PBAM beyond additions to imines, the Michael addition of nitroalkanes was attempted using PBAM as a catalyst. This was inspired by the work of Wulff in this area using a similar increased Brønsted basic catalyst.[112]

Wulff initially screened less Brønsted basic catalyst **102** in this reaction and found that reaction to proceed very sluggishly (Scheme 23). Using catalyst **103**, nitroalkanes were added to nitroalkenes to give addition products with good dr and excellent ee. The yields were generally modest and an excess of nitroalkane was necessary to prevent polymerization.

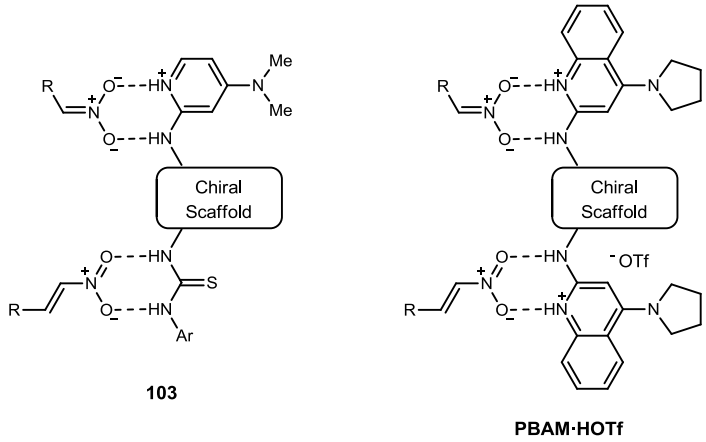
[112] Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524-13525.

Scheme 23. Wulff's Michael Addition of Nitroalkanes to Nitroalkenes



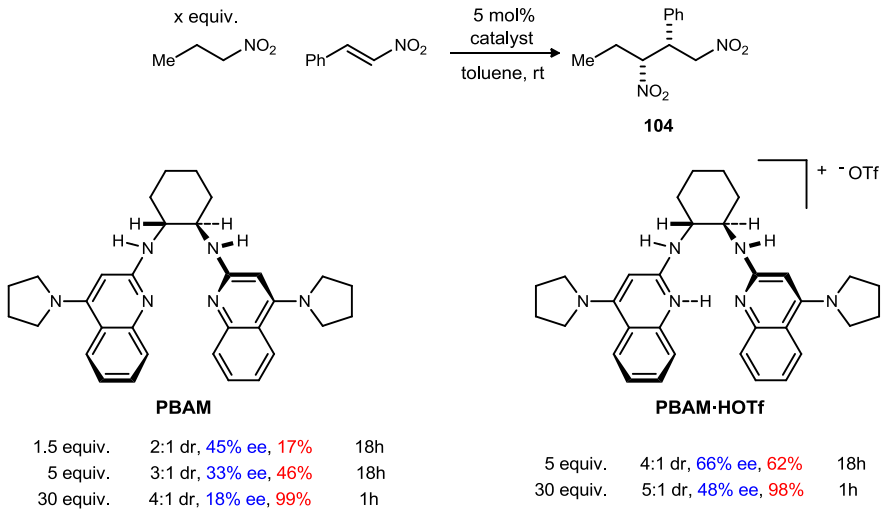
This catalyst **103** is very similar to PBAM on one side with a thiourea moiety on the other side. It is reasonable that the thiourea participates in hydrogen bonding with the nitroalkene while the amidine serves to deprotonate and bind to the nitroalkane (Figure 28). These two interactions can also be envisioned with the triflic acid salt of PBAM. The necessary increased Brønsted basicity is present with PBAM, and the protonated amidine could serve to hydrogen bond with the nitroalkene nucleophile.

Figure 28. Dual Activation by Wulff's Catalyst and PBAM



In a brief study, PBAM and PBAM·HOTf were found to catalyze this Michael addition to nitroalkenes (Scheme 24). We also found that the use of excess nitroalkane

Scheme 24. PBAM Catalyzed Nitroalkane Michael Additions



was necessary to avoid undesired polymerization and obtain high yields. Ultimately, excellent yields were obtained when using 30 equivalents of nitropropane with both catalysts. Unfortunately, this was at the expense of enantioselectivity as ee values decreased. PBAM·HOTf was able to produce **104** with a promising level of stereoselection (4:1 dr, 66% ee) when using 5 equivalents of nitroalkane.

This reaction could perhaps be optimized to get higher enantioselection and more favorable nucleophile stoichiometry in the future. Nevertheless, this presented an example of PBAM promoting an enantioselective reaction without the use of an imine electrophile. There are likely many more prochiral substrates capable of interacting with PBAM to undergo reaction and yield useful chiral, non-racemic products.

CHAPTER III

ASYMMETRIC SYNTHESIS OF A GLYT1 INHIBITOR

3.1 Background

Schizophrenia is a disease characterized by the symptoms of delusions and hallucinations. Apart from the mental health symptoms, patients diagnosed with schizophrenia die 12-15 years earlier than the average population. The lifetime prevalence and incidence are 0.30-0.66%.[113]

Typical treatment of schizophrenia is the administration of antipsychotic drugs that act as dopamine D2 and serotonin 5-HT2a receptor antagonists. These drugs are effective in the management of the positive symptoms such as delusions and hallucinations, but they have a minimal effect on the negative symptoms (lack of motivation, social withdrawal, etc.). Additionally, many of undesired side effects accompany the use of these drugs due to the promiscuous pharmacology exhibited by these medicines.[114]

There exists the need for better therapeutics for the treatment of schizophrenia than the aforementioned antipsychotic drugs. In the last several years, a large amount of evidence has surfaced that reduced function of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors may play an important role in the pathophysiology of schizophrenia.

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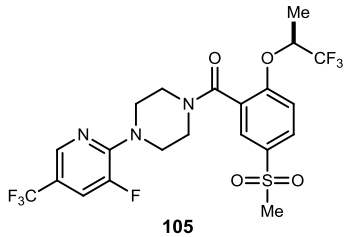
[113] van Os, J.; Kapur, S. *The Lancet* **2009**, *374*, 635-645.

[114]Pinard, E.; Alanine, A.; Alberati, D.; Bender, M.; Borroni, E.; Bourdeaux, P.; Brom, V.; Burner, S.; Fischer, H.; Hainzl, D.; Halm, R.; Hauser, N.; Jolidon, S.; Lengyel, J.; Marty, H.-P.; Meyer, T.; Moreau, J.-L.; Mory, R.; Narquizian, R.; Nettekoven, M.; Norcross, R. D.; Puellmann, B.; Schmid, P.; Schmitt, S.; Stalder, H.; Wermuth, R.; Wettstein, J. G.; Zimmerli, D. *J. Med. Chem.* **2010**, *53*, 4603-4614.

Enhancing the function of NMDA receptors is being explored as a potential therapy for schizophrenia. Glycine has been found to potentiate the NMDA response[115] and is a coagonist for NMDA activation.[116] Increasing the concentration of glycine in the brain without exogenous administration of glycine is a strategy being explored to increase NMDA function. One way to do this is to inhibit glycine uptake by small molecule inhibition of the glycine transporter I receptor (GlyT1).

Sarcosine (*N*-methylglycine), a protypical weak GlyT1 inhibitor, was found to improve positive, negative, and cognitive symptoms in schizophrenia patients. Unfortunately, this compound suffers from a poor pharmacological profile. Better therapeutic agents than sarcosine would be needed to adequately treat schizophrenia. Many modifications of sarcosine's structure were made in an attempt to find better GlyT1 inhibitors but ultimately failed due to the cause of undesirable effects.



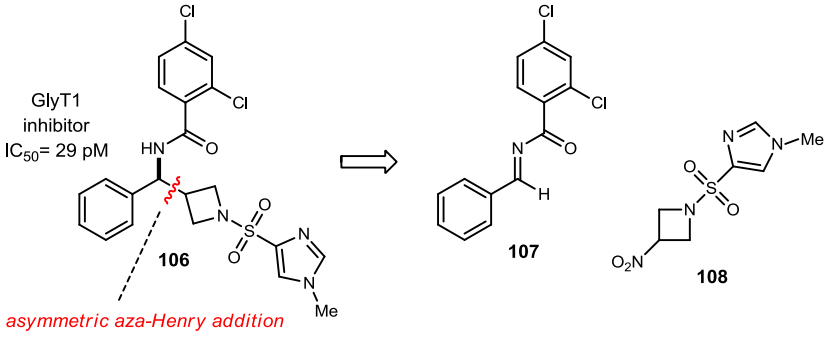
105
RG1678
Hoffmann-La Roche

Pharmaceutical companies are actively pursuing and developing non-sarcosine based GlyT1 inhibitors. Hoffmann-La Roche is developing a molecule RG1678 (**105**) and has recently (2010) reported positive Phase II clinical results for this compound.

[115] Johnson, J. W.; Ascher, P. *Nature* **1987**, *325*, 529-531.
[116] Kleckner, N.; Dingledine, R. *Science* **1988**, *241*, 835-837.

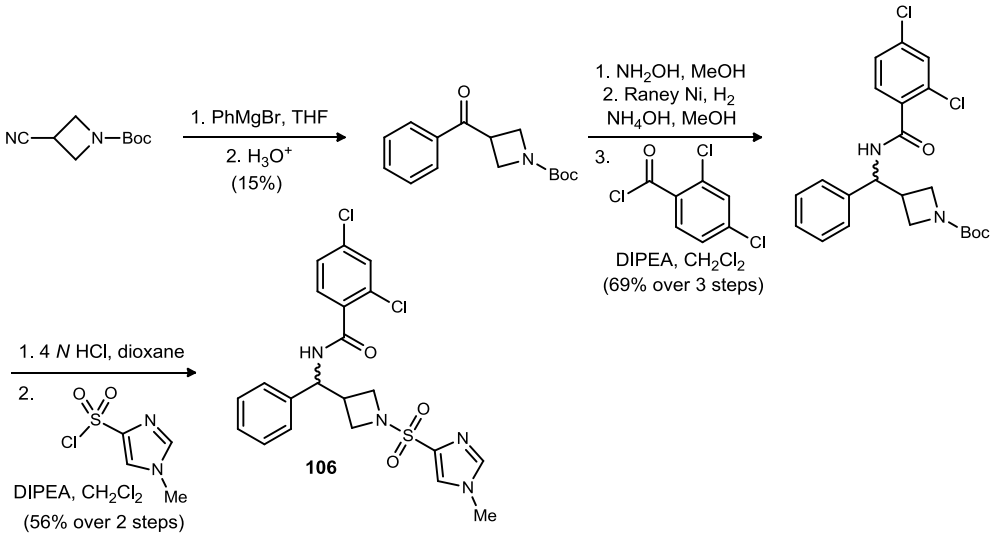
3.2 PBAM Catalyzed Asymmetric Synthesis of a GlyT1 Inhibitor[117]

Scheme 25. Retrosynthetic Analysis of GlyT1 Inhibitor



Similar efforts are being made here at Vanderbilt. Compound **106** has been found to be a potent GlyT1 inhibitor by the Lindsley group.[118] Furthermore, one enantiomer of **106**, whose absolute configuration has yet to be assigned, was found to be 10^4 times more reactive than its antipode.

Scheme 26. Lindsley Patent Medicinal Chemistry Route to GlyT1 Inhibitor **106**

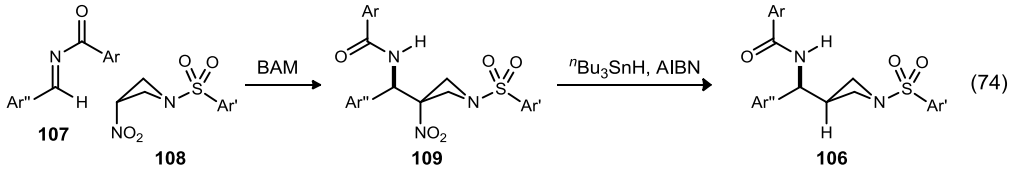


The racemic synthesis of **106** is outlined in the patent. A Grignard addition to a Boc-protected 3-cyanoazetidine and subsequent hydrolysis led to the corresponding ketone in 15% yield over two steps. Reductive amination followed by acylation provided

[117] Davis, T. A.; Danneman, M. W.; Johnston, J. N. *unpublished results*.
[118] Lindsley, C. W.; Conn, P. J.; Williams, R.; Jones, C. K.; Sheffler, D. J. US Patent 7572792

the corresponding Boc-protected azetidine in 69% yield over three steps. This compound was converted to racemic **106** (56% over two steps) after deprotection and acylation.

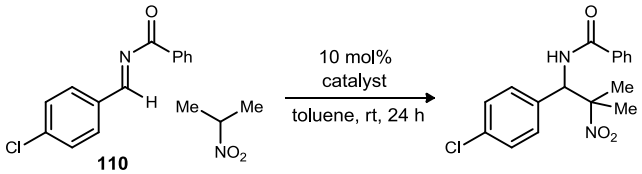
Our desire to use our chiral proton catalysis technology to facilitate the development therapeutics led us to envision an approach to this molecule using an asymmetric aza-Henry reaction between imine **107** and nitroazetidine **108** (Scheme 25). Subsequent denitration of the resulting tertiary nitroalkane **109** could give compound **106**. In the process, absolute stereochemistry of **106** could be assigned by analogy.



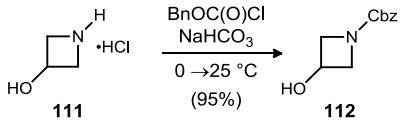
(74)

The most direct and convergent route to GlyT1 inhibitor **106** would involve addition of nitroazetidine **108** to benzoyl imine **107** (eq 74). Attempts to

Scheme 27. Enantioselective 2-Nitropropane Additions



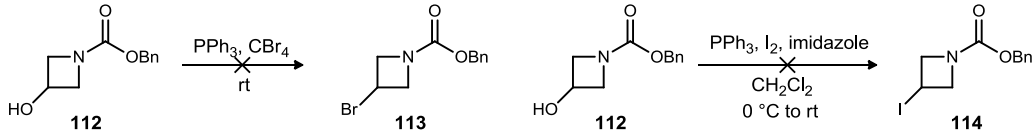
enantioselectively add to benzoyl imines have been unfruitful in our studies as they have led to products with no enantioselection. For example, Scheme 27 shows the BAM catalyzed addition of 2-nitropropane to benzoyl imine **110**. Essentially no enantioselection is observed with PBAM and its triflic acid salt. Alternatively, enantioselective additions of nitroalkanes to aryl *N*-Boc imines have been performed with a high level of enantioselectivity as shown previously in this document.



(75)

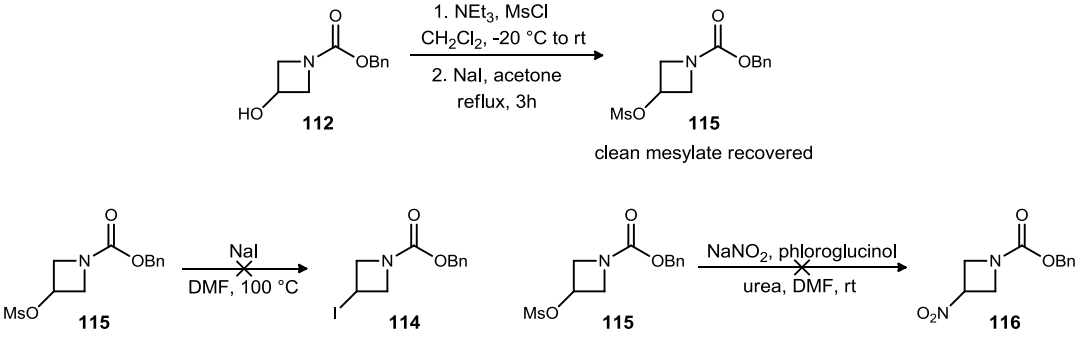
Early attempts to make sulfonyl nitroazetidine **108** were unsuccessful. A –Cbz protected nitroazetidine seemed to be a better substrate for the BAM catalyzed aza-Henry reaction since it would presumably have more desirable solubility and would not contain any Brønsted basic atoms that might self-catalyze the aza-Henry reaction resulting in a competitive, nonselective pathway. It seemed more logical to protect the nitrogen of 3-hydroxyazetidine **111**, then deprotect and acylate at a later stage. 3-Hydroxyazetidine was a good starting point as it is a relatively, cheap commercially available substance.[119] This reaction proceeded smoothly to give a nearly quantitative yield of protected hydroxyazetidine **112** (eq 75).

Scheme 29. Attempts at Direct Halogenation of 3-Hydroxyazetidine



Attempts to directly halogenate **112** were unsuccessful (Scheme 29). Treating **112** with triphenylphosphine and carbon tetrabromide in benzene or CH_2Cl_2 failed to produce

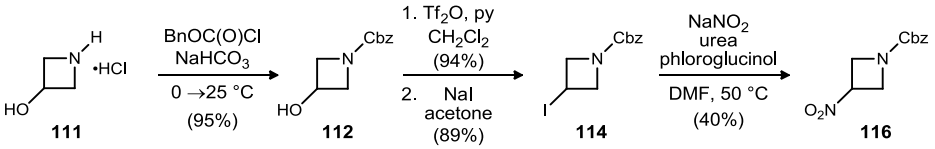
Scheme 28. Synthesis of and Reactions involving 3-MsO Azetidine



[119] Krishna Reddy, V. V. R. M.; Udaykiran, D.; Chintamani, U. S.; Mahesh Reddy, E.; Kameswararao, C.; Madhusudhan, G. *Org. Process Res. Dev.* **2011**, *15*, 462-466.

bromo-azetidine **113**, resulting in an intractable mixture of compounds. Similarly, treating **112** with triphenylphosphine, iodine, and imidazole failed to produce the desired iodo-azetidine **114**. Instead, it seemed necessary to activate the alcohol and isolate it in a discreet synthetic step. Unfortunately, attempts to go through the mesylate failed. The mesylate **115** was easily formed but failed to halogenate or nitrate under all conditions tried. Ultimately, nitroazetidine **116** was constructed in four steps from commercially available 3-hydroxyazetidine HCl salt (**111**, Scheme 30). The protected azetidine **112** was triflated and underwent displacement with sodium iodide to give 3-iodoazetidine **114** in 89% overall yield. A final displacement with sodium nitrite gave the desired aza-Henry substrate **116** in 40% yield.

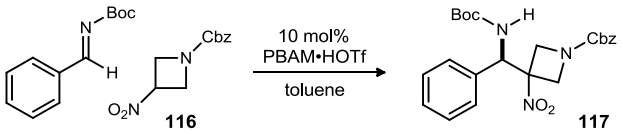
Scheme 30. Synthesis of 3-Nitroazetidine from 3-Hydroxyazetidine



With the desired nitroalkane in hand, we followed conditions previously developed for the aza-Henry addition of secondary nitroalkanes with PBAM·HOTf in Scheme 31. We were delighted to see good enantioselection of 78% ee of aza-Henry product **117** using PBAM·HOTf as a catalyst at room temperature. This reaction was surprisingly fast at this temperature as full conversion was achieved after only 70 minutes. This is in contrast to the addition of 2-nitropropane to aryl *N*-Boc imines for which reaction times of ~24 hours are required to achieve full conversion. With such a relatively reactive system in hand, the reaction temperature was lowered in an attempt to increase the observed enantioselection. Lowering the temperature to 0 °C led to a

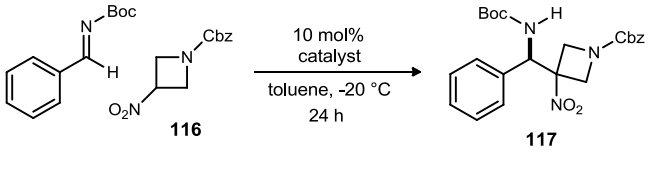
noticeable increase in enantioselection while reactivity was still good as only a four hour reaction time was necessary.

Scheme 31. Aza-Henry Addition of Nitroazetidine Catalyzed by PBAM·HOTf



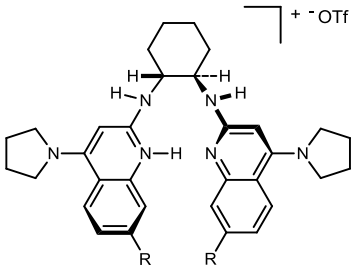
Ultimately, the optimal conditions for stereoselection were found to be -20 °C with a one day reaction time. A brief screen of BAM catalysts was performed to find the best catalyst for this reaction (Table 35). PBAM·HOTf was found to once again provide measurably higher enantioselection than at warmer temperatures as 86% ee was observed. The 7- substituted PBAM catalysts ^{7}MeOPBAM·HOTf (**76b**·HOTf) and ^{7t}BuPBAM·HOTf (**76q**·HOTf) each led to appreciably higher enantioselection of 92% and 90% ee, respectively. Excellent yields were seen with all catalysts screened.

Table 35. BAM Catalyzed Addition of Nitroazetidine



catalyst	ee[a] (%)	yield[b] (%)
PBAM•HOTf	86	87
^{7}MeOPBAM•HOTf	92	93
^{7t}BuPBAM•HOTf	90	99

[a]Enantiomer ratios measured by HPLC using chiral stationary phases. [b]Isolated yields.



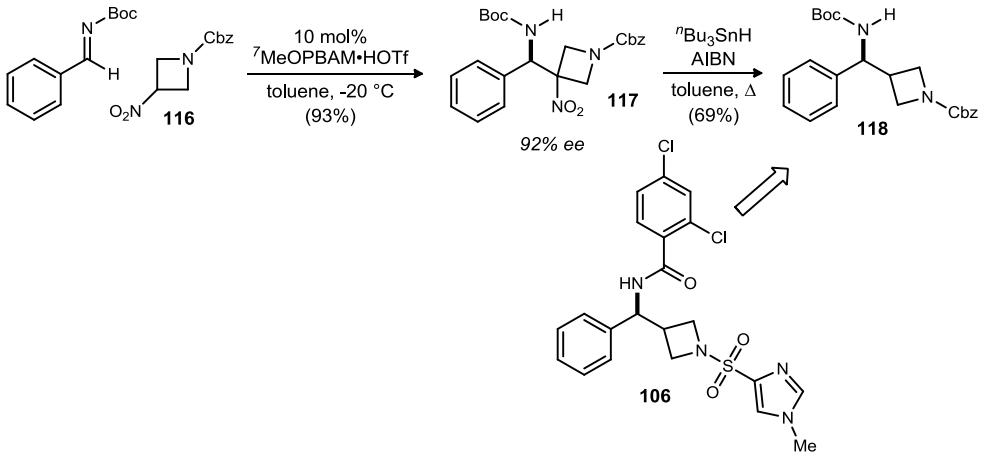
R = H, PBAM•HOTf (**76**•HOTf)
R = OMe, ^{7}MeOPBAM•HOTf (**76b**•HOTf)
R = ^{t}Bu, ^{7t}BuPBAM•HOTf (**76q**•HOTf)

With enantiomerically enriched aza-Henry product **117** in hand, a tin-mediated denitration was attempted (Scheme 32).[120,121] This reaction proceeded smoothly to furnish denitrated product **118** with a yield of 69%. Compound **118** provides a scalemic

[120] Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tet. Lett.* **1981**, *22*, 1705-1708.
[121] Tanner, D. D.; Blackburn, E. V.; Diaz, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 1557-1559.

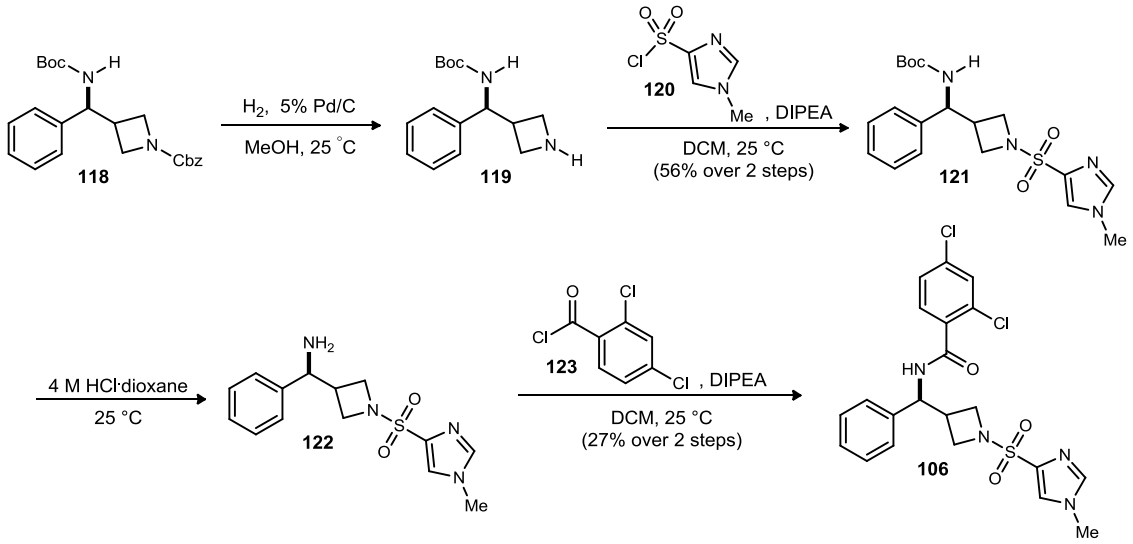
scaffold that can be used to access GlyT1 inhibitor **106** or any number of derivatives through employment of different acyl groups.

Scheme 32. Completion of Scalemic Scaffold for GlyT1 Inhibitor **106**



Scalemic scaffold **118** has been converted to GlyT1 inbibitor **106** (Scheme 33) by Michael Danneman. The –Cbz group of **118** was removed by hydrogenlysis before acylation with sulfonyl chloride **120** to provide **121** (56% yield over two steps). Acid-promoted –Boc deprotection and subsequent acylation provided the GlyT1 inhibitor **106** in 27% yield over two steps.

Scheme 33. Completion of GlyT1 Inbibitor **106**



Apart from the achievement of synthesizing **106** using our chemistry, the demonstration of a method utilizing an important heterocycle is noteworthy. The 4-membered nitrogen-containing heterocycle azetidine is a functional group often seen in bioactive molecules and therapeutics. Furthermore, the synthesis of azetidines and their incorporation into larger molecules is a topic of focus among synthetic organic chemists.[122] The ability to incorporate this functional group into more complex structures while controlling stereochemistry could potentially have many medicinal chemistry applications.

[122] Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988-4035.

CHAPTER IV

ENANTIOSELECTIVE SYNTHESIS OF THE ANTI-CANCER COMPOUND NUTLIN-3

4.1 Background

The tumor-suppressor protein p53 is a very important and well-studied gene and protein. This protein is a transcription factor that plays a major role in cell cycle regulation, particularly programmed cell death (apoptosis). p53 became the object of intense study after Hollstein and co-workers made the discovery that about half of human cancer cell lines contain mutations in the p53 gene.[123] Furthermore, it was found to be the most frequently inactivated protein in human cancer.

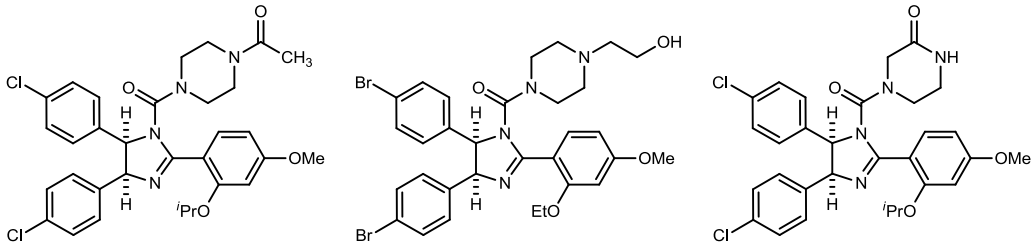
MDM2 is a protein involved in the regulation of p53. MDM2 is subsequently found to be amplified or overexpressed in many malignancies. This p53-MDM2 protein-protein interaction has been characterized by the crystal structure of MDM2 bound to a peptide from the transcriptional domain of p53. It was found that MDM2 possesses a deep hydrophobic pocket filled by three side chains from the helical region of the p53 peptide. This led to the idea that a small molecule could inhibit this MDM2/p53 interaction.

Vassilev and co-workers identified a series of *cis*-imidazoline compounds that effectively displaced p53 from MDM2 at low concentrations.[124] The compounds were

[123] Hollstein, M.; Sidransky, D.; Vogelstein, B.; Harris, C. *Science* **1991**, *253*, 49-53.
[124] Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. *Science* **2004**, *303*, 844-848.

made as racemic mixtures and separated by chiral chromatography. The Nutlins (short for Nutley inhibitors) are displayed in Figure 29. All three feature similar structural elements. Each has two identical aryl rings substituted with a halogen at the *para*-position. Some subtle changes in the piperazine ring ultimately led to the optimal inhibitor, (-)-Nutlin-3 (**124**). The levorotatory enantiomer (also referred to as enantiomer-a) was found to be nearly 150 times more potent as an inhibitor than the other (enantiomer-b).

Figure 29. Nutlins: *cis*-Imidazoline MDM2-p53 Inhibitors



Nutlin-3 is currently being developed by Hoffmann-La Roche and others as a therapeutic. Despite its potential to be a drug in the future, Nutlin-3 has been extensively used by the scientific community as a biological tool. This is evidenced by the avalanche of literature involving the compound since its disclosure to the public in 2004. A simple Scifinder search on the keyword "Nutlin-3" retrieves over 1000 research articles.

If Nutlin-3's only mechanism of action is the inhibition of the MDM2-p53 interaction, then it should only trigger apoptosis in the half of human cancer cell lines in which p53 is wild-type. Recent research has suggested that the mechanism of action of Nutlin-3 might not be that simple, as Nutlin-3 has been found to induce cell death in the absence of wild-type p53.[125]

[125] Lau, L. M. S.; Nugent, J. K.; Zhao, X.; Irwin, M. S. *Oncogene* **2008**, *27*, 997-1003.

p73 shares significant sequence homology to p53, but less is known about its function. In contrast to p53, p73 is rarely mutated or absent in cancers. Irwin and co-workers showed that Nutlin-3 induces apoptosis in p53-mutant and p53-deficient cells through the activation of p73.[125] There are other published examples of this p73 activation by Nutlin-3 in different types of cancer cells.[126,127] This suggests that Nutlin-3 could potentially be used to treat tumors that do not contain wild-type p53.

Several other non-p53 dependent pathways have been demonstrated as targets of Nutlin-3. VanderBorght showed that Nutlin-3 induces p21 expression and G1 cell cycle arrest in p53-deficient lung carcinoma cells.[128] It inhibits the binding of MDM2 to E2F-1 which causes an induction of apoptosis downstream in cells lacking functional p53.[129] The molecule can prevent the association of HDM2 (human MDM2) and HIF1-α (hypoxia-inducible factor 1α) which subsequently decreases VEGF (vascular endothelial growth factor) levels. [130] This reduction is seen as a potential therapy for certain types of cancers. Yoon, and co-workers recently published results demonstrating Nutlin's ability to bind to the anti-apoptotic Bcl family of proteins triggering apoptosis at the mitochondria.[131]

The significance and importance of Nutlin-3 is unquestionable. Unfortunately, no synthetic research on Nutlin-3 has been reported to date outside of the limited patent

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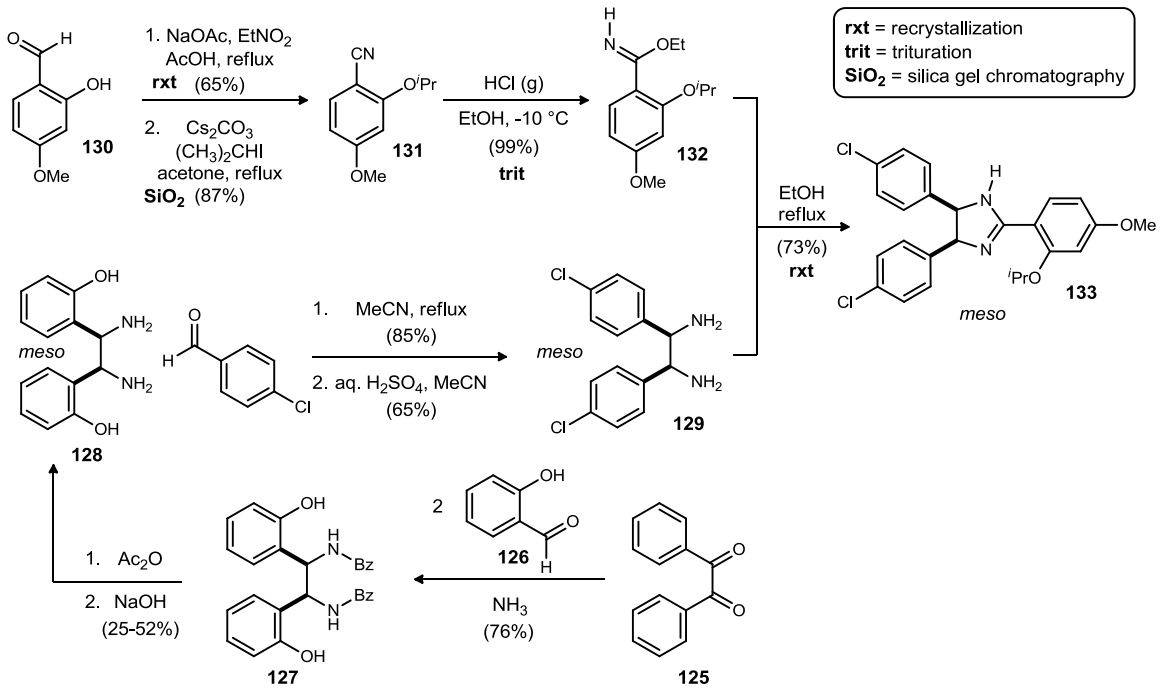
[126] Ray, R.; Bhattacharya, S.; Johnson, L. *Apoptosis* **2011**, *16*, 35-44.
[127] Zheng, T.; Wang, J.; Song, X.; Meng, X.; Pan, S.; Jiang, H.; Liu, L. *Journal of Cancer Research and Clinical Oncology* **2010**, *136*, 1597-1604.
[128] VanderBorght, A.; Valckx, A.; Van Dun, J.; Grand-Perret, T.; De Schepper, S.; Vialard, J.; Janicot, M.; Arts, J. *Oncogene* **2006**, *25*, 6672-6677.
[129] Ambrosini, G.; Sambol, E. B.; Carvajal, D.; Vassilev, L. T.; Singer, S.; Schwartz, G. K. *Oncogene* **2007**, *26*, 3473-3481.
[130] LaRusch, G. A.; Jackson, M. W.; Dunbar, J. D.; Warren, R. S.; Donner, D. B.; Mayo, L. D. *Cancer Res.* **2007**, *67*, 450-454.
[131] Ha, J.-H.; Won, E.-Y.; Shin, J.-S.; Jang, M.; Ryu, K.-S.; Bae, K.-H.; Park, S. G.; Park, B. C.; Yoon, H. S.; Chi, S.-W. *J. Am. Chem. Soc.*, *133*, 1244-1247.

details provided by Hoffmann-La Roche. Nutlin-3 is available in enantiopure and racemic form from various sources. Racemic Nutlin-3 is available from major, domestic supplier Sigma-Aldrich ($52/mg).[132] The necessity to separate the desired enantiomer by chiral column chromatography adds to the cost and inconvenience. The more potent enantiomer is also available domestically from Cayman Chemical for a price of $80/mg (5 mg) or $62/mg (25 mg).[133] This quantity may be practical for cell-based studies involving Nutlin-3 but is cost-prohibitive for most types of animal studies. Recently, we gave 500 mg of (-)-Nutlin-3 to the research group of Jennifer Pietenpol here at Vanderbilt for mouse studies. This amount of the compound would cost $31,160 based on the Cayman 25 mg quote. A bulk quote would likely be significantly lower, still, any price in this range would be prohibitively high for academic researchers.

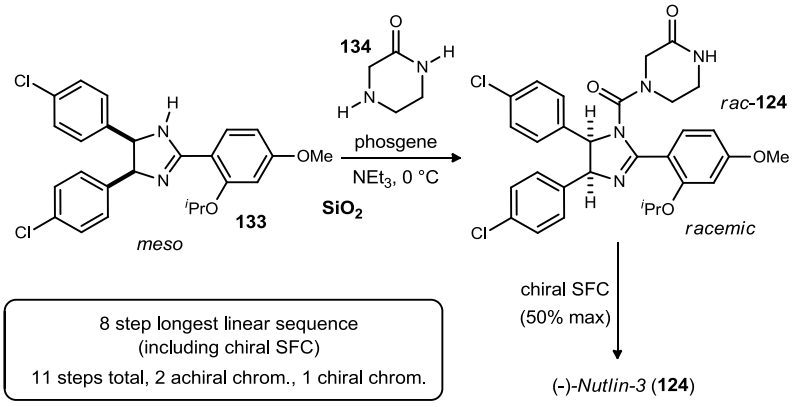
Scheme 34. Hoffmann-La Roche Patent Synthesis of Nutlin-3



[132] Price obtained from sigmaaldrich.com, Jan 28, 2011.
[133] Price obtained from caymanchem.com, Jan 28, 2011.

The synthesis of (-)-Nutlin-3 by Hoffmann-La Roche is outlined in a series of patents (Scheme 34). The synthesis starts as a diaza-Cope rearrangement between benzil (**125**) and salicylaldehyde (**126**) to provide 1,2-diamide **127** in 76% yield. The diamide was then acylated and hydrolyzed to unmask the free *meso*-1,2 diamine **128**. Another condensation with 2 equivalents of *p*-chlorobenzaldehyde and subsequent diaza-Cope rearrangement and hydrolysis provided *meso*-1,2-diamine **129** in 55% yield over 2 steps. The other component for the convergent condensation step was synthesized starting from 4-methoxysalicylaldehyde **130**. The aldehyde was converted to a nitrile by an interesting reaction with NaOAc and nitroethane in refluxing acetic acid. The free hydroxyl group of this nitrile was then appropriately alkylated to provide nitrile **131** in 57% yield over two steps. Nitrile **131** was then reacted with HCl gas in EtOH to give imidate **132** in an exceptional yield of 99%. This imidate was then condensed with *meso*-diamine **129** in refluxing ethanol to give *meso*-imidazoline **133** in good yield.

Scheme 35. Hoffmann-La Roche Synthesis of Nutlin-3



Imidazoline **133** was then converted to racemic Nutlin-3 by reaction with phosgene and oxo-piperazine **134** forming the necessary urea (Scheme 35). Chiral supercritical fluid chromatography was then used to separate (-)-Nutlin-3 (**124**) from the undesired enantiomer.

Overall, Hoffman-La Roche presents a highly convergent racemic synthesis of Nutlin-3. The yields are mostly good with the exception of the sequence to make *meso*-diamine **128** from protected diamide **127**. **128** is available commercially from GLSyntech, LLC for $2988 for 5 grams.[134] It seems likely this price is so high due to the inefficiency of this synthetic sequence.

The fact that this is a racemic synthesis presents the obvious drawback in that 50% of the material produced in the last step will not be used, resulting in a waste of raw material used for the synthesis and material that will have to be disposed of in the end. Asymmetric synthesis is commonly used to avoid these downfalls in scenarios where a chiral, non-racemic reagent or asymmetric catalyst can easily be applied. Unfortunately in this case, that opportunity does not exist as the synthesis goes through achiral intermediates. A new route would have to be designed without the use of achiral intermediates to render the synthesis of (-)-Nutlin-3 enantioselective.

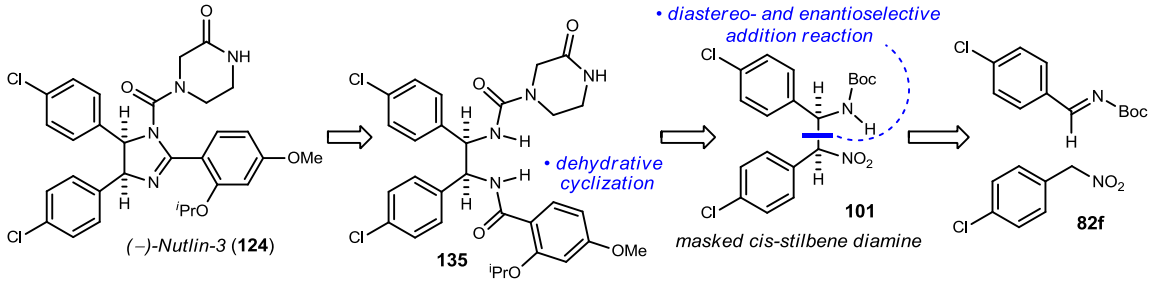
A better route would greatly benefit the scientific community as the need for larger amounts of the compound undoubtedly grows. Particularly, a published route that is enantioselective would allow scientists without access or expertise with chiral SFC to synthesize the active enantiomer of Nutlin-3. This would greatly reduce the cost of research involving Nutlin-3 and perhaps open doors for additional research and development. Additionally, access to the synthesis of new derivatives of Nutlin-3 could be facilitated by a convergent, enantioselective route.

[134] Quoted April 22, 2010

4.2 PBAM-Catalyzed Asymmetric Synthesis of Nutlin-3

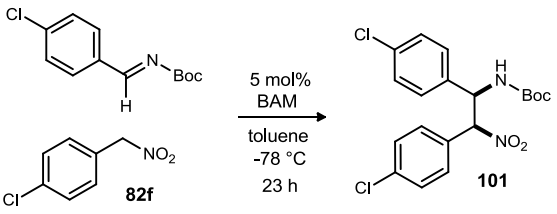
With the development of the phenylnitromethane aza-Henry addition chemistry, Nutlin-3 seemed to offer an excellent application for this asymmetric transformation. It

Scheme 36. Retrosynthesis of Nutlin-3



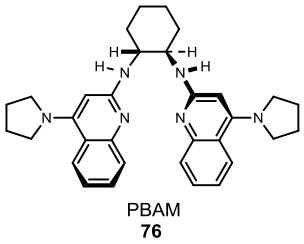
was very obvious that compound **101** could be easily made in high diastereo- and enantioselection. A retrosynthetic analysis of Nutlin-3 (Scheme 36) led to a simple, straightforward deconstruction of the molecule featuring chiral, nonracemic, orthogonally protected, 1,2-diaryl diamine **101**. Care has to be taken in this synthetic approach to avoid *meso* intermediates that would erase the established stereochemistry. Urea **135** is at the correct oxidation state to form Nutlin-3 through a dehydrative cyclization. This urea could be formed from simple functionalization of the masked *cis*-stilbene diamine **101**. A BAM-catalyzed aza-Henry reaction between the corresponding *N*-Boc imine and arylnitroalkane **82f** could provide masked diamine **101** with high stereoselectivity.

Table 36. Effect of Protonation State on Aryl Nitroalkane aza-Henry Addition



entry	catalyst	dr[a] (*anti:syn*)	ee[a] (%)	yield[b] (%)
1	PBAM	9:1	86	97
2	$PBAM_2(HOTf)_1$	5:1	85	99
3	PBAM•HOTf	5:1	85	99

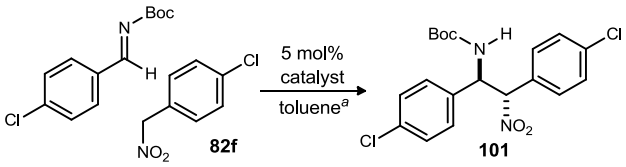
[a]Diastereomer and enantiomer ratios measured by HPLC using chiral stationary phases. [b]Isolated yield.



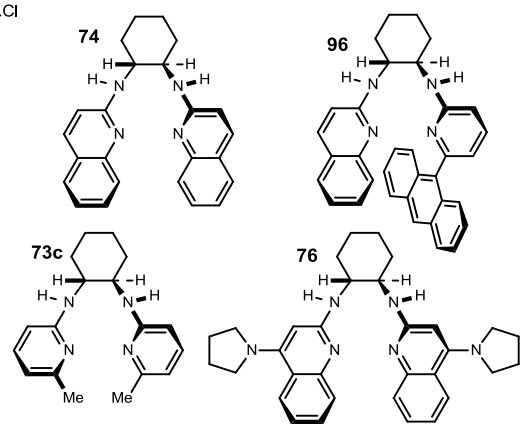
The optimal conditions for arylnitroalkane additions to aryl *N*-Boc imines previously described in this document were used to produce masked *cis*-stilbene diamine **101**. Initial results were good as the desired addition product was formed in good diastereo- and enantioselection with excellent yield (entry 1, Table 36). Once again the use of the triflic acid salts of PBAM did not improve stereoselection (entries 2 and 3).

With the reactivity of the 4-pyrrolidine catalysts seemingly not necessary for this relatively more reactive system, it seemed logical to broaden the scope of catalysts used

Table 37. Broad Screen of BisAMidine Catalysts for Nutlin-3 Precursor **101**



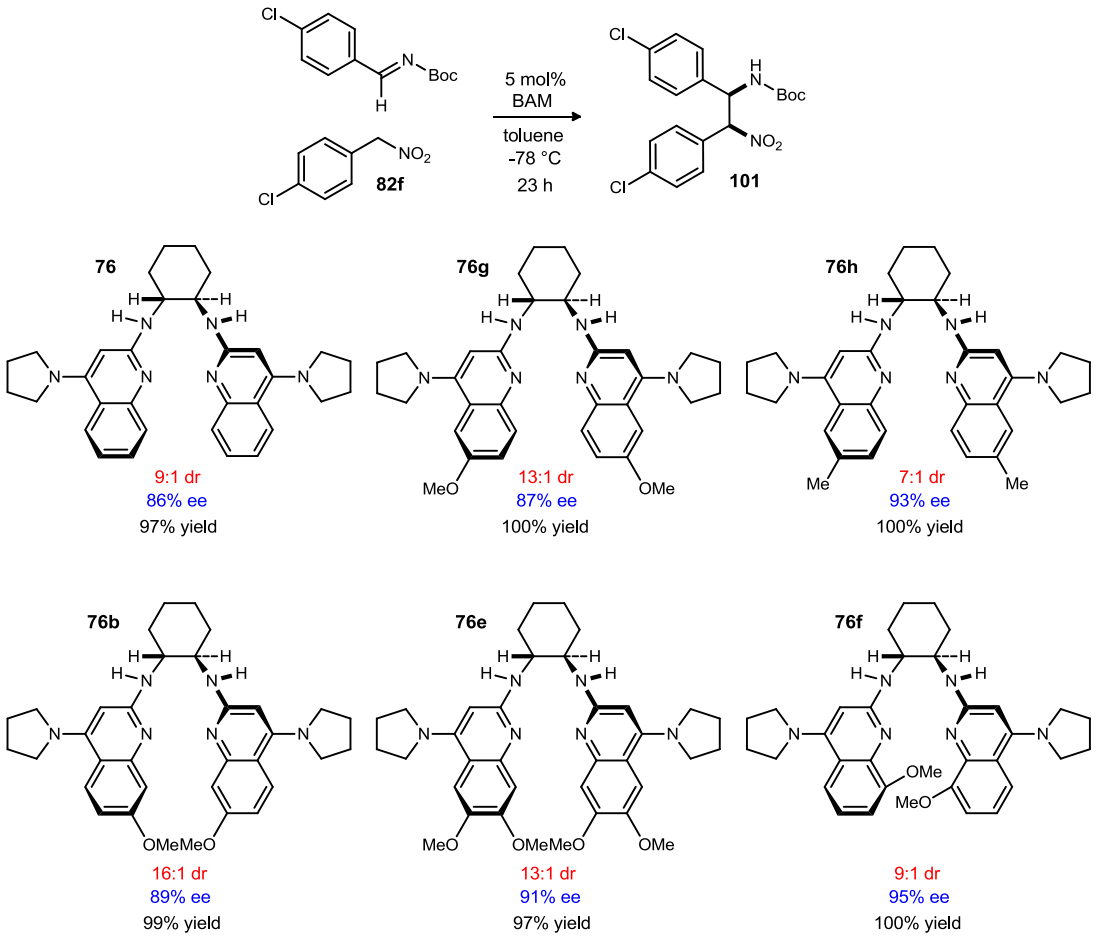
entry	BisAMidine	temp (°C)	TfOH (equiv)	dr	ee (%)	yield[b] (%)
1	**74**[c]	-20	1	13:1	64	81
2	**74**[c]	-20	0	10:1	65	99
3	**96**[c]	-20	1	7:1	80	87
4	**96**[c]	-20	0	6:1	72	98
5	**73c**[c]	-20	1	5:1	58	95
6	**73c**[c]	-20	0	6:1	63	96
7	**76**	-78	1	5:1	85	99
8	**76**	-78	0	9:1	86	97
9	**76**	-20[d]	0	6:1	83	99



[a]All reactions used 1.1 equiv of XX (0.1-0.2 mmol) in toluene (0.1 M) with a 24 h reaction time unless otherwise noted. For assignment of configuration for **101**, see experimental section. Diastereomer ratio (dr) and enantiomeric excess (ee) were determined by HPLC. [b]Isolated yield after column chromatography. [c]10 mol% catalyst used, 48 h reaction time. [d]2 h reaction time

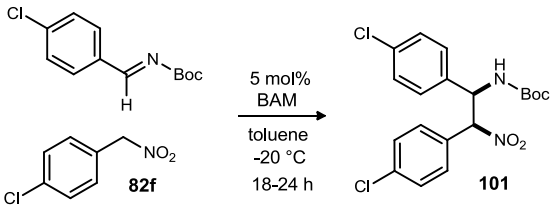
for this particular aza-Henry reaction (Table 37). Less reactive catalyst H,QuinBAM (**74**) and its triflic acid salt performed similarly, leading to modest enantioselection but good diastereoselection. Unsymmetrical protonated catalyst **96** gave higher enantioselection (80% ee) but lower diastereoselection. The free base of catalyst **96** gave slightly lower enantioselection but similar diastereoselection. Both the salt and free base form of the ^{6}Me pyridine BAM catalyst (**73c**) performed similarly (5:1 dr, 58% ee and 6:1 dr, 63% ee, respectively). All of the less Brønsted basic catalysts (entries 1-6) failed to provide the levels of stereoselection that the 4-pyrrolidine catalysts provided.

Figure 30. Catalyst Screen for Aryl Nitroalkane Aza-Henry Addition



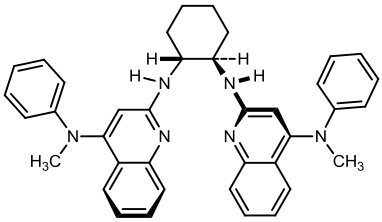
The only noticeable trend seen with this addition thus far was that more Brønsted basic catalysts led to higher enantioselection. In that regard, PBAM catalysts with additional electron donating groups were desired. Through the development of a robust synthetic route, a plethora of substituted 4-pyrrolidine bisamidine catalysts were created with various steric and electronic variations. This allowed for a large number of bisamidine catalysts to be screened for an addition reaction directly relevant to Nutlin-3 (Figure 30). Fortunately, this synthetic effort was not in vain as catalysts with noticeably higher stereoselectivity for this reaction were identified. ^{6}MeOPBAM (**76g**) offered essentially the same enantioselection but higher diastereoselection than PBAM. ^{6}MePBAM (**76h**) gave significantly higher enantioselection but slightly lower enantioselection. The addition of a methoxy group at the 7-position increased enantioselection slightly and diastereoselection significantly. ^{6,7}(MeO)$_2$PBAM (**76e**) proved to be a superior catalyst providing **101** in 13:1 dr and 91% ee. ^{8}MeOPBAM (**76f**) gave the highest enantioselection of all catalysts while diastereoselection was only moderate. This result was somewhat surprising considering a previous result (Table 26, entries 3 and 4) that suggested substitution at the 8-position completely shut down any enantioselectivity. Overall, the installation of EDG at the 6-, 7- and 8- positions were somewhat beneficial. The steric bulk of these groups appear to have no ill effect on the stereoselectivity. Catalysts with EDG at the 5-position were not made due to the interference substitution at that position has on the pyrrolidine's ability to donate electron density to the quinoline.

Table 38. Catalyst Screen for Aryl Nitroalkane Aza-Henry Reaction

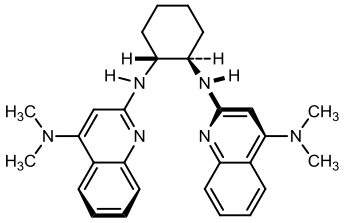


entry	BAM		dr[a]	ee[a] (%)	yield[b] (%)
1	PBAM	**76**	6:1	83	99
2	$PBAM_2$(HOTf)	**76**	6:1	79	97
3	[7]OMePBAM	**76b**	6:1	81	99
4	[6,7]$(OMe)_2$PBAM	**76e**	6:1	80	91
5	[6]MePBAM	**76h**	11:1	85	81
6	[8]OMePBAM	**76f**	7:1	89	99
7	[8]MePBAM	**76i**	4:1	85	85
8	MANBAM	**94d**	8:1	81	86
9[c]	[4]Me_2NBAM	**94i**	2:1[d]	52	67

[a]Diastereomer and enantiomer ratios measured by HPLC using chiral stationary phases. [b]Isolated yield. [c]2 mol% catalyst used. [d]Dr approximated based on isolated yield of single diastereomer.



94d
MANBAM



94i
[4]Me_2NBAM

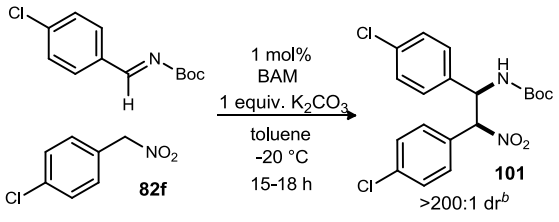
The development of this reaction at warmer reaction temperatures would be beneficial as the ability to perform reactions at -78 °C is not practical or even possible for some laboratories, especially on large scale. Warmer reaction temperatures would also likely result in shortening the reaction times from a day to a period of hours. For these reasons, the reaction was run at -20 °C with a variety of catalysts (Table 38). As expected, a decrease in stereoselectivity was seen at this warmer temperature. All PBAM catalysts (entries 1-7) gave modest diastereoselection (4-11:1 dr) and good enantioselection at this temperature. Encouragingly, the most selective catalyst at -78 °C, [8]MeOPBAM (**76f**), still provided a high level of enantioselection of 89% ee at -20 °C. BAM catalysts with *N*-methylaniline (MANBAM, **94d**) and dimethylamine ([4]Me_2NBAM, **94i**) coupled at the 4- position were screened (entries 8 and 9). MANBAM provided **101** in good diastereoselection and comparable enantioselection (8:1 dr, 81% ee), while catalyst **94i** provided **101** in substantially lower enantio- and diastereoselection (2:1 dr, 52% ee) than the PBAM derivatives.

A quirk of this reaction is that the product is not very soluble in cold toluene and precipitates out of solution as it is formed. This turned out to be very useful as the reaction could simply be filtered and the solid washed as the reaction was scaled up. This filtered and washed solid was sufficiently pure and was routinely carried through without further purification. Additionally, this solid is consistently diastereomerically pure (≥100:1 by HPLC) as the minor diastereomer is significantly more soluble in toluene than the major diastereomer. A reaction with such a simple purification protocol allowed for a rapid screening and optimization of catalysts and conditions. Therefore, the high dr numbers displayed in the figures below may not reflect the true diastereoselection but do reflect the purity of the material isolated.

This aza-Henry reaction suffered from some variability in enantioselection which was thought to be a consequence in varying purities of the imine substrates. Although elimination of the α-amido sulfones to the corresponding *N*-Boc imines is straightforward, it can be difficult to stop the reaction at the proper time. If the reaction is stopped too early, some sulfone will remain. If the reaction is stopped too late, there will be some decomposition of the formed imine which includes aldehyde and carbamate. Due to the instability of the *N*-Boc imine, any purification of the material beyond filtration and evaporation of the solvent is not possible. For this reason, these imines often contain a small amount (1-2%) of sulfone. It has already been established that PBAM is capable acting as a general base for these α-amido sulfones and promoting the elimination to the imine. It was thought that if the reaction was performed with imine that contained sulfone that PBAM might promote the elimination of that small amount of sulfone and form the PBAM-sulfinic acid salt. The acid salts of PBAM have been shown

to behave quite differently from the free base in this reaction. Even though the amount of this PBAM-sulfinic acid salt formed would have to be quite low owing to the small amount of sulfone present, it is possible that it could have an effect on the reaction due to low catalyst loadings. Therefore, a series of reactions were set up to examine this theory.

Table 39. Effect of Heterogenous Base on Aryl Nitroalkane Aza-Henry Reaction



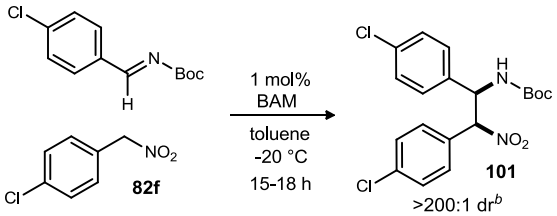
entry	BAM		ee[b] (%)	yield[c] (%)
1	PBAM	**76**	79	70
2	[8]MeOPBAM	**76f**	87	72
3	[8]EtOPBAM	**76j**	88	74
4	[8]MePBAM	**76i**	29	12
5	[8]EtPBAM	**76k**	6	<1
6	[7,8](Me)$_2$PBAM	**76l**	46	29
7	[6,8](MeO)$_2$PBAM	**76m**	84	66
8	[6,8](Me)$_2$PBAM	**76n**	65	74

[a]Imine used contained 1% sulfone and 2% aldehyde by ^{1}H NMR. [b]Diastereomer and enantiomer ratios of isolated material measured by HPLC using chiral stationary phases. [c]Isolated yield after filtration/washing.

First, a series of catalysts were screened in conjunction with the use of one equivalent of a heterogeneous base, K_2CO_3 and the same batch of imine (found to be 1% sulfone and 2% aldehyde by ^{1}H NMR) in Table 39. K_2CO_3 could potentially act as an acid scavenger to quench any sulfinic acid liberated from the elimination of trace amounts of sulfone associated with the imine. No significant change in enantioselection was seen with entries 1-3 and 7. Interestingly, catalysts with alkyl substitution at the 8-position (entries 4-6) suffered from low reactivity under these conditions. Stereoselectivity exhibited by these catalysts was also low, likely due to a non-selective alternate reaction pathway. This apparent significant reactivity difference observed with [8]alkyl substituted PBAM catalysts will be discussed later.

A set of reactions was also performed with imine that contained no detectable α-amido sulfone by ^{1}H NMR (Table 40). Once again, no real trend is seen. Enantioselection did not change much from catalyst to catalyst. Catalysts (**76**, **76f**, **76 j**, and **76 m**) which previously yielded good enantioselection in this reaction gave similar enantioselection values. Once again, PBAM catalysts with alkyl substitution at the 8- position gave lower yields presumably due to their lower reactivities. It is interesting but difficult to rationalize why these ^{8}alkyl PBAM catalysts (entries 4-6, 8) uniformly provided higher enantioselection than the corresponding reactions under the conditions in Table 39. Catalyst **76m** gave the highest enantioselection (88% ee) under these conditions, but still not to a level that is significantly superior to the other catalysts. These results do not shed any light on the reasoning of some reaction to reaction variance in observed stereoselection.

Table 40. Aryl Nitroalkane Aza-Henry Additions in the Complete Absence of Sulfone

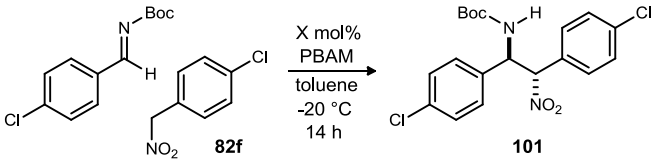


entry	BAM		ee[b] (%)	yield[c] (%)
1	PBAM	**76**	83	66
2	^{8}MeOPBAM	**76f**	83	71
3	^{8}EtOPBAM	**76j**	86	69
4	^{8}MePBAM	**76i**	78	37
5	^{8}EtPBAM	**76k**	72	30
6	^{7,8}(Me)$_2$PBAM	**76l**	81	54
7	^{6,8}(MeO)$_2$PBAM	**76m**	88	65
8	^{6,8}(Me)$_2$PBAM	**76n**	78	56
9	^{6}MePBAM	**76h**	79	71
10	^{6}OMePBAM	**76g**	82	72
11	^{7}OMePBAM	**76b**	66	29
12	^{6,7}(OMe)$_2$PBAM	**76e**	82	74

[a]Imine used contained no detectable sulfone and 5% aldehyde by ^{1}H NMR. [b]Diastereomer and enantiomer ratios of isolated material measured by HPLC using chiral stationary phases. [c]Isolated yield after filtration/washing.

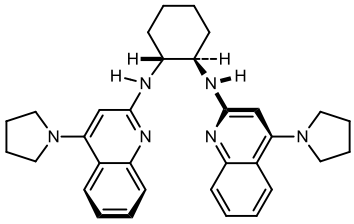
One important finding from the reactions of Table 39 and Table 40 is that low catalyst loadings are possible for this reaction. Loadings of 1 mol % led to essentially the same enantio- and diastereoselection as reactions using 5 mol %.

Table 41. Catalyst Loading Effect Study of PBAM



entry	mol%	product (% ee)[a]	yield[b] (%)
1	20	52.9	39
2	10	64.6	59
3	5	69.6	71
4	2	73.3	76
5	1	74.0	76
6[c]	1	80.0	78

[a]Determined by chiral HPLC. [b]Isolated yield after filtration of reaction, only major diastereomer isolated. [c]0.2 equiv imine added, 30 min intervals



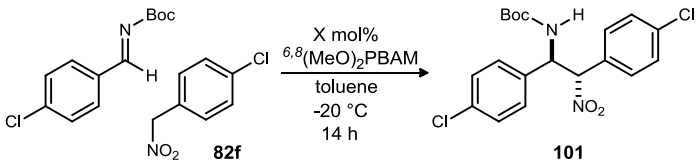
PBAM
76

This led us to do a catalyst loading study on this reaction. PBAM and $^{6,8}(MeO)_2$PBAM were both used with a range of catalyst loadings. A pronounced trend was seen in both cases. With PBAM (Table 41), poor enantioselection was observed when 20 mol% catalyst loading was employed. The yields were also noticeably lower with entries 1 and 2. This is presumably due to lower diastereoselection stemming from low kinetic diastereoselection or post-reaction epimerization. As the catalyst loading decreased, the enantioselection significantly increased. The smallest loading of 1 mol% (entry 5) produced **101** in the highest level of optical purity (74%). The results of entry 6 appear to indicate that the slow addition of the electrophile might also be beneficial for enantioselection.

Lower catalyst loadings also led to higher enantioselection with the $^{6,8}(MeO)_2$PBAM catalyst (Table 42). The highest catalyst loading of 15.4 mol% only

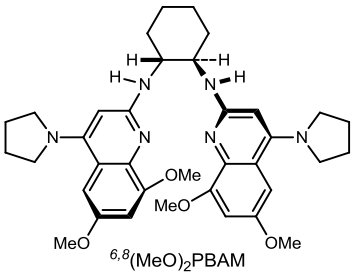
provided **101** in 62% ee (entry 1). Enantioselection increased until loadings below 1 mol% (entries 5-7) provided equally high enantioselection of 86-87% ee. Incredibly, reactivity was still sufficient with only 0.15 mol% catalyst under these more ambient conditions (-20 °C vs. -78 °C).

Table 42. Catalyst Loading Effect Study of $^{6,8}(MeO)_2PBAM$



entry	mol%	product (% ee)[a]	yield[b] (%)
1	15.4	62.1	58
2	7.7	72.8	68
3	3.9	78.9	75
4	1.5	83.7	74
5	0.77	86.0	79
6	0.38	87.3	79
7	0.15	87.3	73

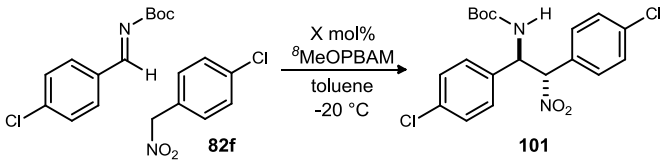
[a]Determined by chiral HPLC. [b]Isolated yield after filtration of reaction, only major diastereomer isolated.



76m

The ability to use low catalyst loadings was quite useful for the scale-up of this reaction. Using ^{8}MeOPBAM as the catalyst, the reaction was found to be quite amenable to relatively large scale. For practical purposes, -20 °C was chosen as the reaction temperature. Table 43 represents the efforts put forth in scaling up this reaction to ultimately a 6 mmol scale (2.2 g **101**). Catalyst loadings were reduced down to 0.5 mol % without a detectable change in enantioselection. Even at such low loadings, reactivity was sufficient for reaction times to be less than one day. The reaction was also run under more concentrated conditions without a loss in yield or stereoselection.

Table 43. Scale-up and Optimization of Nutlin-3 Aza-Henry Reaction

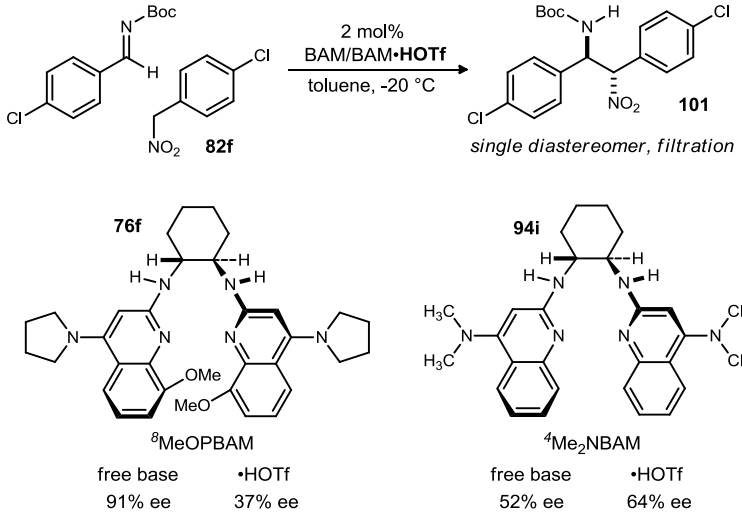


entry	mol%	mmol	conc.	time (h)	purification	dr	ee[a] (%)	yield[b] (%)
1	5	0.1	0.1 M	16	column	7:1	89	100
2	2	0.4	0.1 M	15	filt./wash	>200:1	91	82
3	1	0.4	0.1 M	16	filt./wash	>200:1	92	78
4	1	0.4	0.1 M	7	filt./wash	>200:1	90	52
5	1	0.4	0.1 M	15	filt./wash	>200:1	92	68
6	1	0.4	0.2 M	16	filt./wash	>200:1	92	84
7	1	0.4	0.4 M	16	filt./wash	>200:1	91	84
8	0.5	0.4	0.2 M	16	filt./wash	>200:1	88	72
9	0.5	0.4	0.4 M	18	filt./wash	>200:1	91	81
10	0.5	2	0.4 M	16	filt./wash	180:1	89	86
11	0.75	2	0.4 M	1.5	filt./wash	137:1	90	52
12	1	2	0.4 M	1.5	filt./wash	96:1	91	74
13	0.5	2	0.4 M	20	filt./wash	193:1	87	81
14	1	2	0.4 M	15	filt./wash	119:1	88	78
15	0.5	6	0.4 M	18	filt./wash	>200:1	91	88

[a]Diastereomer and enantiomer ratios of isolated material measured by HPLC using chiral stationary phases. [b]Isolated yield after column chromatography or filtration/washing.

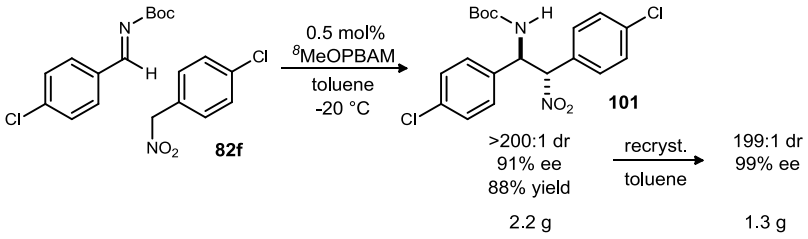
Having fully established ^{8}MeOPBAM to the optimal catalyst for this reaction, we then used its triflic acid salt as a catalyst (Figure 31). Previously in similar reactions, the triflic acid salt of PBAM led to the same or slightly lower levels of stereoselection than the free base of PBAM. Expecting similar results, we were surprised to see that this triflic acid salt led to much lower stereoselection than the free base of ^{8}MeOPBAM. This reaction was performed at -20 °C to produce the adduct **101** in 37% ee. Although it is obvious that this 8-methoxy substituted catalyst functions somewhat differently than PBAM, this drop from 91% ee (entry 2, Table 43) to 37% ee suggests the mechanisms of these two catalysts might be quite different. For comparison, the triflic acid salt of ^{4}Me$_2$NBAM was also used. This catalyst led to slightly higher enantioselection (64% ee) than its free base (52% ee). Still, this enantioselection was much lower than that given by PBAM (and derivatives) offering another example of how critical the pyrrolidine is in the performance of this catalyst.

Figure 31. Enantioselectivity Provided by BAM Triflic Acid Salts



Even with a reaction capable of producing a large amount of aza-Henry product with a simple purification, the desire to increase the enantiopurity of the product existed. Fortunately compound **101** was easily recrystallized from toluene (Scheme 37) to produce material of exceptionally high enantiopurity (99% ee) without any epimerization. This circumvented the need for chiral preparatory chromatography to separate the enantiomers of Nutlin-3 as was needed in the Hoffmann-La Roche patent synthesis of the compound. This proved to be a robust method for producing orthogonally protected diamine scaffold **101**.

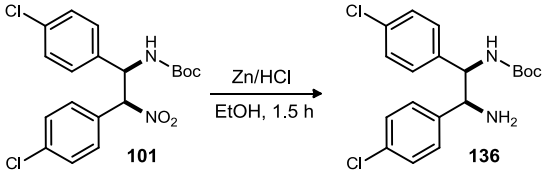
Scheme 37. Optimal Aza-Henry Reaction and Recrystallization



The most logical next step in the synthesis would be to reduce the nitro group to the free amine as deprotection of the Boc group at this stage would most likely lead to the retro aza-Henry reaction. Four attempts are shown in Scheme 38. The first reduction

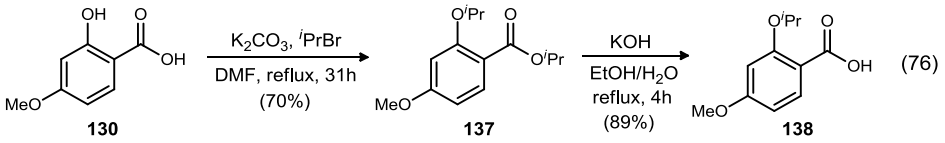
conditions tried were conditions applied by this research group to similar reactions utilizing $CoCl_2$ and $NaBH_4$. The result of this initial reaction was a promising 61% yield. Another previously successful nitro reducing reagent used in this group (Zn/HCl) also proved to be moderately successful in an initial reaction producing **136** in 60% yield. Metal based hydrogenolysis conditions of both Raney Ni and Pd/C did not result in the formation of any amine product.

Scheme 38. Exploration of Reduction Conditions



Conditions:	Result:
$CoCl_2/NaBH_4$, MeOH, rt, 2 h	61% yield
Zn/HCl, EtOH, rt, 1.5 h	60% yield
Pd/C, HCO_2NH_4, MeOH, rt	no product formed
Raney Ni, HCO_2NH_4, MeOH, rt	no product formed

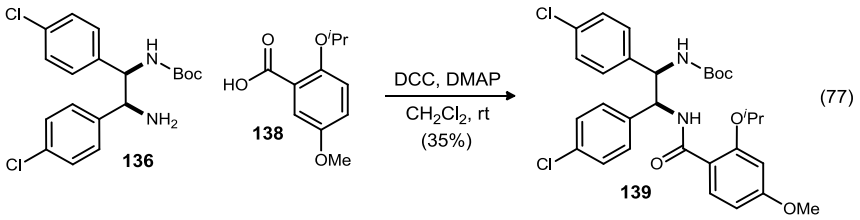
The carboxylic acid needed for the upcoming amide formation step was synthesized in two steps from commercially available 4-methoxysalicylic acid **130**. The



acid **130** was dialkylated in the presence of K_2CO_3 and isopropyl bromide in refluxing DMF to give ester **137** in 70% yield.[135] Saponification of that ester provided the desired carboxylic acid **138** in excellent yield (89%).

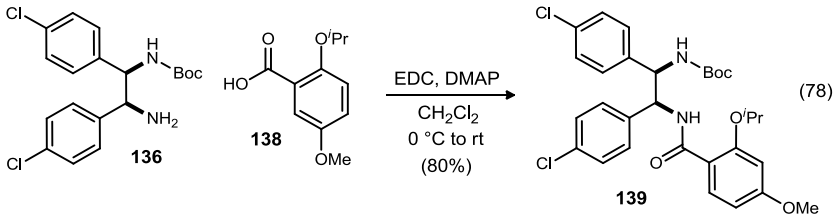
[135] Hattori, T.; Shimazumi, Y.; Goto, H.; Yamabe, O.; Morohashi, N.; Kawai, W.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2099-2108.

Amine **136** was then subjected to typical amide bond formation conditions. When amine **136** and carboxylic acid **138** were reacted with DCC and catalytic DMAP in



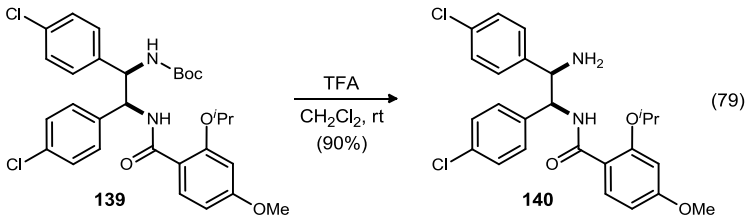
(77)

CH_2Cl_2 (eq 77), amide **139** was formed in 35% yield (with some amide isolated in mixed fractions with DCC). With DCC co-eluting with the desired product, EDC was chosen as the coupling reagent to ease purification. This strategy proved fruitful as this reaction yielded amide **139** in 80% yield (eq 78). Purification proved to be much easier as a simple CH_2Cl_2 and hexanes wash yielded sufficiently pure product.



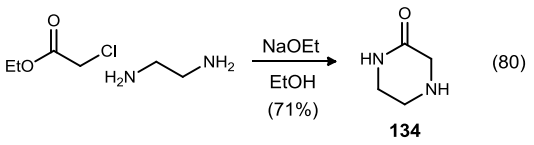
(78)

Amide **139** was then converted to amine **140** in a straightforward Boc deprotection protocol using trifluoroacetic acid in CH_2Cl_2 at room temperature (eq 79). This led to clean conversion of the carbamate to amine **140** in 90% yield.



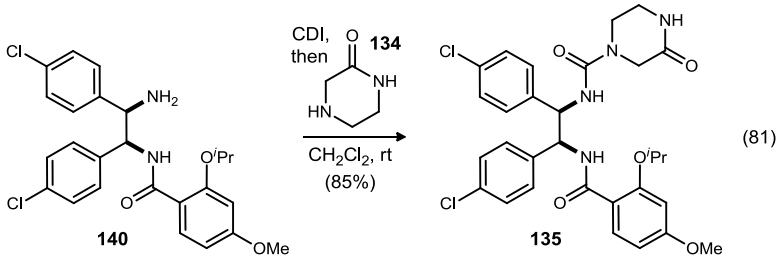
(79)

2-Oxopiperazine **134** was prepared according to a patent procedure. Ethyl 2-chloroacetate and ethylene diamine were condensed in the presence of sodium ethoxide in ethanol to give 2-oxopiperazine **134** in 71% yield (eq 80).



134 (80)

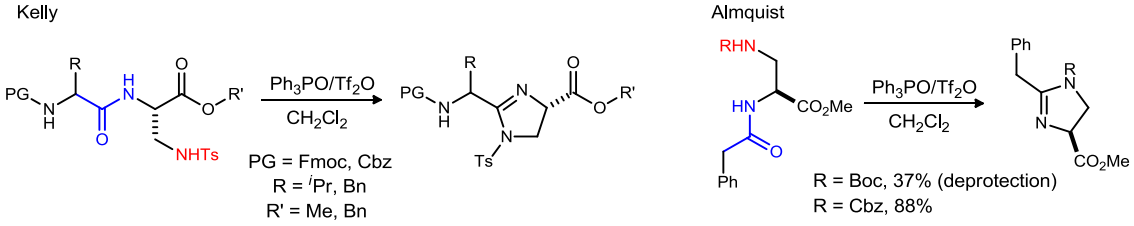
This set the stage to install the desired urea to access the dehydrative cyclization substrate **135** (eq 81). 1,1-Carbonyldiimidazole (CDI) was chosen as the coupling reagent as a phosgene equivalent. An initial attempt to form urea **135** by treating 2-oxopiperazine with CDI then adding amine **140** failed as the amine failed to attack the intermediate urea or isocyanate even after heating. Reversing the order of reagents proved fruitful as urea **135** was formed under mild reaction conditions allowed by formation of the isocyanate *in situ*.



140 **135** (81)

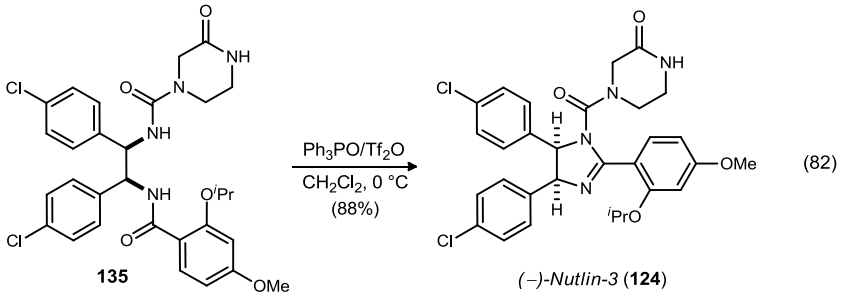
A dehydrative cyclization of compound **135** where a urea cyclizes onto an amide would appear to be an unprecedented reaction. We were encouraged by similar

Scheme 39. Dehydrative Cyclizations using Hendrickson's Reagent



cyclizations in the literature (Scheme 39). Kelly and co-workers successfully demonstrated a sulfonamide cyclization to an amide using a combination of triphenylphosphine oxide and triflic anhydride (Hendrickson's reagent[136]) as a dehydrating reagent.[137] Later, Almquist and co-workers used a very similar procedure to cyclize a carbamate onto an amide.[138] This led us to try similar conditions to that above to attempt this intramolecular cyclization.

Urea **135** was reacted with a mixture of Ph_3PO (4 equiv.) and Tf_2O (2 equiv.) at 0 °C to give a single product in 88% yield (eq 82). Without an authentic sample in hand

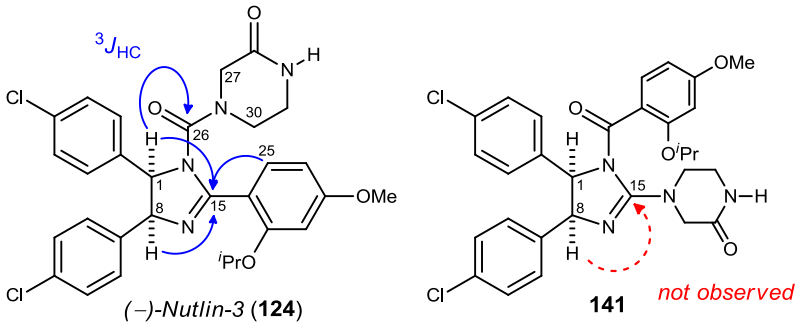


(82)

and with only a reported mass as the available characterization data in the literature, we sought out to fully characterize and definitively assign the structure of our synthetic Nutlin-3. The correct mass was assigned by high resolution mass spectrometry. Proton NMR strongly indicated that a cyclized product had formed, but the alternate, undesired regioisomer **141** (Figure 32) from the cyclization could not be ruled out.

[136] Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 277-280.
[137] You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681-1683.
[138] Pemberton, N.; Pinkner, J. S.; Edvinsson, S.; Hultgren, S. J.; Almqvist, F. *Tetrahedron* **2008**, *64*, 9368-9376.

Figure 32. HMBC Evidence of Formation of Desired Cyclization Regioisomer



An HMBC experiment provided evidence that the urea did cyclize onto the amide to give (-)-Nutlin-3 (Figure 32). C26 (155 ppm) was clearly defined by the correlations to H27/H27` and H30/H30'. A correlation was also seen from C26 to one of the imidazole methines at C1 (but not H8). The amidine carbon C15 (160 ppm) was clearly defined by its correlation to H25 and also showed correlations to both of the imidazoline methines (H1 and H8).

The optical rotation of this Nutlin-3 derived from the aza-Henry product catalyzed by the (*R*,*R*)-configuration of bisamidine catalysts was found to be levorotatory. Using a correlation to aza-Henry product **86g** for which a crystal structure has been solved, the absolute configuration of (-)-Nutlin-3 can be confirmed to be (4*S*,5*R*) by analogy.

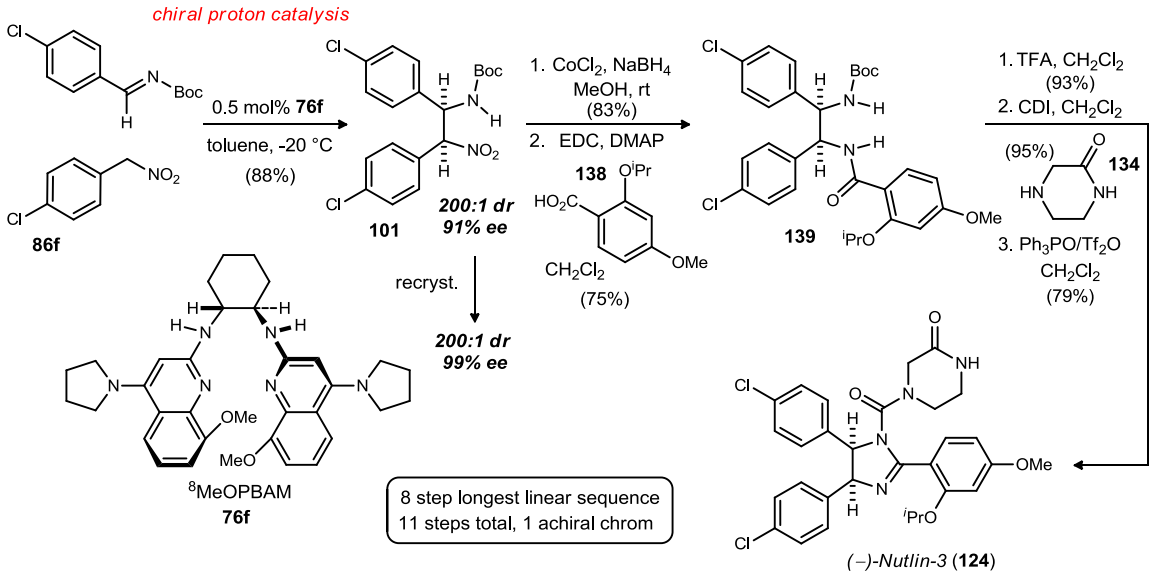
Stereochemical integrity was maintained throughout the synthesis as confirmed qualitatively through optical rotation measurement and quantitatively by comparison to known chiral HPLC retention times.[139]

The biological activity was also assessed. A collaboration with the research group of Dr. Jennifer Pietenpol here at Vanderbilt resulted in the use of this (-)-Nutlin-3 in biological assays reported by Hoffmann-La Roche. The material was found to exhibit the same activity as that has been published previously in the literature.

[139] Wang, Z.; Jonca, M.; Lambros, T.; Ferguson, S.; Goodnow, R. *J. Pharm. Biomed. Anal.* **2007**, *45*, 720-729.

(-)-Nutlin-3 has been synthesized asymmetrically in 11 overall steps (8 steps longest linear sequence).[140] The overall synthesis is displayed in Scheme 40. The yields and results given are the results from the largest scale reactions attempted thus far. aza-Henry product **101** can be produced on a reasonably large scale (2.2 grams) with very low catalyst loading (0.5 mol%). A unique dehydrative cyclization is employed in the final step to produce the *cis*-imidazoline. Over 380 mg of (-)-Nutlin-3 has been synthesized in one batch. All the reactions gave similar results to those of smaller scale. Column chromatography is only necessary after the final step of this sequence as simple workups yield acceptably pure products for the rest of the steps.

Scheme 40. Overall Asymmetric Synthesis of Nutlin-3

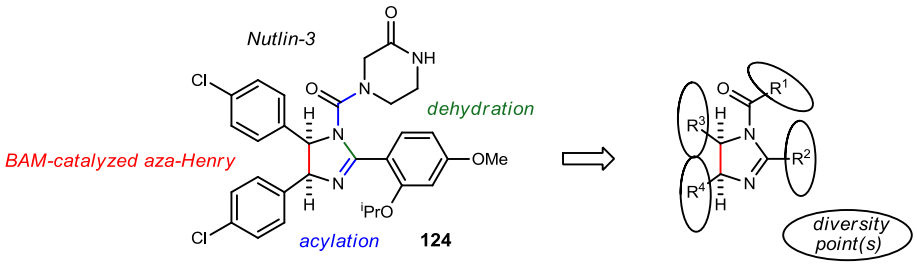


Another advantage of this method is the ease with which different aryl groups can be incorporated on the 1,2-diamine backbone. This would be very difficult with the Hoffmann-La Roche patent synthesis as a mixture of three products would result from the diaza-cope with two different aldehydes. As shown earlier in this document, derivatives

[140] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076-1079.

of compound **101** can be made by the addition of an imine and aryl nitroalkane containing different aryl groups. This highlights a major advantage of this asymmetric synthesis in terms of a medicinal chemistry approach.

Figure 33. Outline and Diversity Points of Nutlin-3 Synthesis

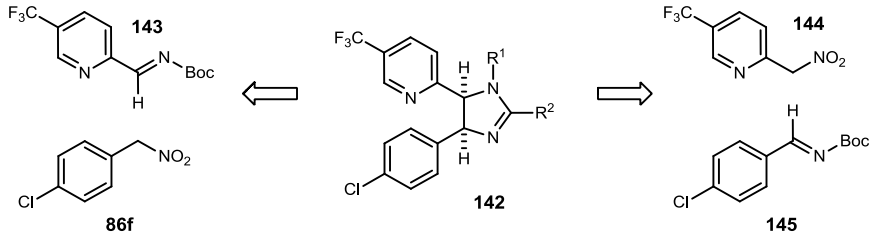


4.3 Efforts Towards Derivatives of Nutlin-3

In collaboration with Dr. Kip Guy from St. Jude Research Hospital, a plan has been made to approach new derivatives of Nutlin-3. Interestingly, five of the six structures featured different aryl groups at the 4- and 5- positions of the imidazoline. These structures with different aryl groups give us the opportunity to use one of the inherent advantages of our enantioselective route.

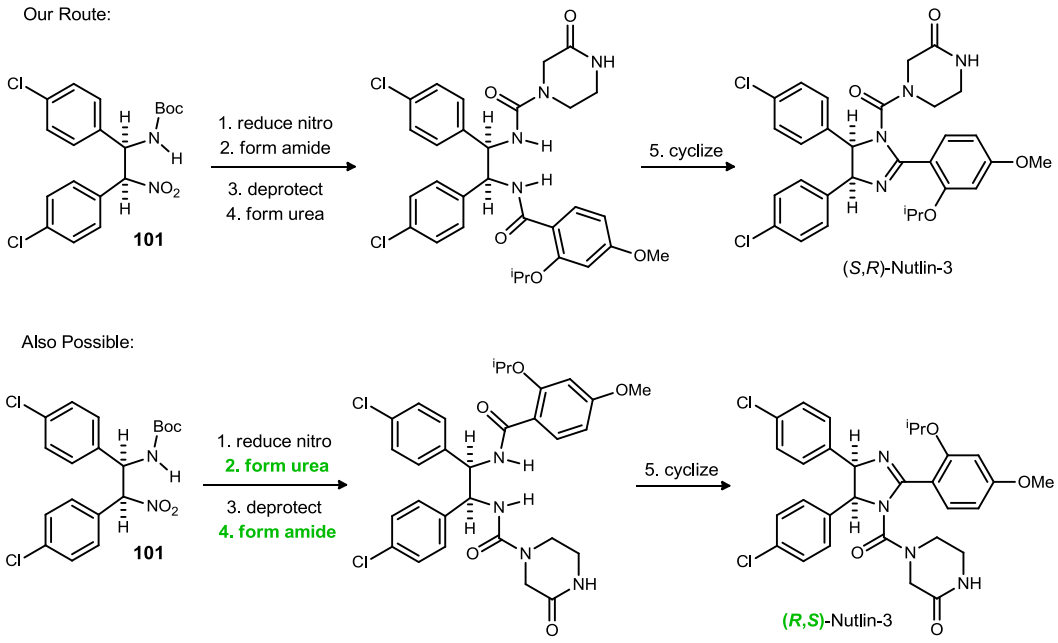
The retrosynthesis of these compounds also reveals options for starting materials. All six of the desired derivatives contain at least one heteroaryl group at the 4- or 5-position of the imidazoline. Unfortunately, none of the necessary heterocycles can be easily obtained through purchase or straightforward synthesis. The retrosynthesis of

Figure 34. Retrosynthesis of Nutlin Derivative **142**



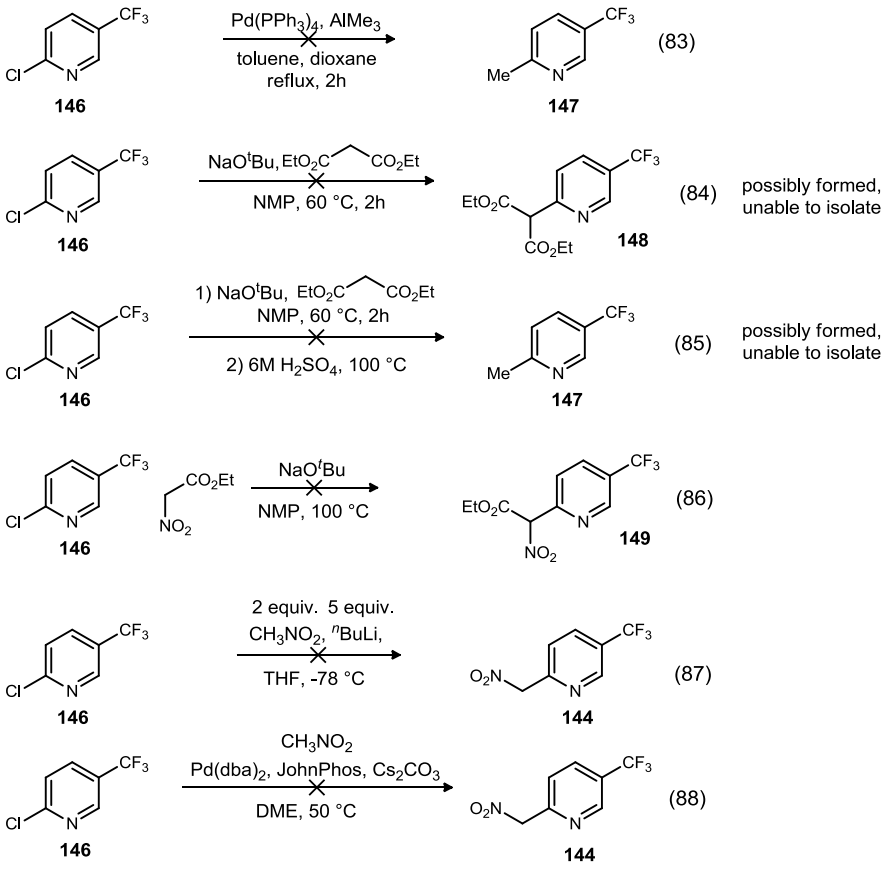
perhaps the most easily accessible derivative, **142**, is shown in Figure 34. This molecule could be synthesized from the aza-Henry product coming from the addition of **86f** to **143** or the addition of **144** to **145**, allowing for a choice depending on availability of starting materials, product yields, or stereoselectivity.

Scheme 41. Nutlin-3 Change in Order of Operations



Scheme 41 explains the ability to use either nitroalkane/imine combination to produce derivative **142**. Using our current route, Nutlin derivative **142** would have to come from an aza-Henry reaction between **86f** and **143**. Assuming the straightforward changes of forming the urea, deprotecting, then forming the amide are possible, **143** could also be formed from the aza-Henry reaction of **144** and **145**. This would form the (*R*,*S*) product when using (*R*,*R*)-PBAM catalyst, but the more active (*S*,*R*) product could still be formed using the (*S*,*S*)-PBAM catalyst.

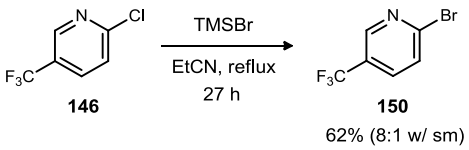
Scheme 42. Attempts Toward the Synthesis of Nitroalkane **144**



Separate attempts at the synthesis of both nitroalkane **144** and imine **143** were made from commercially available chloropyridine **146**. Several methods were attempted to install a one-carbon unit (Scheme 42). No desired methylated product **147** resulted from the treatment of **146** with $AlMe_3$ and $Pd(PPh_3)_4$ (eq 83). Addition of diethylmalonate and subsequent attempted decarboxylation (eq 84,85) resulted in mixtures from which the desired product could not be isolated.[141] A similar addition of ethyl nitroacetate in the presence of sodium *tert*-butoxide (eq 86) only resulted in the isolation of *t*-butoxide adduct to the pyridine. A direct nitromethylation of **146** to form **144** (eq 87) using doubly-deprotonated nitromethane did not result in the formation of

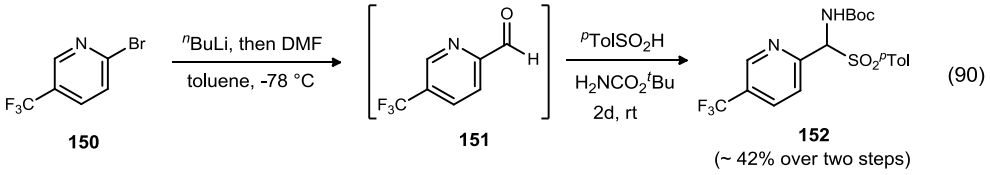
[141] Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357-1360.

detectable product. Also, the palladium-catalyzed nitromethylation protocol of Buchwald produced an intractable mixture (eq 88).[142]



146 **150** 62% (8:1 w/ sm) (89)

Luckily, attempts to make the imine **143** were more fruitful. **146** was smoothly converted to bromopyridine **150** using TMSBr. Hydroformylation of this substrate was achieved through transmetallation and subsequent treatment with DMF. The volatility of the aldehyde **151** prevented successful isolation. Instead, *p*-toluenesulfinic acid and *t*-butyl carbamate were added to the crude extract to form the desired sulfones **152** in one pot (eq 90). This strategy was successful albeit with only modest yield over two steps. Additionally, the sulfone recovered contained a significant amount of carbamate and sulfinic acid after washing the obtained solid with ether. Nevertheless, this material was sufficient to take forward as purification should be possible at a later stage.



150 **151** **152** (~ 42% over two steps) (90)

The attempted elimination of sulfones **152** resulted in the isolation of very impure imine, more than likely the result of the impure sulfone. We previously determined that performing the aza-Henry reaction with the preformed imine is desired as better yields and stereoselectivities result versus the one-pot elimination/addition reaction from the sulfone. Since it did not appear to be easy to obtain the imine, the sulfone was subjected

[142] Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106-111.

to a one-pot elimination/addition reaction that has been moderately successful with other substrates as explained earlier.

Table 44. One-Pot Reaction Towards Nutlin-3 Derivative **142**

entry	BAM		dr[a]	ee[a] (%)	yield[b] (%)
1	PBAM	**76**	1:1	42/41	37
2	[6,7](OMe)$_2$PBAM	**76e**	1:1	38/38	25
3	[6,8](MeO)$_2$PBAM	**76m**	1:1	51/51	23

[a]Diastereomer and enantiomer ratios measured by HPLC using chiral stationary phases. [b]Isolated yield.

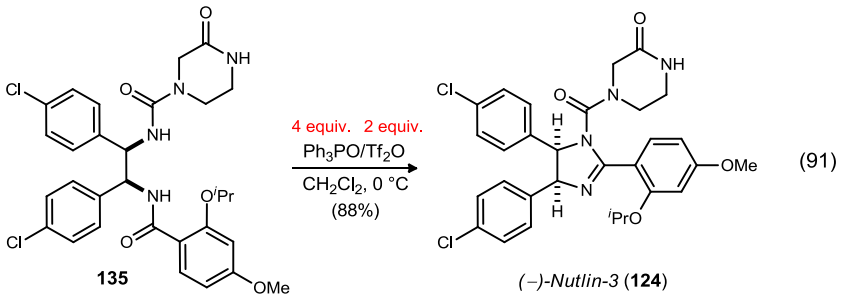
This one-pot reaction was run at room temperature as attempts at -20 °C resulted in no conversion. The results using three different catalysts are shown in Table 44. No diastereoselection is observed, likely due to post-reaction epimerization occurring at warmer than optimal reaction conditions. Enantioselection is low as somewhat expected with the less enantioselective one pot reaction. The yield is also low probably stemming from the low purity of the sulfone.

Still, Nutlin-3 derivative precursor **153** was made with significant enantioinduction. This synthesis highlights the advantage our method possesses as two different aryl groups are incorporated into the 1,2-diamine backbone. It is likely that the synthesis of **153** can be improved by the development of a better method to synthesize the aldehyde, especially in terms of purity. Pure aldehyde **151** should dramatically improve the chances of obtaining pure sulfone **152** and imine **153**. Performing the aza-Henry reaction directly with the imine should allow us to run the reaction at colder temperatures, increasing the enantioselection and preventing the erosion of

diastereoselection through post-reaction epimerization. Nutlin-3 derivative **142** should be obtained from **153** by application of the final five steps of the synthesis.

4.4 Dehydrative Cyclization Reaction

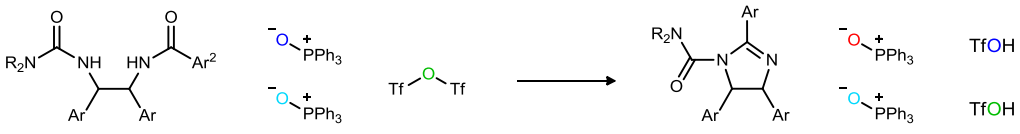
The final reaction of the Nutlin-3 synthesis is an intramolecular dehydrative cyclization to form the imidazoline using Hendrickson's reagent (eq 91). This is a powerful transformation that reacts two relatively unreactive functional groups in an amide and a urea. This reaction consistently produces Nutlin-3 in very good yields after column chromatography (80-90%).



(91)

It is noteworthy that an excess of PPh_3O and Tf_2O (at least 3 and 1.5 equivalents respectively) is necessary for the successful employment of this reagent[137,138] in the literature. This leads to interesting questions about the mechanism of this reaction.

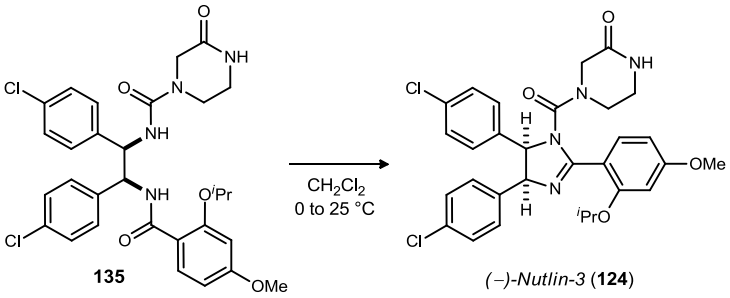
Scheme 43. Molecular Accounting for the Hendrickson Dehydrative Cyclization Reaction



The overall stoichiometry of the reaction is shown in Scheme 43. The two hydrogen atoms and one oxygen atom from the molecule of water lost from the starting materials are incorporated into two molecules of triflic acid as the byproduct. Each

molecule of triflic anhydride is converted to two molecules of triflic acid explaining the necessity for a stoichiometric amount of triflic anhydride. On the other hand, triphenylphosphine oxide is not consumed in this reaction. Therefore, it should be possible to use a catalytic amount of Ph_3PO in this reaction. This is obviously desirable from an economic standpoint, but it also would ease the purification as column chromatography is necessary, primarily to separate Nutlin-3 from the excess Ph_3PO.

Table 45. Effect of Stoichiometry Changes and Base Addition on the Dehydrative Cyclization



Reagents[a]	conv. (%, NMR)[b]
Tf_2O (2 equiv.)	36
Tf_2O (6 equiv.)	35
Tf_2O (2 equiv.), PPh_3O (1 equiv.)	9
Tf_2O (2 equiv.), pyridine (6 equiv.)	0
Tf_2O (2 equiv.), NEt_3 (6 equiv.)	0
Tf_2O (2 equiv.), Na_2CO_3 (10 equiv.)	40
Tf_2O (2 equiv.), DTBMP (6 equiv.)	52

[a]All reactions were initiated at 0 °C and allowed to warm to room temperature and stirred for 6-24 h. [b]Conversion measured by ^1H NMR.

Several attempts to reduce the equivalents of Ph_3PO used in this cyclization were made (Table 45). Departure from the optimal stoichiometry (4 equivalents Ph_3PO, 2 equivalents Tf_2O) of the two reagents resulted in only partial conversion to product at best. The reaction did proceed in the presence of Tf_2O without Ph_3PO but only to 36% conversion. Increasing the equivalents of Tf_2O to six did not improve the conversion. Interestingly, even less conversion (9%) was observed when one equivalent of Ph_3PO was used in conjunction with two equivalents of Tf_2O.

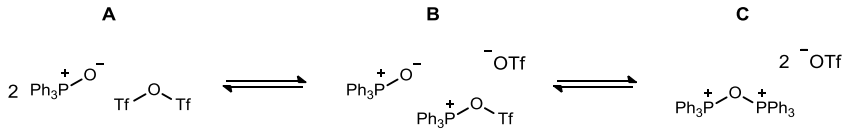
With the confirmation of the requisite excess Ph_3PO for this reaction, Tf_2O was used with various bases. These bases could serve to react with Tf_2O to form a more reactive acylating species or sequester the TfOH formed as a byproduct of the reaction. The addition of pyridine or triethylamine resulted in no conversion to product. However, sodium carbonate and 2,6-di-*tert*-butyl-4-methylpyridine led to slightly higher conversion (40% and 52% conversion, respectively) to Nutlin-3 than Tf_2O alone. Still, no conditions were found that allowed for full conversion to the desired product.

Additionally, thionyl chloride and $POCl_3$ were used as substitutes for Hendrickson's reagent both individually and in combination with other reagents. These reagents are cheaper than Tf_2O/Ph_3PO and would produce water-soluble byproducts, easing purification. Unfortunately, $SOCl_2$ and $POCl_3$ generally produced messier crude reaction mixtures than those observed with Tf_2O. $SOCl_2$ was used as solvent alone and in combination with differing amounts of Ph_3PO, pyridine, and DMF. In most cases, consumption of the starting material was observed by NMR but traces, if any, of the desired product were seen. $POCl_3$ and pyridine in toluene at 50 °C led to 33% conversion but small amounts of unknown byproducts were also observed in the crude NMR. All other reactions with $POCl_3$ led to consumption of starting material with no significant amount of product observed.

This combination of triflic anhydride and triphenylphosphine leads to an equilibrium of at least three different possible species, each possibly a strong electrophile and acylating reagent (Scheme 44). Based on the experiment described above and their outcomes, we hypothesize that species B or C could be the most reactive activating agent

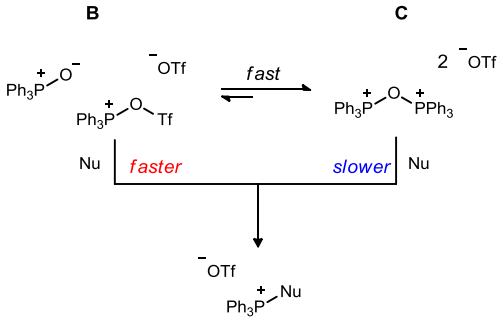
formed in solution.[143] It has been found by ^{31}P NMR studies that this equilibrium heavily favors the phosphonium anhydride (POP) species C in the presence of excess Tf_2O (species B is not observed).[144] This seems to suggest that the POP species is significantly lower in energy (2-3 kcal/mol) than species B. Although the equilibrium appears to favor C, it is not clear whether B or C is the more reactive.

Scheme 44. Equilibrium of Hendrickson's Reagent



A testable hypothesis is that the necessary equivalents of the reagents are crucial for forming a sufficient concentration of the active acylating species. Specifically, the employment of excess Ph_3PO could lead to the formation of species C, which could be the active acylating reagent (Scheme 45). Alteration of the phosphine oxide could have an effect on this equilibrium to favor the formation of species B.

Scheme 45. Potential Pathways for Activation by Hendrickson's Reagent

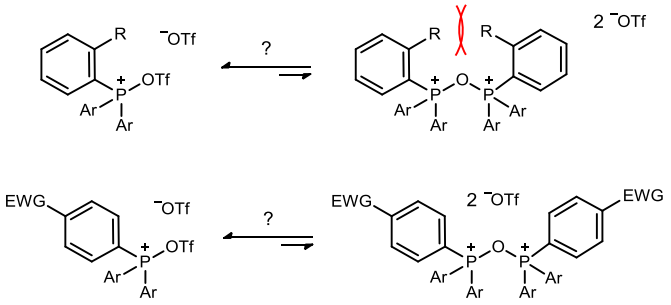


This could be accomplished through the use of more sterically demanding phosphine oxides (Scheme 46). The steric strain between the groups of the two phosphine oxides of the POP species could raise the energy of the POP species and shift this

[143] Fairfull-Smith, K. E.; Jenkins, I. D.; Loughlin, W. A. *Org. Biomol. Chem.* **2004**, *2*, 1979-1986.
[144] Petersson, M. J.; Jenkins, I. D.; Loughlin, W. A. *J. Org. Chem.* **2008**, *73*, 4691-4693.

equilibrium to the left. Also, electronic changes to the phosphine oxide could affect this equilibrium as well as alter the reactivity of the two species. The creation of a more reactive system through this approach could remove the necessity for excess phosphine oxide in this reaction and find use in many other applications.

Scheme 46. Potential Changes to Phosphine Oxides for the Dehydrative Cyclization



CHAPTER V

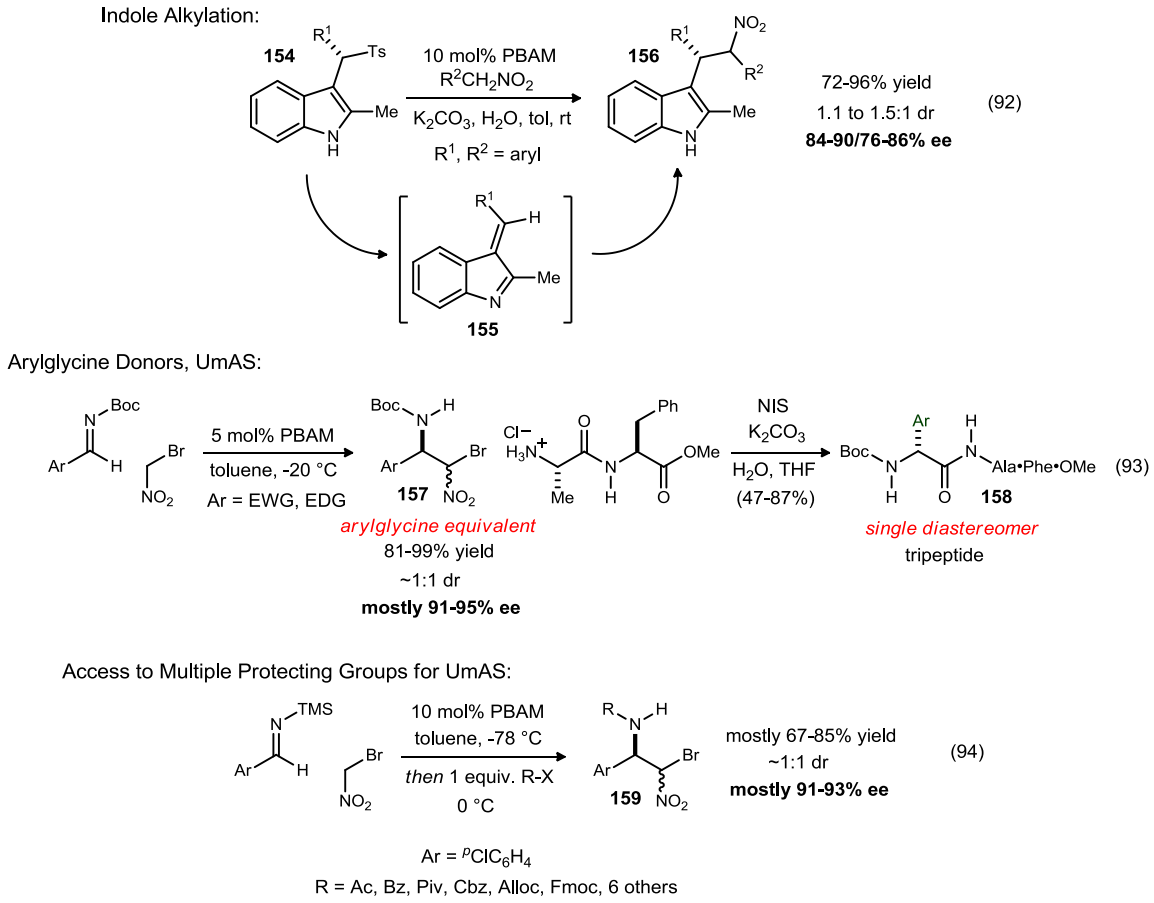
SYNTHESIS OF BAM LIGANDS

5.1 Recent Applications of PBAM in Asymmetric Synthesis

We did not anticipate the success and broad applicability of PBAM as an asymmetric organocatalyst at the genesis of this chemistry. The counterintuitive approach of having a more Brønsted basic catalyst perform as a better chiral Brønsted acid is a design principle under continuing investigation. Furthermore, in each of the following cases, PBAM is the most stereoselective catalyst from the library of BisAMidine catalysts screened.

PBAM has been found to promote the alkylation of indoles of type **154** with high enantioselectivity (eq 92, Scheme 47).[107] This reaction appears to proceed through indolenine intermediate **155** to produce indoles **156**. An *in situ* formed PBAM acid salt may be responsible for the enantioselectivity observed in this reaction through hydrogen bonding with the indolenine intermediate. As observed with the addition of aryl nitroalkanes to aryl *N*-Boc imines, PBAM was found to be a superior catalyst to H,QuinBAM and other less Brønsted basic catalysts.

Scheme 47. Recent Applications of PBAM in Asymmetric Synthesis



PBAM has also been found to promote the aza-Henry addition of bromonitromethane to aryl *N*-Boc imines in very high enantioselectivity to give product **157** (eq 93). This arylglycine equivalent can then be coupled to the *N*-terminus of an amino acid or peptide through umpolung amide synthesis (UmAS) to produce peptides (such as **158**) as a single diastereomer.[145]

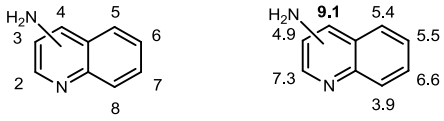
Similarly, bromonitromethane can be added to silyl imines in a highly enantioselective fashion in the presence of catalytic PBAM (eq 94).[146] This adduct is then converted in the same pot to various *N*-protected adducts of general structure **159**. These

[145] Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027-1032.
[146] Makley, D. M.; Johnston, J. N. *unpublished results*

adducts can be used in UmAS, thereby broadening the utility of this process. In all cases in Scheme 47, PBAM was found to be the optimal ligand for enantioselectivity and reactivity.

5.2 Synthesis of PBAM and a Library of other C_2-Symmetric, 4-Pyrrolidine Substituted BAM Ligands

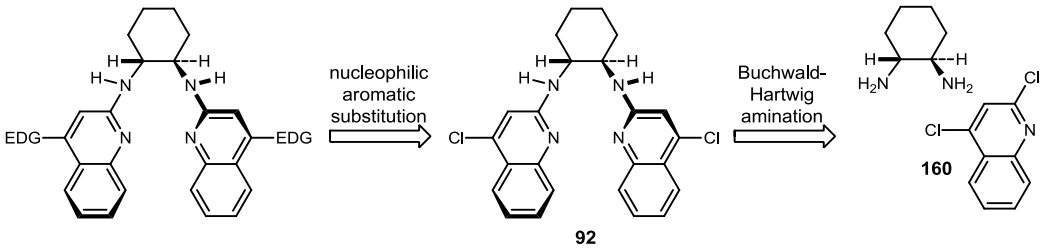
Figure 35. Resulting pK_a of Amino-Substituted Quinoline



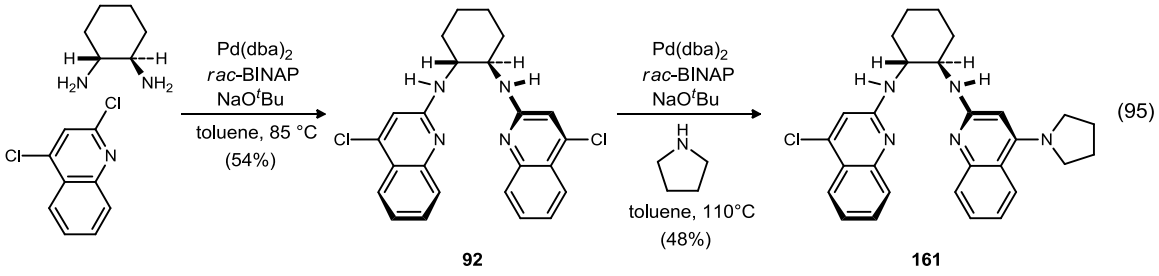
Of the numerous positions an additional electron donating group could be placed on the quinoline ring, the 4-position was determined to be optimal. The pK_a measurements of various substituted quinolines have shown that substitution at the 4-position has the greatest effect on the pK_a of the protonated quinoline nitrogen (Figure 35).[147] Synthetically this seemed to play into our hands as 2,4-dichloroquinoline can be employed as the starting quinoline (Scheme 48). This substance can easily be prepared. The major challenge would be obtaining regioselectivity at the 2-position with the first nucleophilic aromatic substitution of the dihaloquinoline.

[147] Braude, E. A.; Nachod, F. C. *Determination of Organic Structures by Physical Methods*; Academic Press: New York, 1955.

Scheme 48. Retrosynthesis of 4-Substituted Catalysts



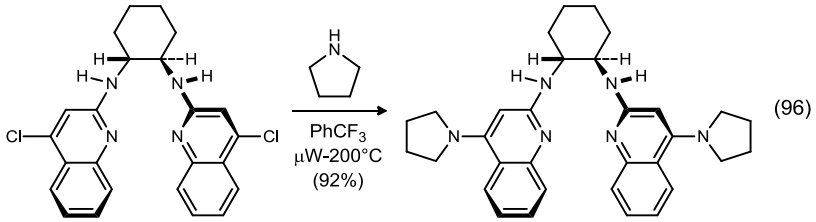
The Buchwald-Hartwig amination proceeded smoothly between (*R*,*R*)-diaminocyclohexane and 2,4-dichloroquinoline **160** with a modest yield of 54% (eq 95). Initially, it was envisioned to use another Buchwald-Hartwig coupling to aminate at the 4-position of **92**. This reaction did successfully produce the mono-aminated product, but was unsuccessful at installing the second amine.[148] This did turn out to be valuable as this mono-aminated product is an interesting non-C_2-symmetric ligand possessing electronically different quinoline rings. This strategy produced only mono-aminated product with no detectable doubly-aminated product, even after variation of the phosphine ligand and base. In some cases, H,QuinBAM was produced as a result of reduction of both chlorides.



Fortunately, heating compound **92** with an excess of pyrrolidine under microwave conditions led to the desired catalyst **76** (simplified to 'PBAM') in excellent yield (92%). PBAM can be purified by column chromatography. The free base of PBAM

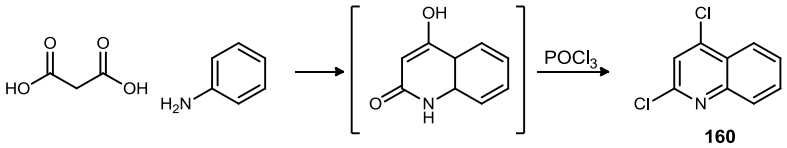
[148] Wilt, J. C.; Johnston, J. N. *unpublished results*

binds strongly to silica and copious amounts of solvent are required to fully elute the compound. The addition of a small amount of acetic acid (0.5%) to the solvent system (5-10% MeOH/CH_2Cl_2) allows for the smooth elution of the acetate salt of PBAM. Treatment of this acetate salt with aqueous NaOH produces the PBAM free base. Both the free base (unprotonated catalyst) and corresponding triflic acid salts are bench stable solids that are indefinitely stable at room temperature. PBAM has been recovered after use, repurified by column chromatography, and reused successfully without a decrease in reactivity or stereoselectivity.



As PBAM's utility as a catalyst became apparent, we decided to explore derivatives to further increase reactivity and/or stereoselectivity. The same three steps used to synthesize PBAM (starting from malonic acid and aniline) could be used to make derivatives of PBAM by simply starting with different anilines. Anilines are particularly good starting materials as they are readily commercially available and cheap.

Scheme 49. 2,4-Dichloroquinoline Synthesis



Although 2,4-dichloroquinoline (**160**) is commercially available, it is quite expensive.[149] This led us to make it ourselves by reacting malonic acid with aniline in

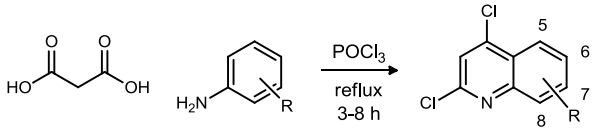
[149] The best price found was $55 per g from JPM2 Pharmaceuticals, Feb 2011.

refluxing phosphorus oxychloride ($POCl_3$). This reaction is a one-pot, two-step reaction where the two reagents initially condense to form the intermediate 4-hydroxyquinolinone and then react with $POCl_3$ to produce the 2,4-dichloroquinoline as shown in Scheme 49.

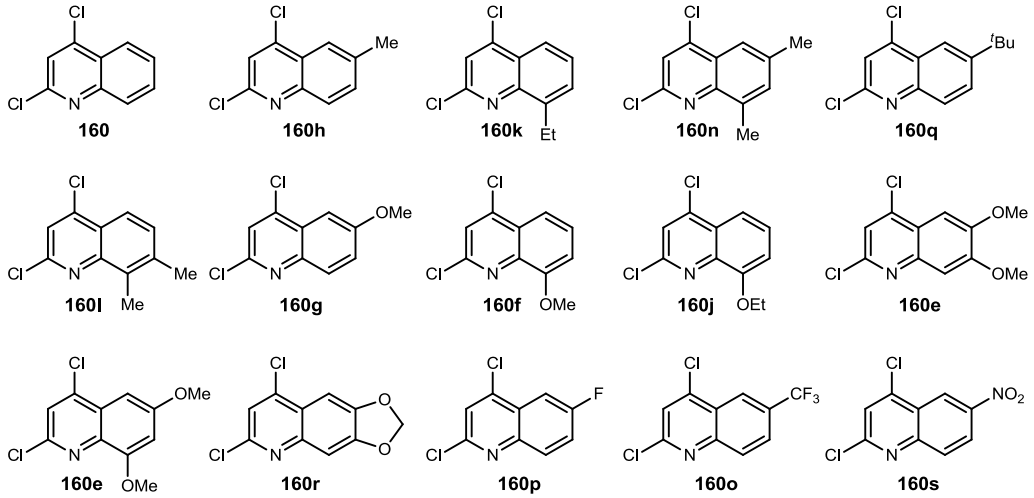
A large number of anilines were ultimately subjected to this reaction with the desire of synthesizing sterically and electronically different BAM catalysts. As experience with this reaction increased, several improvements were made to the reaction conditions and work-up procedure. Initially, column chromatography was used to isolate the quinoline after aqueous work-up. This aqueous work-up featured a dichloromethane extraction of the aqueous mixture that often resulted in emulsions and subsequently the use of large amounts of dichloromethane. It was found that after quenching the reaction by pouring onto ice and adjusting the pH of the solution with conc. aq. NaOH, a filterable crude solid resulted that contained the desired quinoline. Soxhlet extraction with hexanes was eventually implemented to isolate the quinoline from this crude solid without chromatography.[150] In most cases, this soxhlet extract was sufficiently pure to carry on to the next step. The vast majority of these reactions were performed only once, so the yields shown are unoptimized, and modest to low yields were observed. Regardless, this is a convenient reaction as isolation of the intermediate hydroxyquinolinone is unnecessary. Inexpensive and robust starting materials are used, allowing these reactions to be run on relatively large scale. Thus, the material produced from each reaction was always more than enough to carry on to the next step of the catalyst synthesis.

[150] Jones, K.; Roset, X.; Rossiter, S.; Whitfield, P. *Org. Biomol. Chem.* **2003**, *1*, 4380-4383.

Table 46. 2,4-Dichloroquinoline Library Synthesis

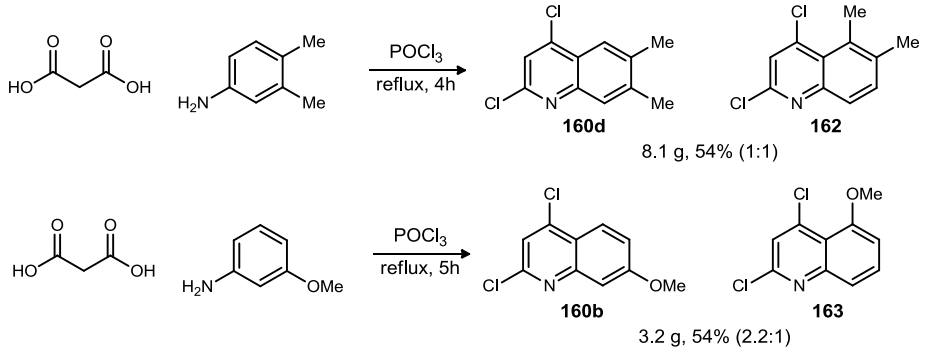


entry	quinoline	mass (g)	yield[b] (%)
1	**160**	44.6	44
2	^{6}Me (**160h**)	14.1	53
3	^{8}Et (**160k**)	2.6	23
4	^{6t}Bu (**160q**)	2.8	34
5	^{6,8}(Me)$_2$ (**160n**)	3.2	28
6	^{7,8}(Me)$_2$ (**160l**)	4.1	36
7	^{6}MeO (**160g**)	4.8	35
8	^{8}MeO (**160f**)	2.6	9
9	^{8}EtO (**160j**)	1.9	15
10	^{6,7}(MeO)$_2$ (**160e**)	8.6	51
11	^{6,8}(MeO)$_2$ (**160m**)	1.4	8
12	^{6,7}-OCH$_2$O- (**160r**)	6.1	34
13	^{6}F (**160p**)	1.9	18
14	^{6}CF$_3$ (**160o**)	2.0	10
15	^{6}NO$_2$ (**160s**)	0.8	6

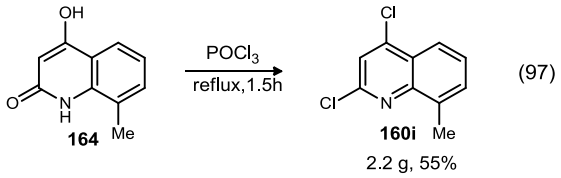


The results for the synthesis of 15 different 2,4-dichloroquinoline derivatives are shown in Table 46. All these reactions were on a reasonable scale and produced a considerable amount of product even with the lower yielding reactions. The best results came with electron-rich anilines (entries 1-7, 10, and 12). Anilines containing alkoxy substituents at the *ortho*-position fared particularly poorly. Electron-poor anilines (entries 13-15) also failed to produce the corresponding quinolines in high yield.

Scheme 50. Regioisomeric Distribution Observed with Anilines Lacking a Plane of Symmetry



Another consideration must be made for entries 10 and 12 (Table 46) where two regioisomeric products are possible. In these cases, complete selectivity was observed for the desired 6,7-isomers as none of the 5,6-isomers were observed by NMR. Two other anilines did not offer this selectivity as a mixture of two quinolines was obtained. 3,4-Dimethylaniline and 3-methoxyaniline each produced a mixture of regioisomers (Scheme 50) but with relatively good yield (54%).[151] Although some separation of the regioisomers occurred with column chromatography, recrystallization was ultimately necessary to isolate the desired 6,7- (**160d**) and 7- (**160b**) isomers.

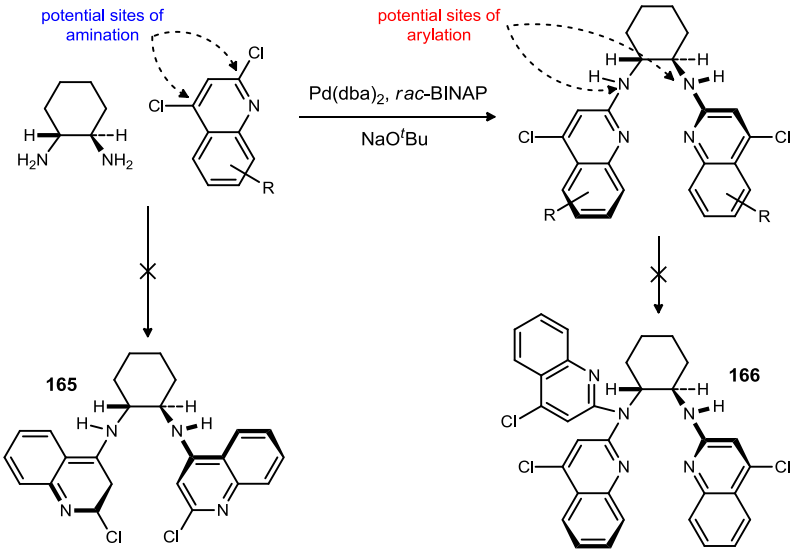


(97)

With hydroxyquinolinone **164** in hand as it was previously synthesized in the group, this 2,4-dichloroquinoline **160i** was made in one step in 55% yield.

[151] Osborne, A. G.; Buley, J. M.; Clarke, H.; Dakin, R. C. H.; Price, P. I. *J. Chem. Soc. Perkin Trans. I* **1993**, 2747-2755.

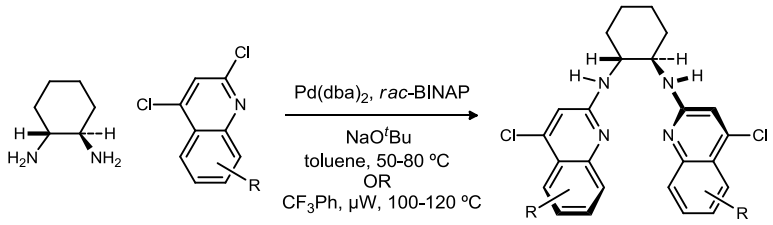
Scheme 51. Reactivity Control in Buchwald-Hartwig Amination of 2,4-Dichloroquinoline



These 2,4-dichloroquinolines proved to be uniformly good substrates for the Buchwald-Hartwig amination reaction.[152] The success of this reaction relies upon the selectivity for reaction at the 2-position of the quinoline and subsequent inertness of the product to further reaction. If amination occurs at the 4-position of the quinoline, undesired compound **165** would be formed. Furthermore, compound **166** could be formed if the desired product undergoes reaction to aminate another molecule of quinoline. Production of this triarylated product was observed by Buchwald when he used diaminocyclohexane as a substrate.[153] If either of the pathways is operational, this synthetic strategy may not be useful because of low yields or purification problems. Luckily, neither of these pathways appear to be prevalent as no significant byproducts like **165** or **166** are observed.

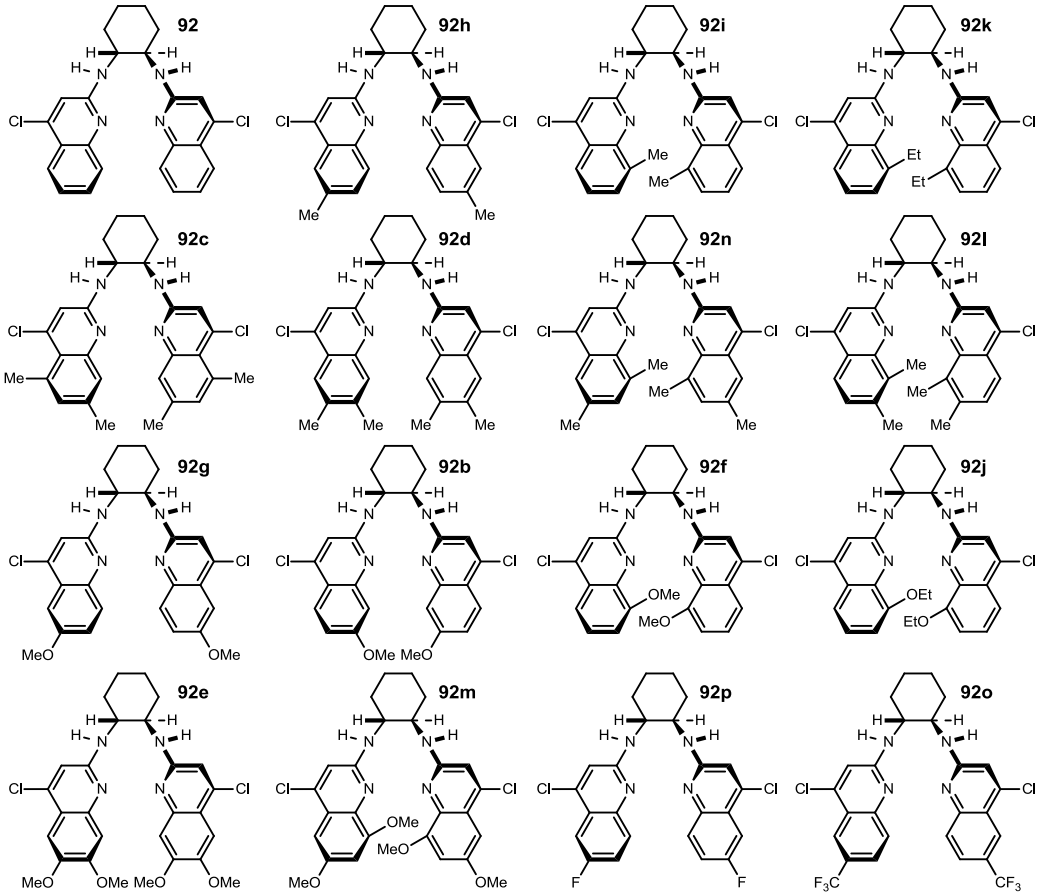
[152] Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158-1174.
[153] Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451-8458.

Table 47. Synthesis of ^{4}Cl-BisAMidines



entry	quinoline	product	yield[c] (%)
1	**160**	**92**	65-75
2	^{6}Me (**160h**)	**92h**	73
3	^{8}Me (**160i**)	**92i**	82
4	^{8}Et (**160k**)	**92k**	61
5	^{5,7}(Me)$_2$ (**160c**)	**92c**	49
6[b]	^{6,7}(Me)$_2$ (**160d**)	**92d**	24
7	^{6,8}(Me)$_2$ (**160n**)	**92n**	62
8	^{7,8}(Me)$_2$ (**160l**)	**92l**	66
9[b]	^{6}MeO (**160g**)	**92g**	77
10[b]	^{7}MeO (**160b**)	**92b**	76
11[b]	^{8}MeO (**160f**)	**92f**	62
12	^{8}EtO (**160j**)	**92j**	72
13	^{6,7}(MeO)$_2$ (**160e**)	**92e**	68
14	^{6,8}(MeO)$_2$ (**160m**)	**92m**	72
15	^{6}F (**160p**)	**92p**	48
16	^{6}CF$_3$ (**160o**)	**92o**	41

[a]All reactions were run using 2-2.5 mol% Pd(dba)$_2$, 2-4 mol% *rac*-BINAP, and 3 equiv. of NaO^{t}Bu in toluene at 50-80 ºC for 1-6 h unless otherwise noted. [b]Heated in the microwave with CF_3Ph as solvent at 100-120 ºC for 10-20 min. [c]Isolated yield.



A variety of different thermal conditions were used in the development of this 4-Cl BisAMidine library, but very similar catalyst and reagent conditions were used across the scope. Some reactions were heated conventionally in an oil bath (60-90 °C) with toluene as the solvent while others were heated in a microwave (100-120 °C) with trifluorotoluene as the solvent. Both methods produced generally good yields for the reaction. The microwave protocol offers the advantage of very short reaction times (10-20 min vs. 1-6 h for conventional). Eventually, the conventional heating method was used simply for uniformity. $Pd(dba)_2$ was used as the palladium source, BINAP was used as the phosphine ligand, and NaO^tBu was the base chosen. Once again, the vast majority of these reactions were performed once, therefore they are likely not under optimal conditions. The results of these reactions are shown in Table 47.

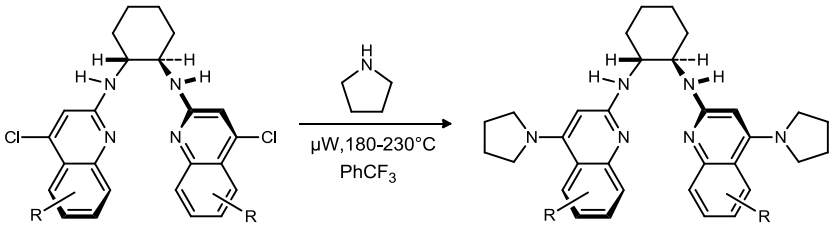
This reaction was shown to be remarkably general with relatively good yields with most substrates. Electron-rich (entries 2-14) and electron-deficient quinolines (entries 15-16) were tolerated, and the presence of steric bulk at carbons 5-8 did not adversely affect yields. In most cases, simple column chromatography was sufficient to purify the product. In some cases, a simple solvent rinse of the crude product provided sufficiently pure product. Sixteen different ^{4}Cl BisAMidines were ultimately synthesized. It is noteworthy that the employment of a single Pd source ($Pd(dba)_2$) and phosphine ligand (BINAP) was sufficient for each of these reactions. Variations in these two reagents are oftentimes necessary for the success of these reactions, but we did not have to optimize this aspect of the reaction.[152]

The last reaction to arrive at the ^{4}Pyrrolidine BisAMidine catalysts is a simple nucleophilic aromatic substitution of the aryl chloride by pyrrolidine. This was achieved

using microwave conditions by heating the ^{4}Cl substrate in the presence of excess pyrrolidine. This proved to be an easy, robust method to make these catalysts.

The results of this reaction using sixteen different ^{4}Cl precursors are displayed in Table 48. Heating the substrates to 180-230 °C with excess pyrrolidine in trifluorotoluene led to a range of yields (unoptimized). The reaction tolerated a variety of sterically and electronically different ^{4}ClBAM substrates. All of the products were purified by column chromatography, then washed with aqueous base to remove any residual acid from the catalyst. One obvious optimization of this process that could be implemented is a non-chromatographic purification. These compounds are quite polar, and a solvent system of 2-10% methanol in dichloromethane with 0.5% acetic acid must be employed. The addition of acetic acid seems to help alleviate the streaking that occurs as these compounds elute. It is very difficult to get many of these compounds to completely elute from the column. It is likely that this is a major source of product loss in this process, as oftentimes the crude NMR spectra look quite clean. The possibility of recrystallization is discussed in the next section.

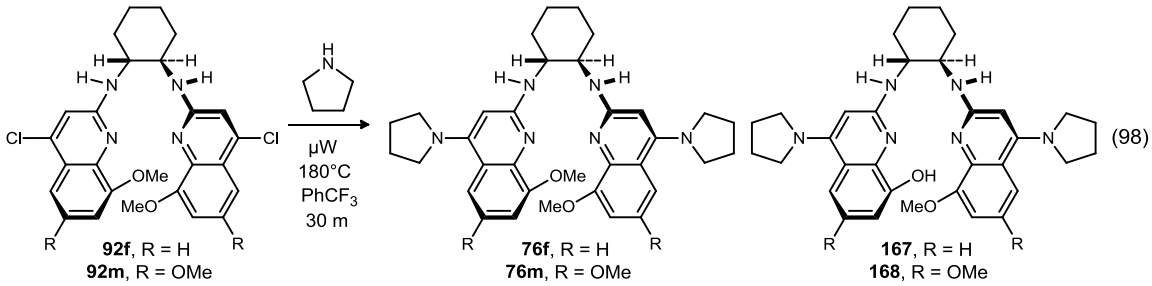
Table 48. Synthesis of ^{4}Pyrrolidine BisAMidine Catalyst Library



entry	^{4}ClBAM	product	time (min)	yield[b] (%)
1	**92**	**76**	30	90-95
2	^{6}Me (**92h**)	**76h**	150	46
3	^{8}Me (**92i**)	**76i**	60	54
4	^{8}Et (**92k**)	**76k**	40	73
5	^{5,7}(Me)$_2$ (**92c**)	**76c**	210	93
6	^{6,7}(Me)$_2$ (**92d**)	**76d**	35	34
7	^{6,8}(Me)$_2$ (**92n**)	**76n**	30	52
8	^{7,8}(Me)$_2$ (**92l**)	**76l**	40	72
9	^{6}MeO (**92g**)	**76g**	20	77
10	^{7}MeO (**92b**)	**76b**	20	54
11	^{8}MeO (**92f**)	**76f**	30	48
12	^{8}EtO (**92j**)	**76j**	10	77
13	^{6,7}(MeO)$_2$ (**92e**)	**76e**	40	31
14	^{6,8}(MeO)$_2$ (**92m**)	**76m**	10	72
15	^{6}CF$_3$ (**92o**)	**76o**	10	50

[a]All reactions were run using 4-20 equiv. of pyrrolidine in $PhCF_3$ at 180-220 °C for 1-6 h unless otherwise noted. [b]Isolated yield.

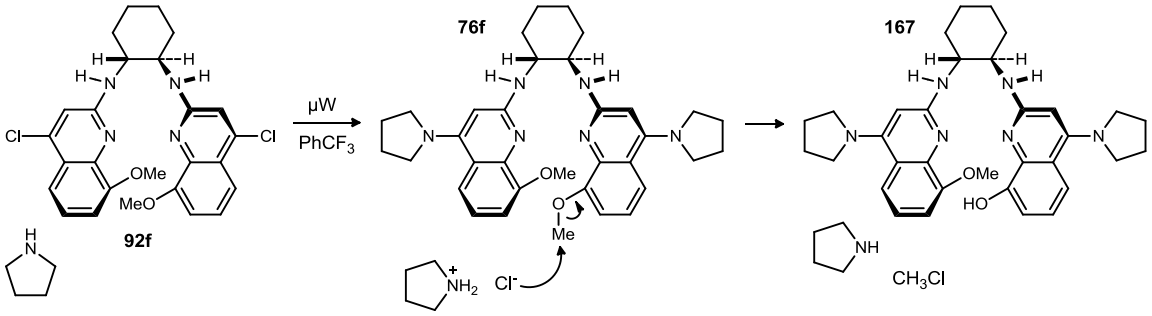
The reaction yielding highly stereoselective catalysts **76f** and **76m** did suffer from the production of one major identifiable byproduct. After column chromatography, some of the fractions containing the desired product contained another compound. The loss of C_2 symmetry and absence of a methyl singlet (^{1}H NMR) combined with a mass spectrum indicating a M+H of 553 (^{8}MeOPBAM, **76f** = 567) verified **167** as the byproduct. This demethylation (compound **168**) was also observed (^{1}H NMR and mass spec confirmed) in the synthesis of **76m**.



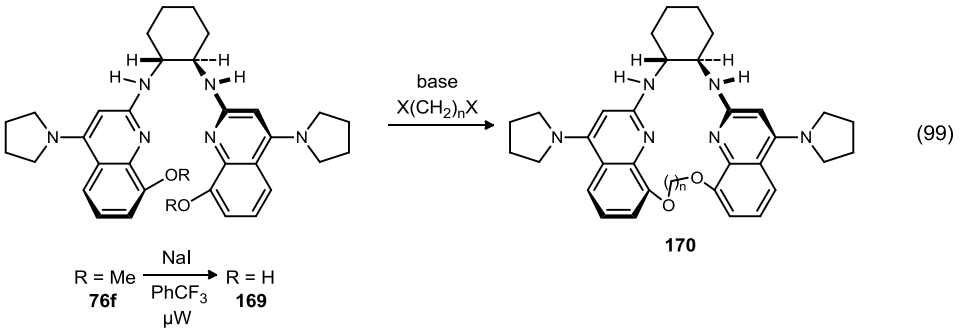
(98)

This is obviously a source of product loss with this reaction and could potentially be detrimental to the synthesis of other methoxy substituted catalysts. Mechanistically, this demethylation of the desired product could be the result of chloride ion attack on the methoxide (Scheme 52). Hydrochloric acid is produced as a byproduct of this reaction and forms a salt with pyrrolidine (used in excess). This source of chloride ion could serve to promote an S_N2 attack of the methyl group leaving the corresponding phenol. The use of silver to scavenge free chloride ions could be an effective strategy to shut down this undesired reaction.

Scheme 52. Potential Mechanism for Demethylation of ^{8}MeOPBAM



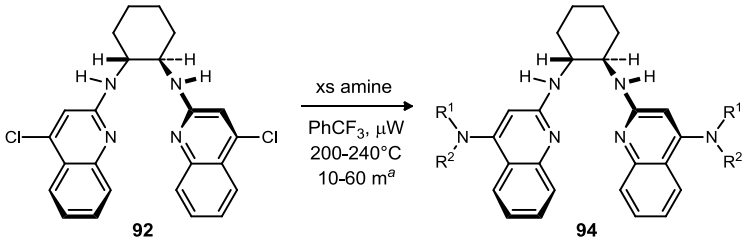
Conversely, conditions for this demethylation could be optimized to produce ^{8}HydroxyPBAM (**169**), which is potentially useful as a catalyst or a precursor to other interesting BAM compounds. Williamson ether synthesis of **169** could provide macrocyclic catalysts of general structure **170** (eq 99). Catalysts of this type would provide useful information about the role of conformational freedom and its relationship to enantioselection in PBAM catalyzed reactions.



(99)

These microwave conditions also permitted other amines to be smoothly coupled to [4]ClBAM to make the corresponding 4-amino catalysts. These results are displayed in Table 49. Various amines were used in excess at 200-240 °C for 10 to 60 minutes to give good to modest yields.

Table 49. Synthesis of 4-Amino BAM Catalysts



entry	amine	R^1	R^2	product	yield[b] (%)
1[c]	$Me_2NH{\cdot}HCl$	Me	Me	**94i**	36
2	*N*-methylaniline	Ph	Me	**94d**	57
3	morpholine	$-(CH_2)_2O(CH_2)_2-$		**94a**	74
4	piperidine	$-(CH_2)_5-$		**94b**	74
5	*N*-methylpiperizine	$-(CH_2)_2N(Me)(CH_2)_2-$		**94c**	85
6	homopiperidine	$-(CH_2)_6-$		**94h**	81

[a]All reactions were run on a 137-457 mol scale with 10-30 equiv. of amine. [b]Isolated yield after column chromatography and aq NaOH wash. [c]16 equiv NEt_3 and 10 equiv $Me_2NH{\cdot}HCl$ used.

5.3 Development of an Organic Syntheses Preparation of PBAM

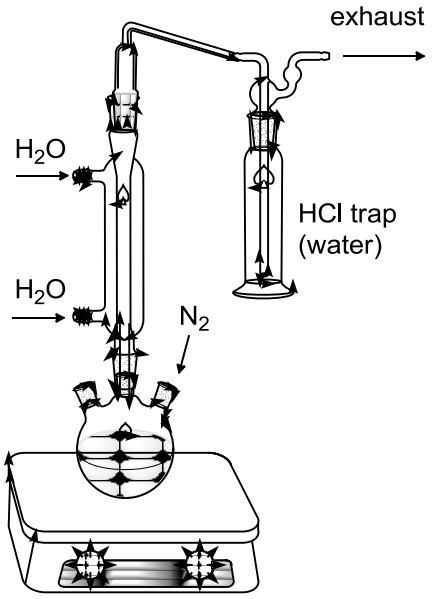
The success of PBAM as a catalyst in many different reactions described in previous parts of this document made clear the need to provide a reliable, convenient synthesis protocol to the scientific community. We already had a fairly robust process in place, but we needed to scale-up the reactions and simplify the work-up.

Although 2,4-dichloroquinoline is commercially available, its cost is too high to use as a starting material,[149] so we chose to make it ourselves. There are many procedures available in the literature to make this compound from aniline, malonic acid, and phosphorus oxychloride. Our procedure most resembles the protocol of Jones[154] and has evolved over time to facilitate our growing need for this compound.

Some care has to be taken with the use of $POCl_3$ as a reagent in this reaction, as it reacts violently with water. Also, this reagent produces HCl gas upon reaction so an HCl trap must be connected to the system to trap the HCl gas liberated. On two occasions, difficulties were encountered. In one incident, a condenser cracked in the middle of the reaction pouring water into the hot $POCl_3$, resulting in an eruption. In another incident, water was siphoned into the reaction from the attached HCl trap due to reduced pressure formation in the system. The first mishap was quite unavoidable. The second was easily avoided in future reactions as continual positive pressure (nitrogen) was placed on the system.

[154] Jones, K.; Roset, X.; Rossiter, S.; Whitfield, P. *Org. Biomol. Chem.* **2003**, *1*, 4380-4383.

Figure 36. Schematic of 2,4-Dichloroquinoline Set-up



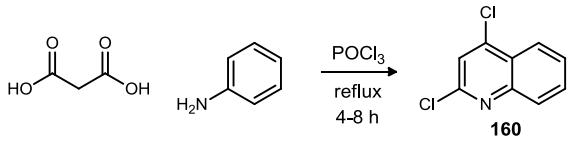
A general depiction of our 2,4-dichloroquinoline set-up is shown in Figure 36. Initially, malonic acid is dispensed into a 3-neck round bottom flask with a stir bar. $POCl_3$ is added to the flask and the suspension is chilled to 0 °C. The apparatus is fully constructed and a slight flow of nitrogen is placed into the system. Aniline is added to the stirring suspension via syringe (usually over 5-10 minutes). After addition, the reaction mixture was heated to ~110 °C and stirring continued for 4-8 hours.

Initially, our workup consisted of pouring the cooled reaction mixture onto crushed ice, adjusting the pH to basic, then extracting with dichloromethane. Unavoidable emulsions usually resulted from this. Eventually, we bypassed this extraction and simply poured the reaction mixture onto ice, adjusting the pH to basic with aqueous sodium hydroxide, and filtering the resulting suspension. We originally purified the crude solid by column chromatography before we came to the realization that a solid-liquid extraction was possible. Ultimately, this filtered red solid was soxhlet extracted

with hexanes to obtain a sufficiently pure product without the necessity of column chromatography.

One major issue of scale-up with this reaction is the large volume of ice/water needed to quench the large volumes of $POCl_3$ used. This caused us to run the reaction under as concentrated conditions as possible to reduce these volumes and lessen the inconvenience of dealing with such volumes. The concentration was increased from 1.3 M to 2.5 M for these large scale reactions without a drop in yield or addition of other complications. The reaction mixture was significantly more viscous which necessitated a pouring of the reaction mixture onto ice (carefully) while it was still warm. If it was allowed to cool, it would congeal and require copious amounts of water and solvent to transfer from the reaction flask for quenching.

Table 50. Large Scale Syntheses of 2,4-Dichloroquinoline



160

trial	chemist	scale (mmol)	mass (g)	yield[b] (%)
1	Schwieter	750	44.6	30
2	Davis	250	15.8	32[c]
3	Davis	250	21.7	44
4	Davis	250	16.5	33

[a]All reactions were run in 2.5 M of $POCl_3$, see *Organic Synthesis* procedure for details. [b]Isolated yield after soxhlet extraction with hexanes. [c]Extracted by stirring crude solid with hot hexanes and decanting for multiple cycles.

The results of four large scale syntheses of 2,4-dichloroquinoline (**160**) are shown in Table 50. Although the yields are low, we were able to make up to 44.6 g of sufficiently pure quinoline without column chromatography in one batch. With the increased concentration, only 300 mL of $POCl_3$ was used in the 750 mmol reaction resulting in less than 1.5 L of aqueous solution created in workup. The use of aqueous NaOH to adjust the pH to basic was also beneficial in reducing workup volume.

The crude material obtained from soxhlet extraction with hexanes was very pure by ^{1}H NMR and was acceptably pure for the next step of the synthesis. For additional purity, the compound was recrystallized from toluene/hexanes or ether/hexanes. Only a small difference in melting points was observed between crude material (62-63 °C), recrystallized material (63.5-64.0 °C), and chromatographed material (64.0-64.5 °C).

The yields are quite low but match what is seen in the literature with similar reactions. The process can be viewed as two reactions in one pot as discussed earlier. Furthermore, the reaction uses very cheap starting materials. Aniline can be purchased for $22 per kg. Malonic acid is available for $153 per kg, and $POCl_3$ is available for $70 per kg.[155] The cost of reagents for this reaction is approximately $16 dollars on the 250 mmol scale. Increasing the concentration to 2.5 M effectively cut this cost in half. Despite the low yields, we still find this to be the easiest and cheapest way to make this compound. This reliable route to our starting material quinoline allowed us to scale up the next reaction of the sequence.

As the Buchwald-Hartwig amination was repeatedly performed on increasing larger scales over the last four years, the work-up procedures were gradually optimized. Initially, *4*ClBAM was purified by column chromatography. This became more difficult as the scale of the reaction was increased. The main problem was the difficulty of dissolving the crude product with dichloromethane to load onto the column. At some point, the sparingly soluble ashy white solid from the crude product was analyzed by ^{1}H NMR. This solid was found to be sufficiently pure. This washed solid was taken through and no difference was observed from the column purified *4*ClBAM. Shortly after this

[155] Prices obtained from Sigma-Aldrich website, Feb. 4, 2011

observation, washing the crude solid with small amounts of solvent (CH_2Cl_2 was found to be a sufficient solvent) supplanted column chromatography as the purification method.

With this knowledge, an *Organic Syntheses* preparation in terms of style and scale seemed appropriate. The two major challenges for this reaction would be obtaining equitable results on multi-gram scale and the development of a reliable, non-chromatographic work-up. There were no major problems encountered when running this reaction on a scale to produce over 4 grams of ^{4}ClBAM. No changes needed to be made in terms of relative amounts of reagents and reaction conditions. There was some optimization of reaction concentration. It seemed likely that the product could precipitate out of the reaction mixture owing to its general insolubility. This would be beneficial as our work-up could be simplified to a simple filtration and washings of the obtained solid on the filter.

The first generation of the ^{4}ClBAM synthesis was run under dilute conditions (0.08 M in toluene) to produce 1.8 grams (54%) on a 7.6 mmol scale after column chromatography. With our initial attempts at 14.3 mmol scale, the concentration was increased to 0.41 M in toluene.[156] This turned out to be just right as the product did indeed precipitate. After five or ten minutes of heating and stirring (stir bar) at 80 °C, the reaction mixture became unstirrable. Manual swirling of the flask by hand broke up this solid, and stirring was able to continue for the duration of the reaction.

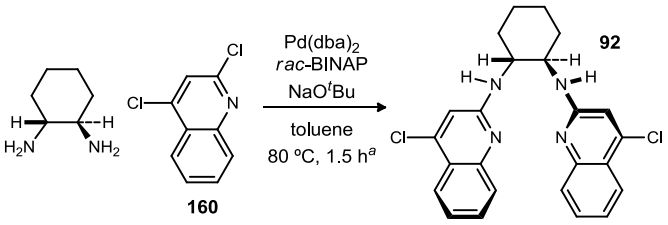
After 1.5 hours of heating at 80 °C, little to no starting material was observed by thin layer chromatography. The reaction mixture was allowed to cool to room temperature. A mild aqueous acid (NH_4Cl) was added to the flask to quench any

[156] With Ken Schwieter

remaining sodium *tert*-butoxide. The resulting suspension was then chilled in an ice bath to influence any additional product to precipitate.

A simple filtration through a Buchner funnel left a considerable amount of a light yellow solid which was washed on the filter with water (50 mL) and then hexanes (150 mL). This solid, found to be sufficiently pure by ^{1}H NMR, amounted to 4.18 grams (68%) on the first attempt. Satisfied with this result, we repeated this exact procedure

Table 51. Reproducibility of the Organic Synthesis Procedure for ^{4}Cl BAM



trial	chemist	mass (g)	yield[b] (%)
1	Schwieter	4.18	68
2	Schwieter	4.68	75
3	Schwieter	4.10	65
4	Dobish	4.54	73
5	Dobish	4.54	72
6	Davis	4.77	76
7	Davis	4.32	69

[a]All reactions were run using an identical procedure, see *Organic Synthesis* procedure for details.

several times with multiple sets of hands.[157] The results of these trials are shown in Table 51. Three chemists executed the procedure to give 4.10-4.77 grams of desired compound **92** in 65-76% yield. With good yields and reproducibility established, we moved on to the scale-up and optimization of the final step of the synthesis.

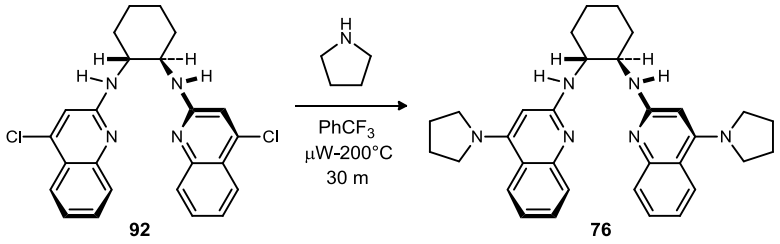
The microwave-assisted nucleophilic aromatic substitution was found to be a simple, high-yielding reaction without any optimization. These conditions (20 equiv. pyrrolidine in $PhCF_3$ at 200 °C for 3.5 h) produced 635 mg of **76** (92%) on a 1.37 mmol

[157] Schwieter, K.; Dobish, M.; Davis T.; Johnston, J. N. *unpublished results.*

scale. Even though the reaction was very high yielding, the chromatographic purification of PBAM was very inconvenient. PBAM is a quite polar compound, and it binds strongly to silica gel. What results is a very "streaky" column where copious amounts of solvent (methanol and dichloromethane) must be used to flush the desired compound off the column. The addition of a small amount of acetic acid to the eluent did somewhat lessen this problem, but this was still a major issue in terms of developing a robust procedure on an appreciable scale.

Initially, adjustments had to be made in consideration of the capacity of our microwave system. We were limited to the volume we could fit into one 10-20 mL vial, the maximum vessel size for our microwave system. The equivalents of pyrrolidine were reduced from 20 to 4. The amount of solvent was also reduced resulting in a very concentrated reaction (1.5 M). This concentration allowed us to run the reaction in one microwave batch. Fortunately, equitable results were obtained under these conditions. With the first trial, 4.51 g (94%) of crude product was observed on a 9.6 mmol scale. A simple base wash (aqueous NaOH) followed by water washes yielded material that was acceptably pure by ^{1}H NMR. This process was quite reproducible in terms of yield, but a consistent, true melting point could not be found. This indicated the need for a better method for purification.

Table 52. Reproducibility Study of PBAM Synthesis



92 76

trial	chemist	scale (mmol)	mass (g)	theoretical mass (g)	yield[b] (%)
1	Schwieter	9.6	4.51	4.86	94
2	Schwieter	10.7	4.97	5.40	92
3	Schwieter	9.4	4.50	4.76	95
4	Dobish	10.3	5.43	5.22	n/a[d]
5	Dobish	9.8	5.23	4.98	n/a[d]
6	Davis	9.8	5.08	4.98	n/a[d]
7	Davis	9.8	5.32	4.98	n/a[d]

[a]All reactions were run using an identical pro-rated procedure, see *Organic Synthesis* procedure for details. [b]Isolated yield of crude compound after aqueous workup and evaporation of solvent by rotavap and high vacuum, contains 0-12% solvent by mass. [d]Mass was greater than theoretical yield due to presence of solvent.

Despite the inability to obtain a melting point, other issues existed. It was quite difficult to remove solvent completely from the compound. Although the amounts varied from run to run, a significant amount of triflourotoluene and sometimes pyrrolidine was still seen after subjection to high vacuum. The results of seven different trials are shown in Table 52. The inability to completely remove solvent was seen with the solvent inflated yields of trials 4 through 7. In each case, the only noticeable impurities seen by crude NMR were trifluorotoluene, pyrrolidine and to a lesser extent, dichloromethane. It appeared that the only reproducibility issue was the removal of these volatile impurities. The use of a drying pistol (refluxing toluene) to thoroughly remove this residual solvent was fairly successful, but a trace of these impurities could still be seen by ^{1}H NMR after rigorous drying for a few days. Furthermore, the increased purity of the compound from the drying did not result in a consistent melting point.

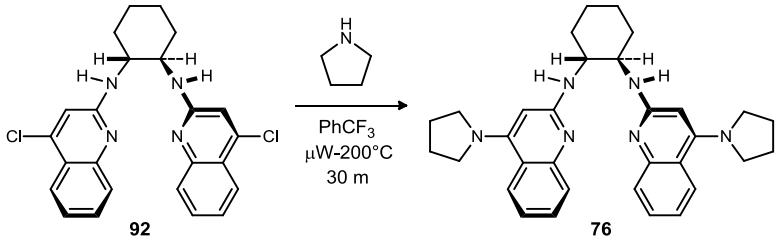
Shortly after the initial synthesis of PBAM (**76**), single crystals of the catalyst were grown. Two crystal structures of the free base were obtained from crystals grown

from acetone and nitromethane. Each crystal structure had a molecule of the corresponding solvent in the crystal lattice. This served as a hint that acetone might be a good choice for a recrystallization solvent. Indeed, the catalyst did recrystallize from acetone. A myriad of other solvents and solvent combinations of ethyl acetate, diethyl ether, dichloromethane, ethanol, acetonitrile, hexanes, and toluene among others failed to produce crystals.

Although PBAM did recrystallize from acetone, it was difficult to reproduce consistently. The main problem was that the compound was quite insoluble in acetone. Oftentimes so much acetone was required to dissolve the material that the solution was too dilute to produce crystals upon cooling. Even when crystals were formed, the recovery was quite low. Through these recrystallization attempts and other experiences handling the compound, toluene was found to be the best solvent for dissolving PBAM by far. This led to the use of an acetone/toluene mixture for recrystallization as acetone would provide the proper medium for crystal growth and toluene could help solvate the compound. A 90:10 mixture of acetone/toluene was ultimately found to be the best solvent.

The resulting crystals were washed with cold acetone and placed under high vacuum to remove the solvent. The crystalline material was found to be exceptionally pure by ^{1}H NMR with the exception of the presence of about one equivalent of acetone. Drying in a drying pistol was found to be necessary to remove the acetone. Furthermore, it was deemed necessary to pulverize the solid after partial drying to aid the complete evaporation of the residual solvent. Upon evaporation of the acetone, the solid changed from a light bronze color to nearly white. A consistent melting point of 242.5-244.0 °C

was observed. It appeared some decomposition occurred as the material turned to a light brown when heated above 200 °C. Still, a discreet melting happened at 242.5-244.0 °C. Additionally, the material was found to be exceptionally pure by elemental analysis.



92 76

trial	chemist	mass (g)	yield[b] (%)
1	Dobish	3.12	63
2	Davis	3.35	67

[a]All reactions were run using an identical, 9.83 mmol scale procedure, see *Organic Synthesis* procedure for details. [b]Isolated yield of recrystallized compound.

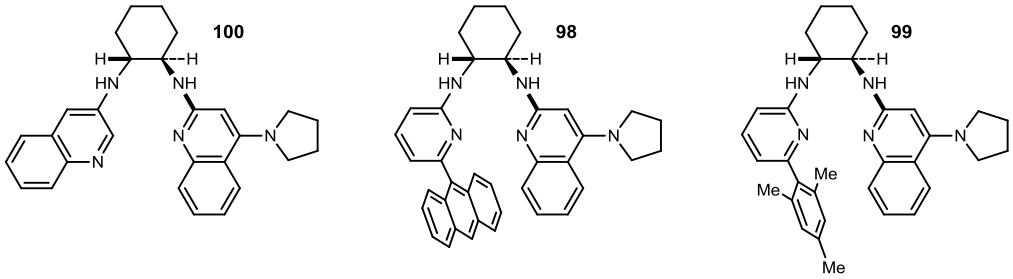
Very similar results for this last optimized step of the PBAM synthesis were obtained by two chemists demonstrating reproducibility. Amounts of 3.12 and 3.35 grams were produced in two experiments, corresponding to 63% and 67% yield respectively. In each case, identical melting points were obtained. Also, it was demonstrated that the mother liquor could be concentrated and resubjected to the recrystallization procedure to give an additional 800 mg of product raising the overall yield of the step to 81-85%.

We have developed a practical, reproducible, large-scale protocol for the synthesis of PBAM in 3 steps. This protocol is most likely translatable to other derivatives of PBAM as well. This procedure has been submitted for review to *Organic Syntheses* and will provide the scientific community the means to synthesize this compound.[158] This should help others to use the reactions developed in this group for various applications as well as encourage the development of new methodologies using PBAM.

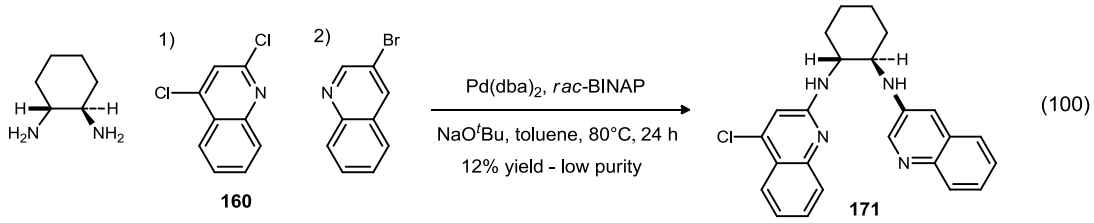
[158] Davis, T. A.; Dobish, M. C.; Schwieter, K. E.; Chun, A. C.; Johnston, J. N. *Org. Synth.*, *submitted*.

5.4 Synthesis of Non-C_2-Symmetric BAM Ligands

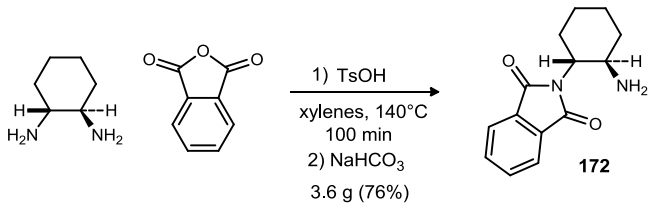
Figure 37. Desired Non-C_2-Symmetric BAM Ligands



The synthesis of non-C_2-symmetric BAM ligands is more difficult than that of C_2-symmetric BAM ligands. The structures **100**, **98**, and **99** in Figure 37 are more Brønsted basic versions of effective catalyst motifs. The most straightforward route to the compounds is a Buchwald-Hartwig type amination with two different aryl halide coupling components.

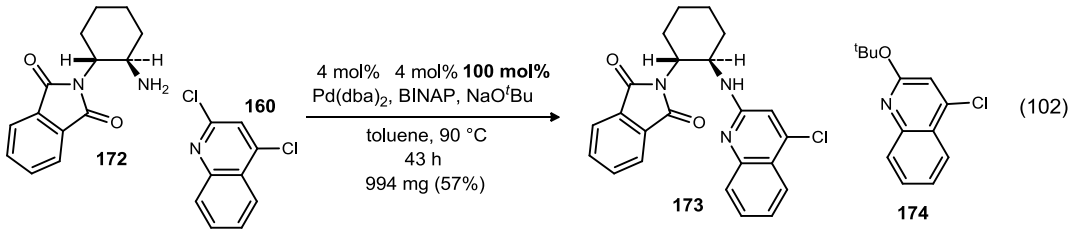


This direct route was attempted in the synthesis of **171** from cyclohexane diamine, 2,4-dichloroquinoline (**160**), and 3-bromoquinoline (eq 100). **160** was added first until consumption of that quinoline, then 3-bromoquinoline was added. The desired compound (**171**) was isolated after column chromatography, but the yield was low and the material was not appreciably pure. An effort to isolate the monoarylated diamine also failed. Although 3-bromoquinoline is commercially available, the precursor aryl bromides to make **98** and **99** are not. A more robust route to this class of catalysts was needed.



(101)

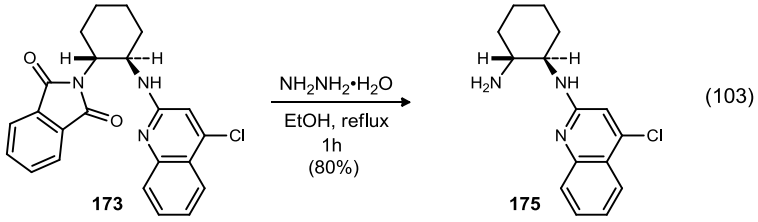
The use of a mono-protected cyclohexane diamine is a strategy that has been successfully used previously in this group. Despite the increase in the number of steps needed to access the desired catalysts, this route has the advantages of associated with a common intermediate. Cyclohexane diamine is treated with phthalic anhydride in the presence of tosic acid to yield the protected acid salt (eq 101). This salt is then treated with base to liberate the free protected diamine **172** in good yield. It is convenient to leave this stored as the tosic acid salt until ready to use.



(102)

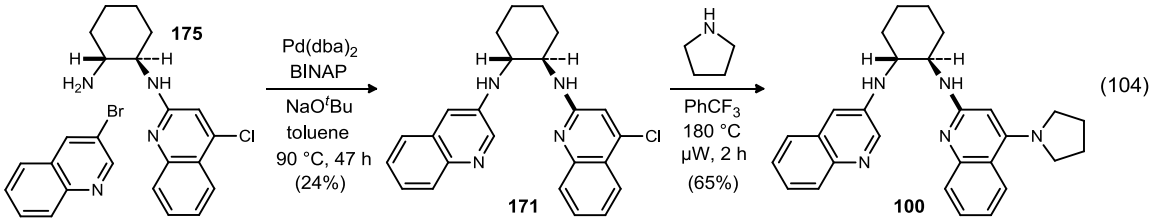
Next, singly protected diamine **172** was subjected to a Buchwald-Hartwig amination reaction with 2,4-dichloroquinoline **160** (eq 102). Several initial attempts at this reaction failed. This reaction was sluggish as compared to the amination reactions involving the unprotected diamine. Also, sodium *tert*-butoxide competitively added to the quinoline to give **174** as a byproduct. Changing the palladium source from $Pd(dba)_2$ to $Pd(OAc)_2$ did not improve the reaction. JohnPhos was used in place of BINAP as a phosphine ligand but also did not improve this reaction. Although changing the base to K_3PO_4 was futile, reducing the equivalents of NaO^tBu from 3 to 1 while using a slight

excess of amine **172** (1.2 equivalents) did effectively limit the formation **174**. After a reaction time of 43 hours at 90 °C, nearly a gram of **173** was produced in 57% yield.



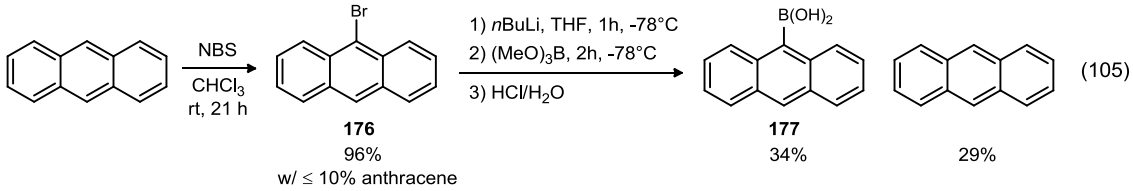
(103)

173 was then deprotected cleanly by treatment with hydrazine hydrate in refluxing ethanol for one hour (eq 103). This produced free amine **175**, a common intermediate towards all three desired non-C_2-symmetric catalysts, in 80% yield. Reaction of this free amine **175** with 3-bromoquinoline under Buchwald-Hartwig amination produced aryl chloride **171**, albeit in low yield (eq 171). This material was then heated with pyrrolidine in the microwave to produce 50 mg of catalyst **100** in 65% yield.



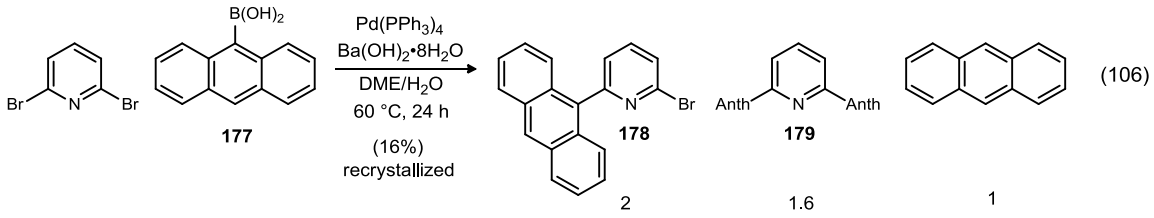
(104)

The other two targets **98** and **99** required preparation of the halopyridine substrate for the amination reaction. A Suzuki coupling would be used to make both of these halopyridines.



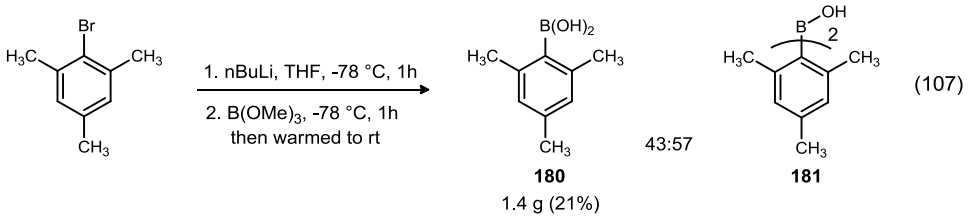
(105)

Following a route previously developed in this group, boronic acid **177** was made from anthracene in two steps (eq 105). 9-Bromoanthracene **176** is made from an electrophilic aromatic substitution of anthracene with *N*-bromosuccinimide in good yield. Metallation of **176** followed by a quench with trimethylborate gives boronic acid **177** upon aqueous acid workup. Anthracene is produced as a major byproduct of this reaction, and its reproducibility was generally troublesome. Ultimately, Mark Dobish found that concentration of the crude material in the presence of acid led to the decomposition of the boronic acid to anthracene. He has reported consistently higher yields with this reaction now using a recrystallization-purification protocol.

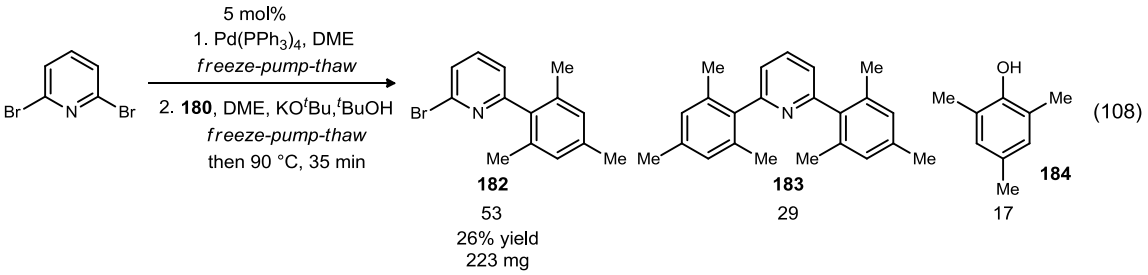


(106)

A Suzuki coupling between 2,6-dibromopyridine and boronic acid **177** was used to produce bromopyridine **178** (eq 106). This suffered from competitive formation of anthracene as well. Diarylated pyridine **179** and 9-hydroxypyridine were major undesired products from the reaction. After column chromatography, the desired compound was isolated as a nearly 1:1 mixture with starting material dibromopyridine. Recrystallization provided pure desired bromopyridine **178** in 16% yield with significant material left in the mother liquor.



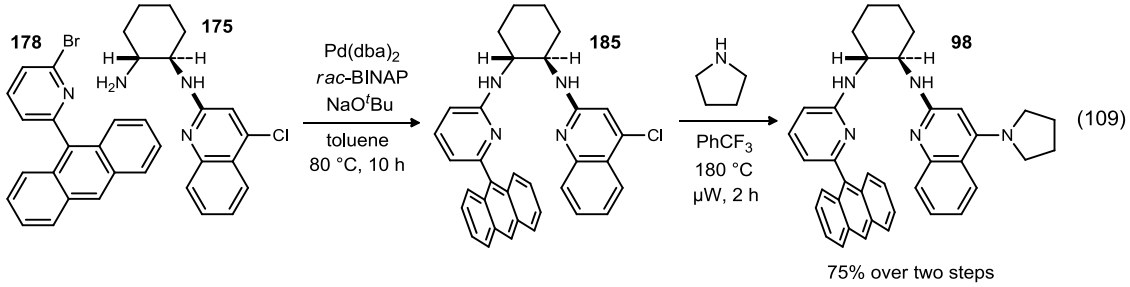
Similarly, commercially available bromomesitylene was converted to the corresponding boronic acid en route to catalyst **99** (eq 107). Following a modified procedure[159], 2-bromomesitylene was metallated and then treated with trimethylborate to produce 1.4 g of boronic acid **180** in 21% yield following washing with EtOAc and hexanes. The majority of the mass balance was the diarylboronic acid (**181**) which was produced in a 57:43 ratio to the desired product. Adding an excess of trimethylborate quickly (instead of dropwise) had no effect on product distribution.



Again, 2,6-dibromopyridine was coupled to boronic acid **180** (eq 108). This reaction was attempted twice as the first reaction suffered from the formation of phenol **184**. In the first reaction, a satisfactory ratio of desired product **182** to diarylated product **183** of 5:1 was observed. The second attempt incorporated freeze-pump-thaw cycles to ensure no oxygen was in the system.[160] This strategy did somewhat minimize the formation of the undesired phenol as the ratio of the product to the phenol increased from

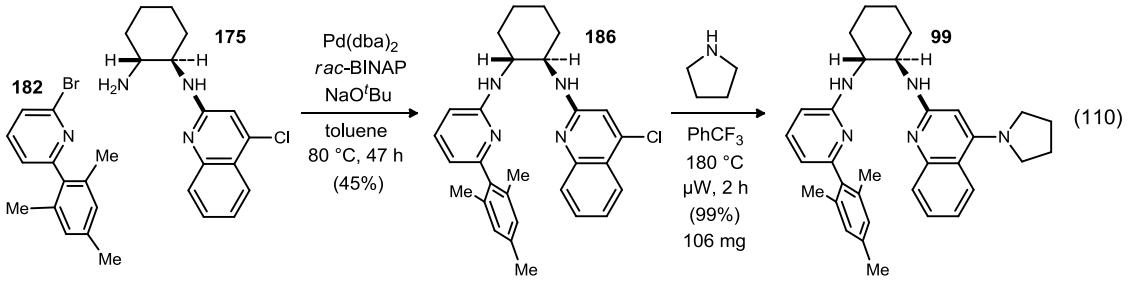
[159] Morgan, J.; Pinhey, J. T. *J. Chem. Soc. Perkin Trans. I* **1990**, 715-720.
[160] Zhang, H.; Tse, M. K.; Chan, K. S. *Synth. Comm.* **2001**, *31*, 1129 - 1139.

nearly 2:1 to 3:1. Still, the formation of the diarylated product was prevalent and only a 26% yield of **182** resulted.



(109)

The Buchwald-Hartwig reaction smoothly produced ^{4}Cl bisamidine **185** (eq 109). This compound was reacted with pyrrolidine under microwave conditions to produce 301 mg of the desired catalyst (**98**) in 75% yield in over two steps.



(110)

The same sequence was used to make catalyst **99** (eq 110). The Buchwald-Hartwig coupling between bromopyridine **182** and amine **175** produced ^{4}Cl bisamidine **186** in fair yield (45%). Aromatic substitution of **186** with pyrrolidine produced 106 mg of desired catalyst **99** in excellent yield (99%).

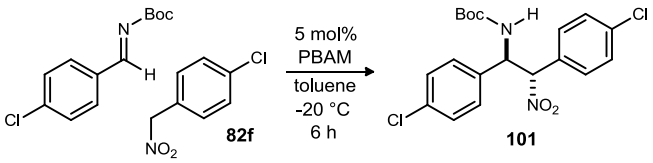
Overall, sufficient material was produced to test these catalysts performance despite the low yield observed for their preparation. Despite the increased difficulty in synthesis, the ability to make non-C_2-symmetric catalysts allows access to a larger library of structural motifs. These catalysts may allow for better reactivity and selectivity than C_2-symmetric ligands in future investigations.

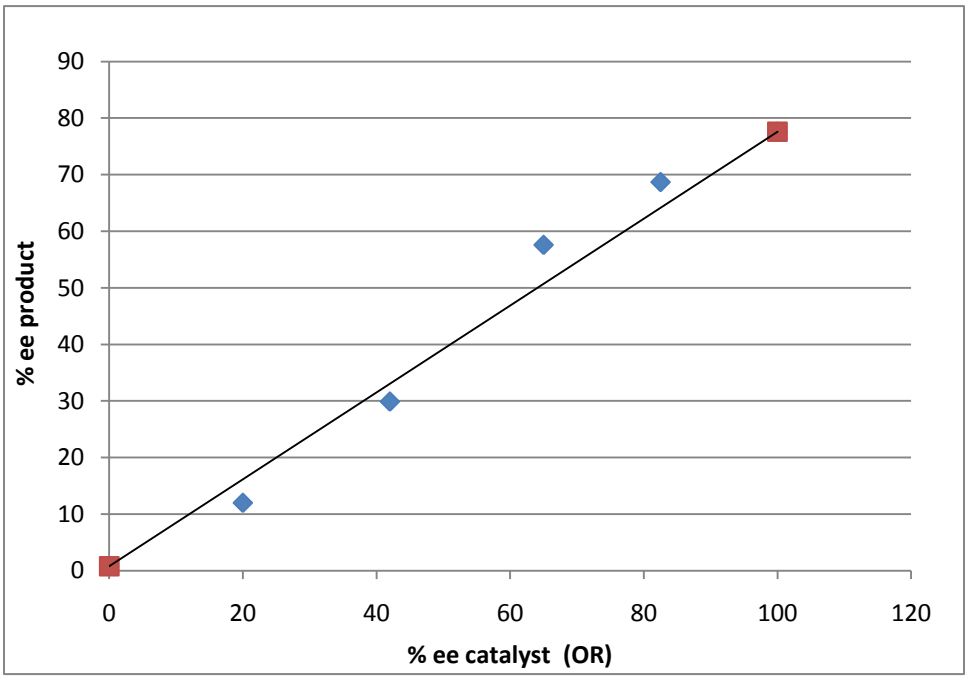
CHAPTER VI

NEW MECHANISTIC INSIGHT

Much of the information available about the mechanism of the BAM-catalyzed aza-Henry reaction was obtained at the very beginning of the chiral proton catalysis program. Most of this work involved the establishment of key structural elements of the BAM catalyst for the aza-Henry reaction of aliphatic nitroalkanes and silyl nitronates. These elements have been incorporated in the structure of PBAM, a highly enantioselective catalyst that has promoted a broader range of reactions. Although there are likely mechanistic similarities between the BAM-catalyzed addition of aliphatic nitroalkanes and aryl nitroalkanes, important differences exist with the addition of the latter species. These unique aspects warrant individual mechanistic consideration for this reaction.

Figure 38. Non-linear Effect Study



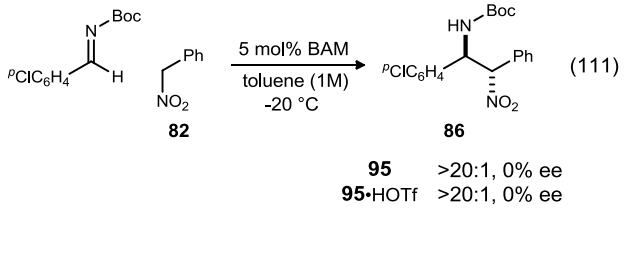


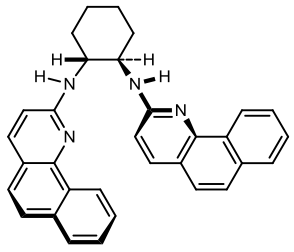
The free base of PBAM is more enantioselective than its triflic acid salt in nearly all cases in the phenynitromethane addition reaction. Conversely, the free base is substantially less enantioselective in the aliphatic nitroalkane additions. It is likely that the *in situ* formed nitronate salt of the catalyst is functioning as a chiral Brønsted acid in this reaction. This presents interesting mechanistic scenarios.

There lies the possibility that two molecules of catalyst are involved in the transition state. A non-linear effect study was performed on the *p*-chloro phenylnitromethane addition to *p*-chloro aryl *N*-Boc imine to address this possibility. If two molecules of catalyst are involved in the transition state, a positive or negative non-linear effect could result from differences in energies of the diastereomeric transition

states.[161] Six different batches of PBAM with varying optical purity were used and the results are shown in Figure 38. No significant deviation from linearity was observed with this reaction. Although it is still possible for multiple catalyst molecules to be involved in the transition state, this study failed to provide evidence for that scenario.

As discussed briefly earlier, a stereochemical model (shown again in Figure 39) has been developed to explain the stereochemical outcome of these BAM catalyzed reactions. This model has not been disclosed in a publication to this point due to fact that it is constructed from many circumstantial trends and observations. Nevertheless, this model does incorporate many key findings made in early catalyst development. 1) It explains the increase in stereoselectivity observed with a larger quinoline system versus the smaller pyridine system. 2) It incorporates the bidenticity that is suggested by the necessity of the catalyst possessing two quinoline rings. 3) It allows for hydrogen bonding of the cyclohexyl N-H with the carbonyl of the imine electrophile which explains the importance of the presence of the cyclohexyl N-H.





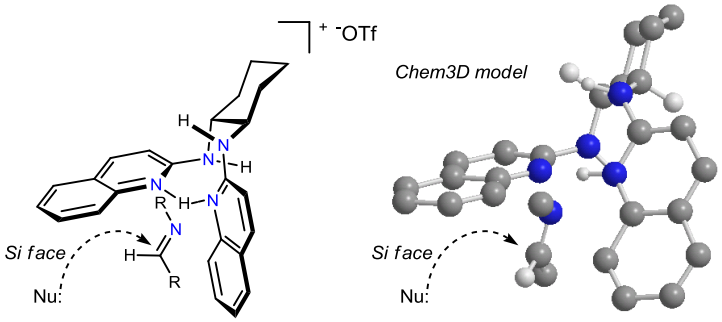
95
H,^{2}(^{7,8}benzoQuin)-BAM

Another piece of evidence that supports this model is the performance of H,^{2}(^{7,8}benzoQuin)-BAM (**95**) in the phenylnitromethane addition reaction. This catalyst bears resemblance to the helical chiral amidine catalyst used by Takenaka to promote

[161] Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 456-494.

enantioselective additions of 4,7-dihydroindoles to nitroalkenes.[162] This catalyst promoted the formation of completely racemic product, seemingly an indication that the usual binding pocket was completely disrupted and a totally different, non-selective pathway was being accessed. This is in agreement with the model in Figure 39 as steric bulk near the 8-position of the quinoline would occupy the docking area of the imine.

Figure 39. Previous Model for Stereoselectivity in BAM Catalyzed aza-Henry Reaction



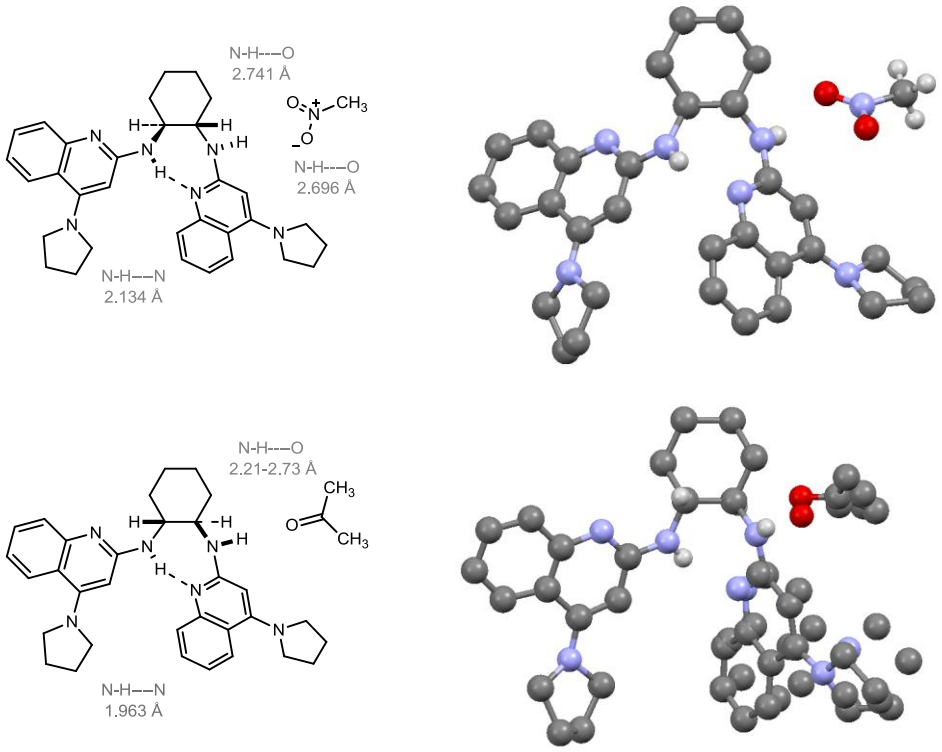
Although this model is consistent with many of the observed trends, there are other possibilities that have not yet been disproven. The only bidentate hydrogen bonding that has been suggested by crystallographic evidence is an intramolecular hydrogen bond between the quinoline nitrogen and the N-H of the opposite cyclohexylamine. Even though a solid state structure has limited direct applicability to the transition state complex, this crystal structure can at least suggest a low energy conformation that might also exist in solution. This intramolecular hydrogen bond has been observed in multiple crystal structures of different BAM catalysts.

Two different X-ray crystal structures of PBAM were obtained from single crystals grown in nitromethane and acetone. The two structures are displayed in Figure 40. Both structures are overall remarkably similar. Each features an intramolecular

[162] Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A. *J. Am. Chem. Soc.* **2010**, *132*, 4536-4537.

hydrogen bond between the N-H of the cyclohexyl diamine and the opposing quinoline N. The N-H---N distances of 2.134 Å and 1.963 Å for the nitromethane and acetone crystal respectively suggest a medium-strong H-bond.[163],[164]

Figure 40. X-ray Crystal Structure of PBAM with Nitromethane and Acetone

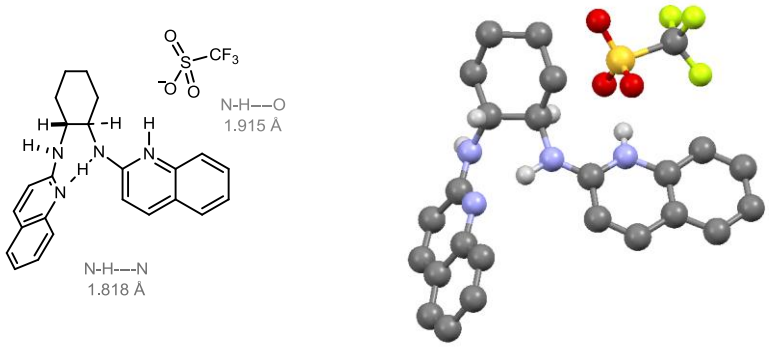


These structures are similar to the crystal structure obtained for H,QuinBAM·HOTf (Figure 41). This triflic acid salt (as opposed to the structures of the free base of PBAM) possesses a comparable hydrogen bond between the cyclohexyl N-H and the opposing quinoline as the N-H---N distance is 1.818 Å. The protonated quinoline ring is swung out and is hydrogen bonded to the triflate counterion. Although the conformation in solution cannot be inferred from a solid state structure, the crystal

[163] Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48-76.
[164] Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997.

structures obtained for different BAM catalysts provide an alternative intramolecular hydrogen-bonded catalyst for consideration relative to that illustrated in Figure 39.

Figure 41. X-ray Crystal Structure of H,QuinBAM·HOTf



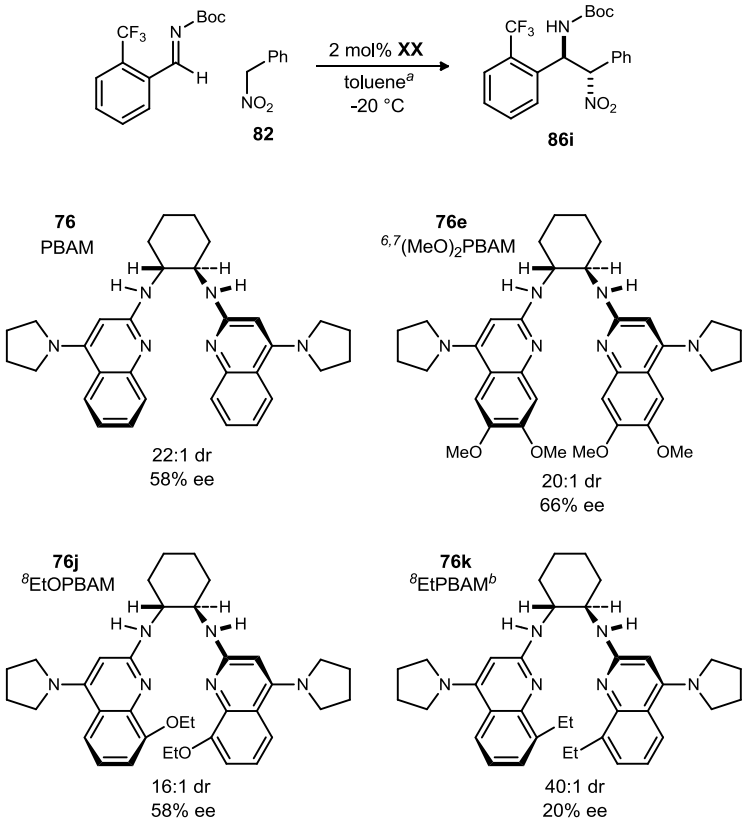
Despite the data (eq 111) that suggested substitution at the 8-position of the BAM catalysts detrimentally changes the transition state, this position was still considered a location where beneficial changes could be made owing to its distance to the binding site. To this point, a series of 8-substituted PBAM catalysts were synthesized to explore potential differences in reactivity and stereoselectivity. In contrast to H,^{2}(^{7,8}benzoQuin)-BAM, these catalysts offered similar and sometimes better enantioselectivity than PBAM in the phenylnitromethane aza-Henry reaction (Tables 33, 38-40, Figure 30).

These results offer strong evidence that the model in Figure 39 is not operational for this reaction. The Chem3D figure shows the imine docked perpendicularly to the quinoline ring to which it is associating through hydrogen bonding. Bonding in this space would be impossible with the 8-alkoxy substituted PBAM catalysts which have proven to be the most enantioselective for this reaction. It is likely that PBAM and the 8-alkoxy substituted PBAM catalysts are operating through a similar mechanism, one that is not similar to Figure 39. Furthermore, a bidentate hydrogen bond between the two quinolines

would be highly sterically disfavored with the 8-substituted PBAM catalysts. On the basis of these trends, the stereochemical model akin to Figure 41 is advance as an alternative to that in Figure 39.

A study was performed to measure the relative reactivity of PBAM and PBAM derivatives in the phenylnitromethane addition reaction. This was inspired by the yields in Table 39 and Table 40 which suggest that 8-alkyl substituted catalysts are significantly less reactive then other PBAM derivatives. The key discovery of two addition products that were appreciably stable to gas chromatography conditions (all other products screened decomposed mainly due to the retro-aza-Henry reaction) allowed for the

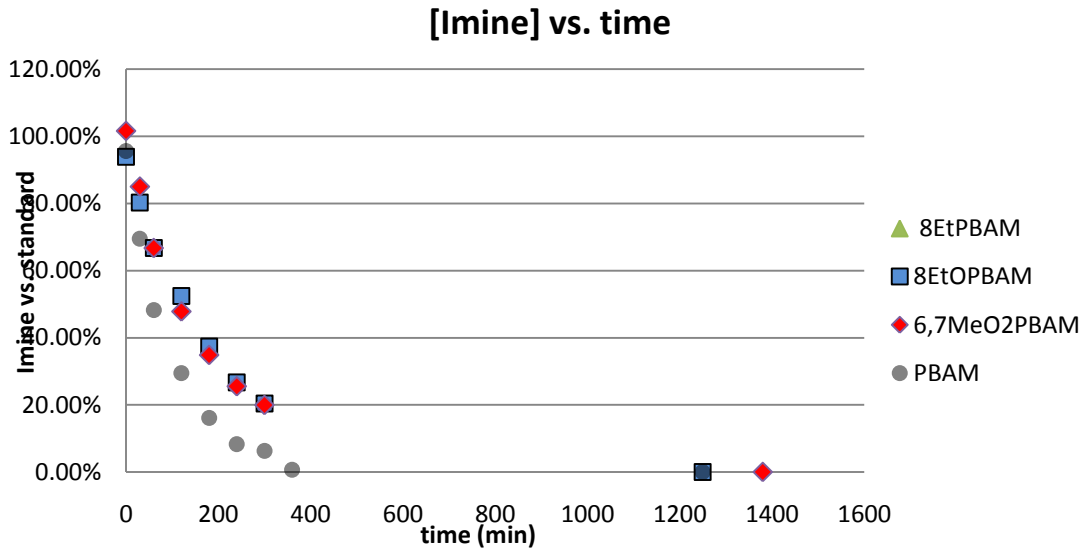
Figure 42. Catalyst Reactivity Study, Phenylnitromethane Addition Reaction



[a]All reactions were 0.1 M in toluene with 1,3,5-trimethoxybenzene and [o]tolunitrile used as internal standards unless otherwise noted. Material isolated by column chromatography. Diastereomer and enantiomer ratios of isolated material measured by HPLC using chiral stationary phases. [b]Only 1,3,5-trimethoxybenzene used as internal standard.

reaction to be conveniently monitored by comparison of the starting material imine to an internal standard. The addition products of the most electron-deficient imines ($^{o}CF_3$, **86l** and $^{p}CF_3$, **86q**) both produced only a small amount of retro product (2-5%) under GC conditions. The ^{o}CF3 product was chosen to ensure homogeneity in the reaction as this compound was relatively soluble in toluene. Furthermore, the *ortho*- substitution renders this imine relatively less reactive which should accentuate reactivity differences of the catalysts.

Figure 43. Plot of Imine Concentration vs. Time, Phenylnitromethane Addition Reaction



The results of this study are plotted in Figure 43. PBAM was found to be the most reactive catalyst under these conditions. The more electron-rich and presumably more Brønsted basic $^{6,7}(MeO)_2$PBAM was found to be less reactive than PBAM. This was somewhat unexpected as the increased reactivity of PBAM appeared to be due to its increased Brønsted basicity. ^{8}EtOPBAM was only marginally less reactive than $^{6,7}(MeO)_2$PBAM, which was also surprising due to the increased steric bulk near the binding site.

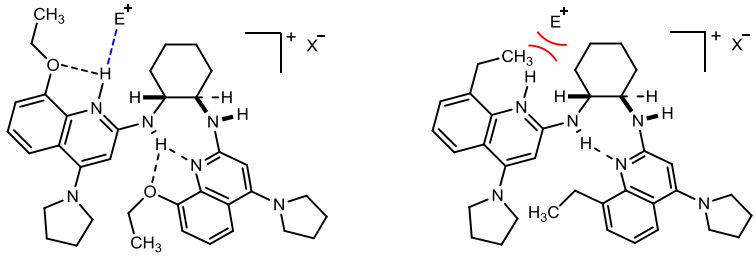
Remarkably, ^{8}EtPBAM was drastically less reactive than the other three catalysts. Five days of reaction were required to achieve 50% conversion compared to approximately 1 and 2 hours respectively for PBAM and the alkoxy-substituted PBAM catalysts.[165] This decreased reactivity for ^{8}EtPBAM could easily be explained by the presence of steric bulk in the vicinity of the binding site of the catalyst, but the similarly sterically encumbered ^{8}EtOPBAM does not exhibit this low reactivity. It is possible that the oxygen atom is sufficiently small compared to the methylene to not substantially hinder substrate binding. A comparison of the A-values[166] of an ethoxy group versus an ethyl group (0.89 versus 2.09 kcal/mol, respectively[167]) suggests that these groups may be effectively different in terms of sterics. The observed reactivity trend, particularly the lower reactivity of ^{6,7}(MeO)$_2$PBAM relative to PBAM, might also suggest a beneficial local electronic effect of the oxygen of ^{8}EtOPBAM.

Products from the reactions monitored by GC were isolated by column chromatography and analyzed by chiral HPLC. Similar diastereo- and enantioselectivities (16-22:1 dr and 58-66% ee) were observed (Figure 42) for PBAM, ^{6,7}(MeO)$_2$PBAM, and ^{8}EtOPBAM. Substantially lower enantioselection (20% ee) was observed with ^{8}EtPBAM. The absence of a background rate suggests that a less enantioselective pathway is being accessed. It is likely that the imine is binding in a different way to the catalyst because the typical PBAM transition state is too crowded due to the bulky imine. This less enantioselective pathway is not accessed with the more reactive catalysts.

[165] No detectable background (non-PBAM catalyzed) reaction occurred under these conditions. A reaction without catalyst yielded no product (GC) after 10 days.
[166] Hirsch, J. A. In *Topics in Stereochemistry*; John Wiley & Sons, Inc.: 2007, p 199-222.
[167] Noyce, D. S.; Dolby, L. J. *J. Org. Chem.* **1961**, *26*, 3619-3626.

In another reaction involving a less sterically hindered imine, PBAM and its 8-alkoxy and 8-alkyl derivatives provided similar stereoselectivities (Table 38, Table 40). These common stereochemical outcomes offer strong evidence that each catalyst is utilizing a similar transition state. Although the reaction rate is severely retarded with ^{8}EtPBAM, the steric nature of this catalyst does not seem to prevent a common transition state from being accessed with this less sterically hindered imine.

Figure 44. Binding Considerations of ^{8}EtOPBAM and ^{8}EtPBAM Catalysts



^{8}EtOPBAM ^{8}EtPBAM

The most likely affected mechanistic step is imine binding. The sterics imparted by the ethyl group at the 8-position crowd the binding site which likely discourages imine binding. However, once imine is bound to the chiral proton, the reaction could proceed through the same transition state as less sterically hindered catalysts. ^{8}EtOPBAM should have similar crowding near the imine binding site, but hydrogen bonding between the oxygen and the chiral proton could serve to orient the alkyl chain away from the binding site. This should lessen the entropic burden of that chain and render the chiral proton more available to bind to the imine.

Another possible advantage of the alkoxy group at the 8- position is the participation of that oxygen in an intramolecular hydrogen bond (Figure 44) with the cyclohexyl N-H. As shown in the displayed crystal structures (Figure 40 and Figure 41), a hydrogen bond exists between the quinoline and the opposing cyclohexyl N-H. The low

energy conformation implied by the crystal structures places the oxygen of ^{8}EtOPBAM close enough to the opposing N-H for hydrogen bonding. This additional hydrogen bonding may rigidify the catalyst structure and increase the concentration of catalyst in a reactive conformation.

The use of a PBAM derivative with a hydroxy group at the 8-position could provide evidence supporting this hypothesis. The presumed reactivity consequence of substitution at the 8-position of the catalyst should be greatly diminished. The ability for that oxygen to hydrogen bond with the opposing cyclohexyl N-H should be increased due to decreased steric strain. Compounds **167** and **168** (eq 98) have been synthesized but not completely isolated as a byproduct in the synthesis of corresponding PBAM catalysts. It is possible that these catalysts could exhibit even higher reactivity than PBAM. Further demethylation of **167** could produce ^{8}(OH)PBAM, which might also be a more reactive catalyst.

At this point, there is not enough data to generate a new stereochemical model for this reaction. Still, recently obtained information has increased our understanding of the mechanism of this reaction. The interesting trends observed may not be fully explained currently, but their discovery will likely lead to more fruitful experiments. The development of a monitorable reaction by GC could allow for a complete kinetic study which could reveal the molecularity of this reaction. Further elucidation of the mechanism should inspire future catalyst design and aid the discovery of new enantioselective reactions with BAM catalysts.

CHAPTER VII

EXPERIMENTAL

All reagents and solvents were commercial grade and purified prior to use when necessary. The following reagents were used as supplied by Sigma-Aldrich without further purification: nitroethane, 1-nitropropane, 2-nitropropane, and 1-nitrobutane. 2-methyl-1-nitropropane and (nitromethyl)cyclohexane were prepared using the Kornblum procedure.[168] Aldimines were prepared as reported in the literature.[169] Toluene was dried by passage through a column of activated alumina as described by Grubbs[170]. Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Sorbent Technologies. UV light, and/or the use of potassium iodoplatinate and potassium permanganate solutions were used to visualize products.

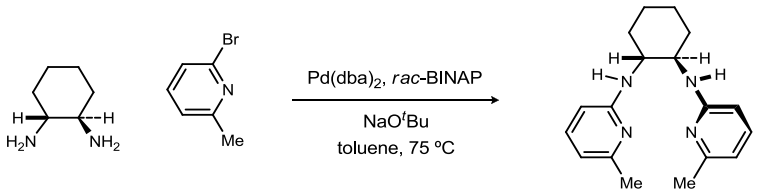
Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker DRX-500 (500 MHz), Bruker AV-400 (400 MHz) or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$). IR spectra were recorded on a Thermo Nicolet IR100 spectrophotometer and are reported in wavenumbers (cm^{-1}). Compounds were analyzed

[168] Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc*. **1956**, *78*, 1497-1501.
[169] Kanazawa, A. M.; Denis, J.; Greene, A. E. *J. Org. Chem*. **1994**, *59*, 1238-1240.
[170] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

as neat films on a NaCl plate (transmission). Mass spectra were recorded on a Waters LCT spectrometer by use of the ionization method noted.

Gas Chromatography (GC) was performed on a Varian CP-3800 gas chromatograph equipped with flame ionization detectors. The column used was a WCOT fused silica column with CP-Sil 5 CB stationary phase (15 m x 0.25 mm). The following settings were used: flow = 2.0 mL/min, oven = 1 min at 60 °C, to 220 °C at 10°C/min, 2 min at 220 °C; detector = 300 °C, injector = 200 °C.

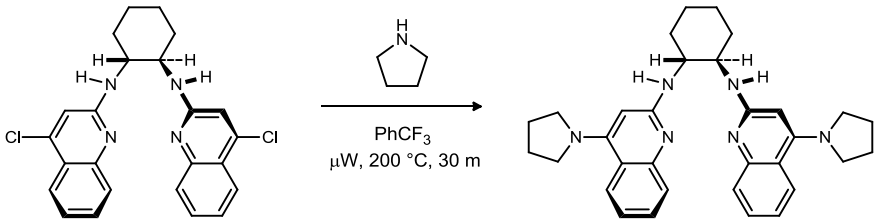
Absolute and relative configurations of **77**, **77b**-**77r**, **79**, and **117** were assigned by analogy to a chemically correlated product.[171] Absolute and relative configurations of **86**-**86f**, **86h**-**86v** and **101**-**101g** were assigned by analogy to the crystal structure obtained for **86g**.



H,^{6}Me-BAM (73c). $Pd(dba)_2$ (10.1 mg, 17.5 μmol), *rac*-BINAP (21.8 mg, 35.0 μmol), and sodium *tert*-butoxide (286.4 mg, 2.98 mmol) were loaded into a round bottom flask in a glove box. Toluene (10 mL, 0.10M) was added to the mixture, followed by (*R*,*R*)-diaminocyclohexane (100.0 mg, 876.0 μmol). 2-Bromo-6-methylpyridine (301.5 mg, 1.75 mmol) was added as a solution in toluene. The reaction was allowed to stir at 80 °C and monitored by TLC. The reaction was then cooled to room temperature, concentrated, and purified by flash column chromatography on silica gel (5% triethylamine, 10% ethyl

[171] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418-3419.

acetate in hexanes) affording a white solid (200 mg, 77%). $[\alpha]_D^{20}$ +110 (*c* 0.10, $CHCl_3$); mp 126-128 °C; R_f = 0.17 (5% Et_3N, 10% EtOAc/hexanes); IR (neat) 3256, 3051, 2927, 2855, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.0, 8.0 Hz, 2H), 6.35 (d, *J* = 7.2 Hz, 2H), 6.11 (d, *J* = 8.4 Hz, 2H), 5.16 (br s, 2H), 3.73-3.64 (m, 2H), 2.37 (s, 6H), 2.27-2.18 (m, 2H), 1.78-1.65 (m, 2H), 1.50-1.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.2, 156.5, 137.3, 111.3, 104.2, 55.0, 32.1, 24.4, 24.3; HRMS (EI) Exact mass calcd for $C_{18}H_{24}N_4$ $[M]^+$ 296.2001, found 296.1994.

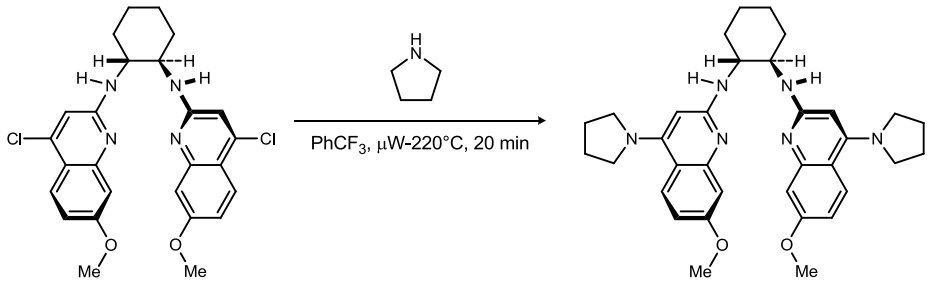


PBAM (76).[172] A 10-20 mL microwave vial was charged with the corresponding ^{4}ClQuinBAM (600 mg, 1.37 mmol), pyrrolidine (2.24 mL, 27.3 mmol), and trifluoromethylbenzene (9 mL). This suspension was heated at 200 °C and stirred in the microwave for 3.5 h. The reaction was then concentrated and purified by column chromatography (5-10-20% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3M NaOH. The combined organic layers were dried over sodium sulfate and concentrated. The material was then triturated with hexanes to afford a light brown powder (635 mg, 92%); mp 243.0-245.0; $[\alpha]_D^{20}$ +406 (*c* 1.2, $CHCl_3$); R_f = 0.38 (10% MeOH/CH_2Cl_2 with 0.5% acetic acid); IR (film) 3259, 3056, 2927, 2855, 2935, 1591, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.40 (dd, *J* = 7.2, 7.2 Hz,

[172] See Appendix for larger scale *Organic Syntheses* manuscript procedure.

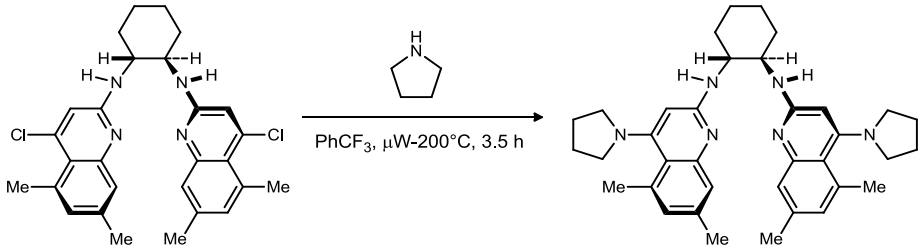
2H), 7.01 (dd, *J* = 7.2, 7.2 Hz, 2H), 5.70 (br s, 2H), 5.28 (s, 2H), 4.09 (br s, 2H), 3.35-3.22 (m, 4H), 3.16-3.05 (m, 4H), 2.37-2.23 (m, 2H), 1.90-1.75 (m, 10H), 1.58-1.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.4, 153.2, 149.9, 128.3, 126.4, 124.7, 119.1, 118.7, 93.0, 56.3, 51.5, 33.4, 25.5, 25.1; HRMS (ESI): Exact mass calcd for $C_{32}H_{39}N_6[M+H]^+$ 507.3236, found 507.3250. Anal. calcd for $C_{32}H_{38}N_6$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.80; H, 7.72; N, 16.45. PBAM purified by column chromatography has been stable upon storage in a screw cap vial on the benchtop for several years without sign of decomposition.

PBAM·HOTf (76·HOTf). To a flame-dried vial with stir bar was added H,^{4}PyrrolidineQuin-BAM (286.3 mg, 565.1 μmol) and dichloromethane (2 mL). Trifluoromethanesulfonic acid (50.0 μL, 565 μmol) was added dropwise to the stirring solution at room temperature. The reaction mixture was allowed to stir an additional 10 minutes before concentration to a light brown solid that was used without further purification. *Other catalyst acid salts were made in a similar fashion.*



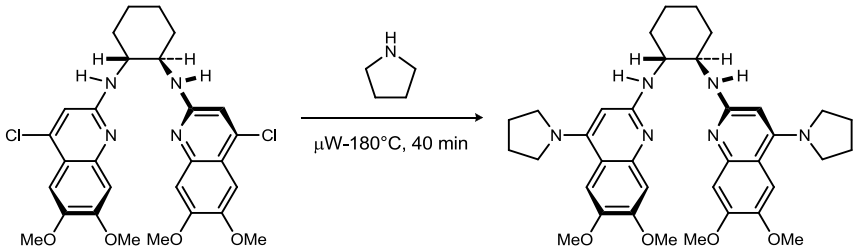
^{7}MeOPBAM (76b). A 2-5 mL microwave vial was charged with the corresponding ^{4}ClBAM (200 mg, 402 μmol), pyrrolidine (660 μL, 8.041 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 220 °C and stirred in the

microwave for 20 min. 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 then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (123.5 mg, 54%); $[\alpha]_D^{20}$ +480 (*c* 0.13, $CHCl_3$); R_f = 0.39 (10% MeOH/CH_2Cl_2); IR (film) 3253, 2930, 2855, 1616, 1589, 1526 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.0 Hz, 2H), 7.09 (s, 2H), 6.65 (dd, *J* = 9.5, 2.5 Hz, 2H), 5.77 (br s, 2H), 5.23 (s, 2H), 4.04 (br s, 2H), 3.88 (s, 6H), 3.35-3.25 (m, 4H), 3.20-3.10 (m, 4H), 2.33-2.25 (m, 2H), 1.90-1.78 (m, 10H), 1.55-1.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 159.9, 158.6, 153.2, 151.5, 125.9, 112.7, 110.4, 105.8, 90.7, 56.3, 55.2, 51.5, 33.3, 25.6, 25.0; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6O_2$ $[M+H]^+$ 567.3447, found 567.3467.



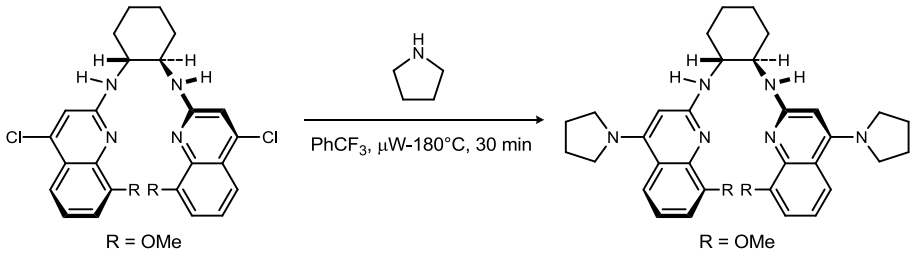
^{5,7}(Me)$_2$PBAM (76c). A 2-5 mL microwave vial was charged with the corresponding ^{4}ClBAM (150.0 mg, 304.0 μmol), pyrrolidine (500 μL, 6.08 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 200 °C and stirred in the microwave for 3.5 h. The reaction was then concentrated and purified by column chromatography (2-8% methanol in dichloromethane w/ 0.5% AcOH) to afford a light brown powder (158.7 mg, 93%). mp 126.0-128.0 °C; $[\alpha]_D^{20}$ +423 (*c* 1.04, $CHCl_3$); R_f =

0.31 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3249, 2930, 2856, 1598, 1539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 325 K) δ 7.33 (s, 2H), 6.73 (s, 2H), 5.82 (br s, 2H), 5.66 (s, 2H), 4.10-3.98 (m, 2H), 3.00-2.76 (br m, 4H), 2.76-2.55 (br m, 4H), 2.66 (s, 6H), 2.38 (s, 6H), 2.36-2.26 (m, 2H), 1.90-1.70 (m, 10H), 1.55-1.35 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 157.5, 155.8, 150.5, 137.7, 134.3, 126.2, 123.6, 117.7, 97.6, 56.3, 51.8, 33.2, 25.0, 23.4, 21.1, 20.7; HRMS (ESI): Exact mass calcd for $C_{36}H_{47}N_6$ $[M+H]^+$ 563.3862, found 563.3868.



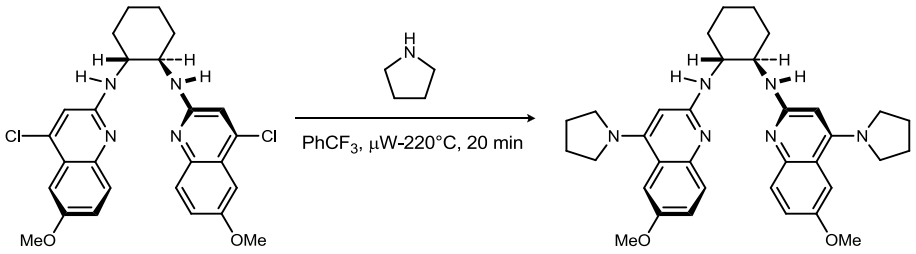
[6,7](MeO)$_2$PBAM (76e). A 2-5 mL microwave vial was charged with the corresponding [4]ClBAM (1.000 g, 1.794 mmol) and pyrrolidine (2.9 mL, 36 mmol). This suspension was heated at 180 °C and stirred in the microwave for 40 min. The reaction was then concentrated and purified by column chromatography (2-5-10% methanol in dichloromethane with 1% AcOH) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated. The material was then triturated with hexanes to afford a light brown viscous foam (351.1 mg, 31%); $[\alpha]_D^{20}$ +340 (*c* 0.11, $CHCl_3$); R_f = 0.22 (10% MeOH/1% AcOH/CH_2Cl_2); IR (film) 3391, 2931, 2855, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 2H), 7.10 (s, 2H), 5.51 (br s, 2H), 5.37 (s, 2H), 3.99 (br s, 2H), 3.99 (s, 6H), 3.89 (s, 6H), 3.37-3.26 (m, 4H), 3.23-3.13 (m, 4H),

2.35-2.25 (m, 2H), 1.91-1.79 (m, 10H), 1.52-1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.6, 152.8, 150.7, 146.0, 143.5, 111.7, 106.5, 105.2, 91.9, 56.3, 55.8, 55.5, 51.2, 33.3, 25.3, 25.0; HRMS (CI): Exact mass calcd for $C_{36}H_{47}N_6O_4$ $[M+H]^+$ 627.3653, found 627.3658.

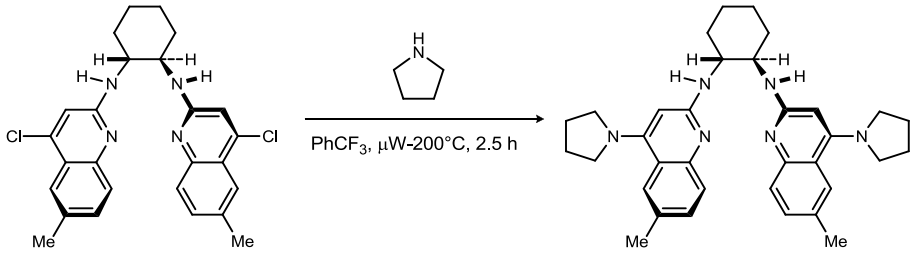


***8*MeOPBAM (76f).** A 0.5-2.0 mL microwave vial was charged with the corresponding *4*ClBAM (200.0 mg, 402.1 μmol), pyrrolidine (132 μL, 1.61 mmol), and trifluoromethylbenzene (1.2 mL). This suspension was heated at 180 °C and stirred in the microwave for 30 min. The reaction mixture was purified by column chromatography (2-5% methanol in dichloromethane with 0.5% AcOH) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting solid was dissolved in EtOAc and washed with water, dried over $MgSO_4$, filtered, and concentrated to a light brown solid (108.4 mg, 48%). $[\alpha]_D^{20}$ +320 (*c* 0.14, $CHCl_3$); R_f = 0.24 (10% MeOH/CH_2Cl_2); IR (film) 3244, 2933, 2857, 1637, 1593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 6.93 (dd, *J* = 7.6, 7.6 Hz, 2H), 6.88 (d, *J* = 7.2 Hz, 2H), 5.78 (br s, 2H), 5.52 (br s, 2H), 4.10-4.00 (m, 2H), 4.00 (s, 6H), 3.41-3.29 (m, 4H), 3.28-3.15 (m, 4H), 2.40-2.27 (m, 2H), 1.90-1.73 (m, 8H), 1.73-1.65 (m, 2H), 1.60-1.40 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, 325 K) ppm 157.5, 153.8, 153.7, 141.6,

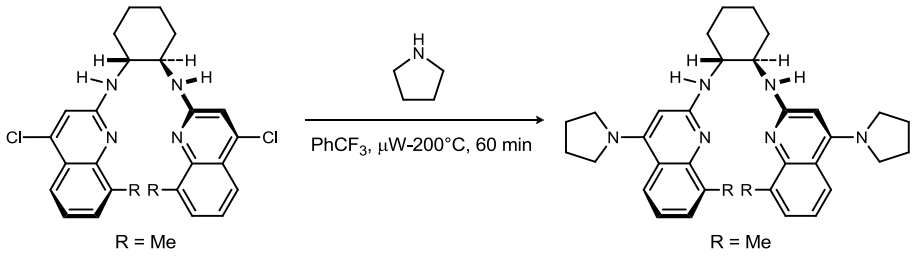
119.5, 118.5, 117.3, 109.0, 93.3, 56.5, 56.3, 51.7, 33.1, 25.4, 24.9; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6O_2$ $[M+H]^+$ 567.3448, found 567.3431.



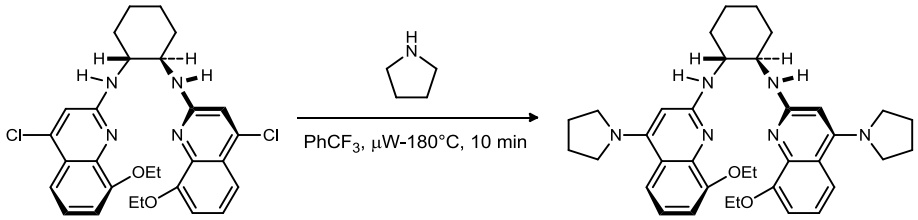
[6]MeOPBAM (76g). A 2-5 mL microwave vial was charged with the corresponding [4]ClBAM (200 mg, 402 μmol), pyrrolidine (660 μL, 8.041 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 220 °C and stirred in the microwave for 20 min. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (174.4 mg, 77%); $[\alpha]_D^{20}$ +350 (*c* 0.14, $CHCl_3$); R_f = 0.29 (10% MeOH/CH_2Cl_2); IR (film) 3261, 2930, 2856, 1595, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 9.2 Hz, 2H), 7.27 (d, *J* = 2.8 Hz, 2H), 7.11 (dd, *J* = 8.8, 2.8 Hz, 2H), 5.57 (br s, 2H), 5.35 (s, 2H), 4.03 (br s, 2H), 3.82 (s, 6H), 3.32-3.20 (m, 4H), 3.15-3.05 (m, 4H), 2.32-2.25 (m, 2H), 1.90-1.75 (m, 10H), 1.50-1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.3, 153.0, 152.8, 144.8, 127.5, 118.9, 118.4, 106.0, 94.0, 56.4, 55.6, 51.4, 33.4, 25.4, 25.1; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6O_2$ $[M+H]^+$ 567.3448, found 567.3442.



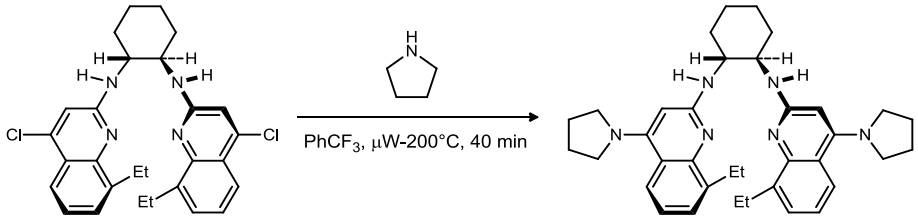
^{6}MePBAM (76h). A 0.5-2.0 mL microwave vial was charged with the corresponding ^{4}ClBAM (300.0 mg, 644.6 μmol), pyrrolidine (212 μL, 2.58 mmol), and trifluoromethylbenzene (1.3 mL). This suspension was heated at 200 °C and stirred in the microwave for 2.5 h. The reaction mixture was purified by column chromatography (2-5% methanol in dichloromethane with 0.5% AcOH) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting solid was dissolved in EtOAc and washed with water, dried over $MgSO_4$, filtered, and concentrated to a light brown solid (158.3 mg, 46%). $[\alpha]_D^{20}$ +370 (*c* 0.13, $CHCl_3$); R_f = 0.35 (10% MeOH/CH_2Cl_2); IR (film) 3253, 2927, 2857, 1591, 1531 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.24 (dd, *J* = 8.4, 1.6 Hz, 2H), 5.56 (br s, 2H), 5.28 (s, 2H), 4.11-4.01 (m, 2H), 3.31-3.21 (m, 4H), 3.12-3.02 (m, 4H), 2.39 (s, 6H), 2.33-2.23 (m, 2H), 1.90-1.75 (m, 10H), 1.55-1.35 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 158.0, 153.1, 148.0, 130.0, 128.3, 126.2, 124.1, 118.6, 93.5, 56.3, 51.5, 33.4, 25.4, 25.1, 21.5; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6$ $[M+H]^+$ 535.3549, found 535.3538.



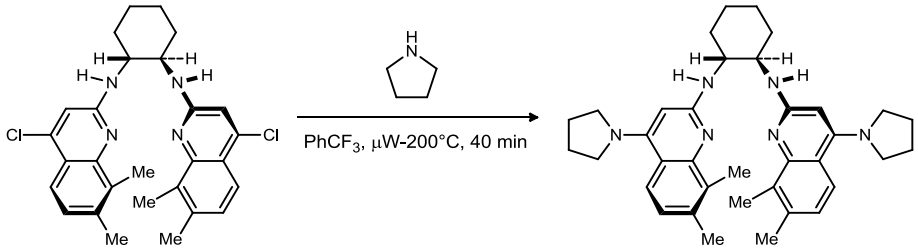
[8]MePBAM (76i). A 0.5-2.0 mL microwave vial was charged with the corresponding [4]ClBAM (400.0 mg, 859.4 μmol), pyrrolidine (420 μL, 5.2 mmol), and trifluoromethylbenzene (1.3 mL). This suspension was heated at 200 °C and stirred in the microwave for 60 min. The reaction mixture was purified by column chromatography (3-10% methanol in dichloromethane with 0.5% AcOH) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting solid was dissolved in EtOAc and washed with water, dried over $MgSO_4$, filtered, and concentrated to a light brown solid (249.8 mg, 54%). $[\alpha]_D^{20}$ +340 (*c* 0.10, $CHCl_3$); R_f = 0.42 (10% MeOH/CH_2Cl_2); IR (film) 3263, 2926, 2856, 1592, 1531 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 6.6 Hz, 2H), 6.94 (dd, *J* = 7.8, 7.2 Hz, 2H), 5.79 (br s, 2H), 5.42 (s, 2H), 4.15-4.05 (m, 2H), 3.38-3.28 (m, 4H), 3.25-3.15 (m, 4H), 2.70 (s, 6H), 2.46-2.36 (m, 2H), 1.92-1.70 (m, 10H), 1.55-1.45 (m, 2H), 1.45-1.35 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 157.4, 154.0, 148.5, 133.7, 128.7, 122.6, 118.6, 118.2, 92.8, 56.9, 51.7, 33.4, 25.5, 25.3, 18.9; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6$ $[M+H]^+$ 535.3549, found 535.3529.



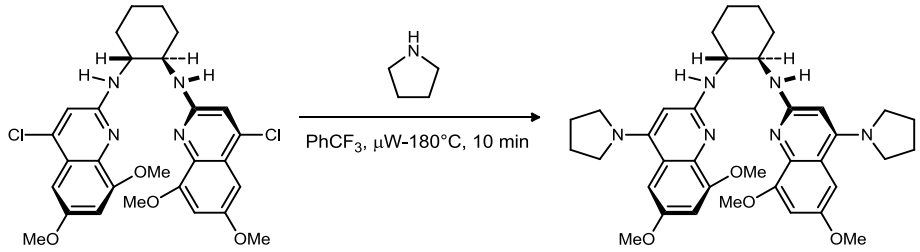
[8]EtOPBAM (76j). A 0.5-2.0 mL microwave vial was charged with the corresponding [4]ClBAM (350.0 mg, 666.1 μmol), pyrrolidine (330 μL, 3.996 mmol), and trifluoromethylbenzene (650 μL). This suspension was heated at 180 °C and stirred in the microwave for 10 min. The reaction was then concentrated and purified by column chromatography (0-4% methanol in dichloromethane w/ 0.5% AcOH). This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (306.6 mg, 77%). mp 120.0-122.0 °C; $[\alpha]_D^{20}$ +354 (*c* 1.02, $CHCl_3$); R_f = 0.17 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3237, 3062, 2973, 2929, 2867, 1593, 1540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 4.8,4.8 Hz, 2H), 6.93-6.87 (m, 4H), 6.17 (br s, 2H), 5.54 (s, 2H), 4.32-4.14 (m, 4H), 4.12-3.98 (m, 2H), 3.40-3.25 (m, 4H), 3.25-3.12 (m, 4H), 2.43-2.30 (m, 2H), 1.90-1.75 (m, 10 H), 1.54 (t, *J* = 7.2 Hz, 6H), 1.50-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.3, 153.5, 152.8, 141.6, 119.4, 118.4, 117.5, 110.8, 93.1, 64.9, 56.5, 51.6, 33.2, 25.4, 25.0, 15.0; HRMS (CI): Exact mass calcd for $C_{36}H_{47}N_6O_2$ $[M+H]^+$ 595.3755, found 595.3760.



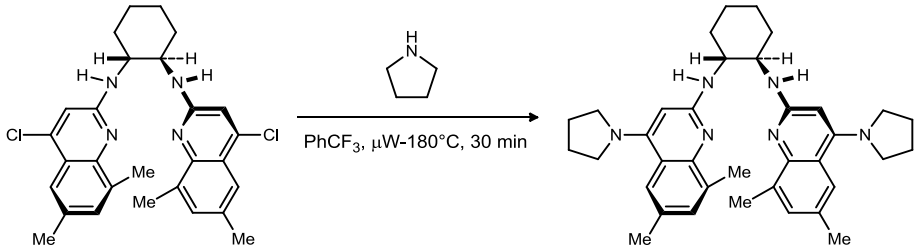
^{8}EtPBAM (76k). A 0.5-2.0 mL microwave vial was charged with the corresponding ^{4}ClBAM (200.0 mg, 405.3 μmol), pyrrolidine (333 μL, 4.05 mmol), and trifluoromethylbenzene (300 μL). This suspension was heated at 200 °C and stirred in the microwave for 40 min. The reaction was then concentrated and purified by column chromatography (0-5% methanol in dichloromethane w/ 0.5% AcOH). This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (165.6 mg, 73%). mp 83.0-85.0 °C; $[\alpha]_D^{20}$ +417 (*c* 1.00, $CHCl_3$); R_f = 0.21 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3265, 2928, 2866, 1592, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.33 (d, *J* = 6.8 Hz, 2H), 6.99 (dd, *J* = 8.4, 7.2 Hz, 2H), 5.64 (br s, 2H), 5.45 (s, 2H), 4.15-4.05 (m, 2H), 3.35-3.18 (m, 10H), 3.12 (dq, *J* = 14.4, 7.2 Hz, 2H), 2.47-2.37 (m, 2H), 1.92-1.80 (m, 10 H), 1.54-1.46 (m, 2H), 1.46-1.35 (m, 2H), 1.40 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.3, 154.1, 147.9, 139.6, 127.1, 122.6, 118.8, 118.4, 92.9, 56.8, 51.8, 33.6, 25.5, 25.4, 25.3, 14.8; HRMS (CI): Exact mass calcd for $C_{36}H_{47}N_6$ $[M+H]^+$ 563.3857, found 563.3865.



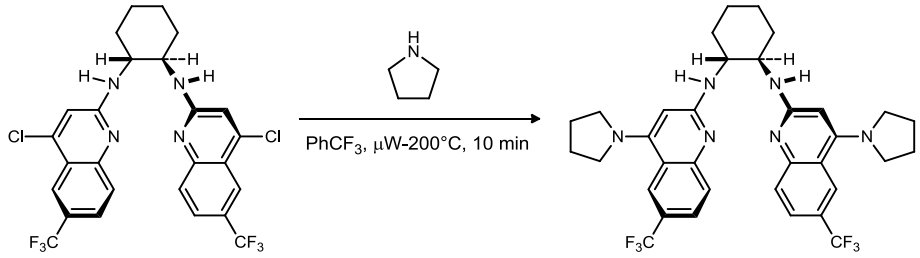
***7,8*(Me)$_2$PBAM (76l).** A 0.5-2.0 mL microwave vial was charged with the corresponding *4*ClBAM (200.0 mg, 405.3 μmol), pyrrolidine (333 μL, 4.05 mmol), and trifluoromethylbenzene (500 μL). This suspension was heated at 200 °C and stirred in the microwave for 40 min. The reaction was then concentrated and purified by column chromatography (0-5% methanol in dichloromethane w/ 0.5% AcOH). This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown solid (164.4 mg, 72%). Mp 115.5-117.5 °C; $[\alpha]_D^{20}$ +403 (*c* 1.18, $CHCl_3$); R_f = 0.21 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3257, 2927, 2858, 1595, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.80 (br s, 2H), 5.38 (s, 2H), 4.15-4.04 (m, 2H), 3.36-3.26 (m, 4H), 3.24-3.14 (m, 4H), 2.68 (s, 6H), 2.50-2.40 (m, 2H), 2.42 (s, 6H), 1.92-1.78 (m, 10H), 1.55-1.46 (m, 2H), 1.46-1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.4, 154.0, 148.3, 135.9, 131.1, 121.6, 121.5, 116.6, 92.1, 56.9, 51.7, 33.5, 25.5, 25.3, 20.5, 13.8; HRMS (ESI): Exact mass calcd for $C_{36}H_{47}N_6$ $[M+H]^+$ 563.3862, found 563.3839.



^{6,8}(MeO)$_2$PBAM (76m). A 0.5-2.0 mL microwave vial was charged with the corresponding ^{4}ClBAM (125.0 mg, 224.2 μmol), pyrrolidine (200 μL, 2.44 mmol), and trifluoromethylbenzene (600 μL). This suspension was heated at 180 °C and stirred in the microwave for 10 min. The reaction was then concentrated and purified by column chromatography (0-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a brown/red powder (100.9 mg, 72%). mp 112.0-114.0 °C; $[\alpha]_D^{20}$ +274 (*c* 1.03, $CHCl_3$); R_f = 0.14 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3257, 2930, 2858, 1607, 1538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 2.4 Hz, 2H), 6.58 (d, *J* = 2.4 Hz, 2H), 5.71 (br s, 2H), 5.60 (s, 2H), 4.05-3.92 (m, 2H), 3.97 (s, 2H), 3.82 (s, 6H), 3.34-3.23 (m, 2H), 3.23-3.12 (m, 4H), 2.35-2.24 (m, 2H), 1.93-1.82 (m, 8H), 1.82-1.74 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 156.5, 154.4, 153.6, 152.6, 136.7, 119.0, 100.2, 96.8, 94.4, 56.3, 56.2, 55.3, 51.6, 33.1, 25.4, 24.9; HRMS (CI): Exact mass calcd for $C_{36}H_{46}N_6O_4$ $[M]^+$ 626.3575, found 626.3550.



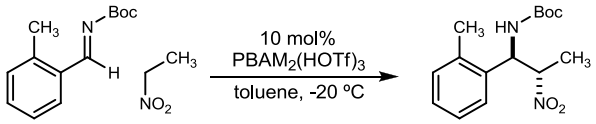
***6,8*(Me)$_2$PBAM (76n).** A 0.5-2.0 mL microwave vial was charged with the corresponding *4*ClBAM (200.0 mg, 405.3 μmol), pyrrolidine (300 μL, 3.63 mmol), and trifluoromethylbenzene (600 μL). This suspension was heated at 180 °C and stirred in the microwave for 30 min. The reaction was then concentrated and purified by column chromatography (0-5% methanol in dichloromethane). This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (119.3 mg, 52%). mp 122.5-124.5 °C; $[\alpha]_D^{20}$ +304 (*c* 1.06, $CHCl_3$); R_f = 0.20 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3263, 2925, 2859, 1591, 1527 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53 (s, 2H), 7.18 (s, 2H), 5.76 (br s, 2H), 5.43 (s, 2H), 4.14-4.02 (m, 2H), 3.36-3.26 (m, 4H), 3.25-3.14 (m, 4H), 2.67 (s, 6H), 2.45-2.35 (m, 2H), 2.38 (s, 6H), 1.92-1.80 (m, 10 H), 1.55-1.35 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 156.9, 153.8, 146.5, 133.4, 130.6, 127.6, 121.9, 118.1, 93.2, 56.9, 51.7, 33.3, 25.4, 25.2, 21.5, 18.7; HRMS (CI): Exact mass calcd for $C_{36}H_{47}N_6$ $[M+H]^+$ 563.3857, found 563.3845.



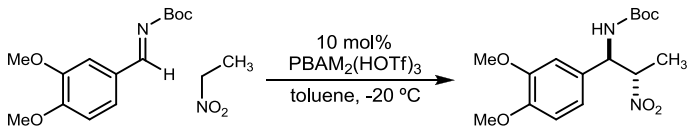
$^{6}CF_3PBAM$ (76o). A 0.2-0.5 mL microwave vial was charged with the corresponding ^{4}ClBAM (150.0 mg, 261.6 μmol), pyrrolidine (122 μL, 1.49 mmol), and trifluoromethylbenzene (122 μL). This suspension was heated at 200 °C and stirred in the microwave for 10 min. The reaction was then concentrated and purified by column chromatography (0-5% methanol in dichloromethane w/ 0.5% AcOH). This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a yellow/brown solid (145.6 mg, 87%). mp 229.0-231.0 °C; $[\alpha]_D^{20}$ +278 (*c* 1.01, $CHCl_3$); R_f = 0.44 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3222, 2933, 2856, 1586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 5.57 (br s, 2H), 5.19 (s, 2H), 4.20-4.05 (m, 2H), 3.40-3.20 (m, 4H), 3.15-3.00 (m, 4H), 2.32-2.20 (m, 2H), 1.95-1.80 (m, 10H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.5, 153.0, 151.8, 126.8, 124.9 (q, $^{1}J_{CF}$ = 270 Hz), 124.4, 122.7, 120.5 (q, $^{2}J_{CF}$ = 32.0 Hz), 117.5, 92.8, 56.3, 51.6, 33.2, 25.6, 25.1; ^{19}F NMR (282 MHz, $CDCl_3$) ppm -59.3; HRMS (CI): Exact mass calcd for $C_{34}H_{37}F_6N_6$ $[M+H]^+$ 643.2978, found 643.2976.

General Procedure for the Synthesis of Adducts 77-77r, 79. To a flame-dried vial with stir bar was added imine (100 μmol), $PBAM_2(HOTf)_3$ (7.3 mg, 10 μmol), toluene (100 μL). The reaction mixture was then cooled to -20 °C before nitroalkane (150 μmol) was

added, and then stirred at -20 °C for 24 h. The solution was then filtered while cold through a pad of silica gel using CH_2Cl_2 and EtOAc.

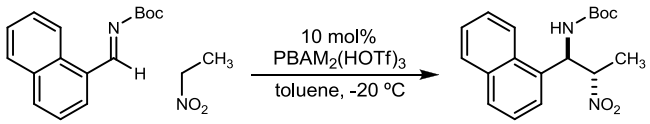


***tert*-Butyl (1*R*,2*S*)-2-nitro-1-*ortho*-tolylpropylcarbamate (77b).** The imine (21.9 mg, 100 µmol) was treated with nitroethane according to the general procedure. The reaction was stirred for 24 h and concentrated to a colorless solid determined to be 11:1 dr by GC (major diastereomer: t_r = 12.60 min, minor diastereomer: t_r = 12.24 min). Flash column chromatography (SiO_2, 8-25% ethyl acetate in hexanes) yielded the addition product as a colorless solid (19.4 mg, 66%); the major diastereomer was determined to be 90% ee by chiral HPLC analysis (Chiralcel IA, 3% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 15.2 min, t_r(*anti*, minor) = 12.5 min, t_r(*syn*, major) = 14.4 min, t_r(*syn*, minor) = 19.2 min); mp 80.0-82.0 °C; R_f = 0.41 (20% EtOAc/hexanes); IR (film) 3339, 2978, 2918, 1702, 1553 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (m, 4H), 5.57 (br s, 1H), 4.98 (br s, 1H), 4.89 (br s, 1H), 2.45 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.9, 136.3, 135.7, 131.2, 128.4, 126.6, 124.9, 85.1, 80.5, 53.0, 28.2, 19.4, 15.5; HRMS (ESI): Exact mass calcd for $C_{15}H_{22}N_2NaO_4$ $[M+Na]^+$ 317.1477, found 317.1481.



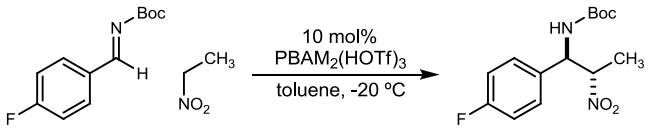
***tert*-Butyl (1*R*,2*S*)-1-(3,4-dimethoxyphenyl)-2-nitropropylcarbamate (77d).** The imine (26.5 mg, 100 µmol) was treated with nitroethane according to the general procedure.

The reaction was stirred for 23 h and concentrated to a colorless solid determined to be 20:1 dr by GC (major diastereomer: t_r = 15.49 min, minor diastereomer: t_r = 15.22 min). Flash column chromatography (SiO_2, 20-30% ethyl acetate in hexanes) yielded the addition product as a colorless solid (27.7 mg, 80%); the major diastereomer was determined to be 90% ee by chiral HPLC analysis (Chiralcel IA, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 14.0 min, t_r(*anti*, minor) = 17.2 min, t_r(*syn*, major) = 15.0 min, t_r(*syn*, minor) = 26.1 min); mp 142.0-143.0 °C; $[\alpha]_D^{20}$ -25.0 (*c* 1.6, $CHCl_3$); R_f = 0.24 (30% EtOAc/hexanes); IR (film) 3361, 2977, 2936, 1694, 1551, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81-6.72 (m, 3H), 5.35 (br s, 1H), 5.09 (m, 1H), 4.89 (br s, 1H), 3.82 (s, 6H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.9, 149.1 (2C), 128.9, 118.4, 111.2, 110.1, 85.8, 80.3, 57.2, 55.83, 55.75, 28.1, 15.4; HRMS (ESI): Exact mass calcd for $C_{16}H_{24}N_2NaO_6$ $[M+Na]^+$ 363.1532, found 363.1514.



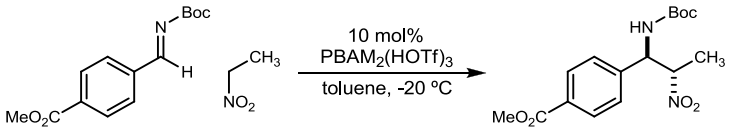
***tert*-Butyl (1*R*,2*S*)-1-(naphthalen-1-yl)-2-nitropropylcarbamate (77e).** The imine (25.5 mg, 100 μmol) was treated with nitroethane according to the general procedure. The reaction was stirred for 23 h and concentrated to a colorless oil determined to be 8:1 dr by GC (major diastereomer: t_r = 15.85 min, minor diastereomer: t_r = 16.18 min). Flash column chromatography (SiO_2, 8-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (31.9 mg, 97%); the major diastereomer was determined to be 87% ee by chiral HPLC analysis (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 15.0 min, t_r(*anti*, minor) = 13.4 min, t_r(*syn*, major) = 17.1 min, t_r(*syn*, minor) = 19.0 min); R_f = 0.73 (40% EtOAc/hexanes); IR (film) 3347, 3052, 2979, 2933, 1701 cm^-

[1]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.64 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.55 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.48-7.40 (m, 2H), 6.31 (dd, *J* = 8.8, 6.0 Hz, 1H), 5.24 (br s, 1H), 5.15 (br s, 1H), 1.57 (d, *J* = 6.0 Hz, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 134.0, 133.2, 130.5, 129.3, 129.1, 127.2, 126.2, 125.1, 123.0, 122.5, 84.4, 80.6, 52.8, 28.2, 14.5; HRMS (ESI): Exact mass calcd for $C_{18}H_{22}N_2O_4$ $[M]^+$ 330.1580, found 330.1571.

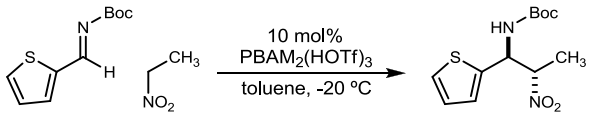


***tert*-Butyl (1*R*,2*S*)-1-(4-fluorophenyl)-2-nitropropylcarbamate (77h).** The imine (22.3 mg, 100 μmol) was treated with nitroethane according to the general procedure. The reaction was stirred for 23 h and concentrated to a colorless solid determined to be 26:1 dr by GC (major diastereomer: t_r = 11.88 min, minor diastereomer: t_r = 11.58 min). Flash column chromatography (SiO_2, 8-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (19.6 mg, 66%); the major diastereomer was determined to be 93% ee by chiral HPLC analysis (Chiralcel IA, 5% ^{i}PrOH:hexanes, 1 mL/min, 230 nm, t_r(*anti*, major) = 12.6 min, t_r(*anti*, minor) = 12.1 min, t_r(*syn*, major) = 15.6 min, t_r(*syn*, minor) = 16.1 min); mp 129.5-130.5 °C; $[\alpha]_D^{20}$ -18.5 (*c* 1.3, $CHCl_3$); R_f = 0.31 (20% EtOAc/hexanes); IR (film) 3334, 2980, 2929, 1700, 1553, 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 7.04 (dd, *J* = 8.8, 8.4 Hz, 2H), 5.40 (br s, 1H), 5.15 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.90 (br s, 1H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.6 (d, $^1J_{CF}$ = 246.0 Hz), 154.8, 132.3, 128.6 (d, $^3J_{CF}$ = 8.0

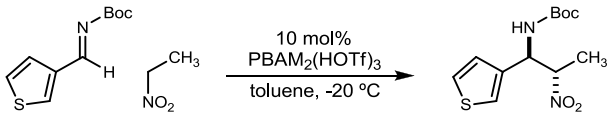
Hz), 115.9 (d, $^2J_{CF}$ = 21.0 Hz), 85.7, 80.7, 56.8, 28.2, 15.3; HRMS (ESI): Exact mass calcd for $C_{14}H_{18}FN_2O_4$ $[M-H]^-$ 297.1251, found 297.1250.



Methyl 4-((1*R*,2*S*)-1-(*tert*-butoxycarbonylamino)-2-nitropropyl)benzoate (77i). The imine (26.3 mg, 100 μmol) was treated with nitroethane according to the general procedure. The reaction was stirred for 23 h and concentrated to a colorless solid determined to be 12:1 dr by GC (major diastereomer: t_r = 15.69 min, minor diastereomer: t_r = 15.45 min). Flash column chromatography (SiO_2, 8-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (21.2 mg, 63%); the major diastereomer was determined to be 91% ee by chiral HPLC analysis (Chiralcel IA, 5% ^{i}PrOH:hexanes, 1 mL/min, 230 nm, t_r(*anti*, major) = 25.5 min, t_r(*anti*, minor) = 30.0 min, t_r(*syn*, major) = 32.9 min, t_r(*syn*, minor) = 38.2 min); mp 121.0-123.0 °C; R_f = 0.57 (40% EtOAc/hexanes); IR (film) 3362, 2980, 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 5.48 (br s, 1H), 5.25 (dd, *J* = 8.8, 5.6 Hz, 1H), 4.92 (br s, 1H), 3.90 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.4, 154.8, 141.4, 130.4, 130.2, 126.9, 85.4, 80.8, 57.1, 52.2, 28.2, 15.1; HRMS (ESI): Exact mass calcd for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ 339.1556, found 339.1544.

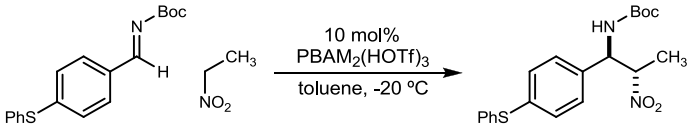


***tert*-Butyl (1*S*,2*S*)-2-nitro-1-(thiophen-2-yl)propylcarbamate (77k).** The imine (21.1 mg, 100 μmol) was treated with nitroethane according to the general procedure. The reaction was stirred for 24 h and concentrated to a colorless solid determined to be 20:1 dr by GC (major diastereomer: t_r = 12.06 min, minor diastereomer: t_r = 11.66 min). Flash column chromatography (SiO_2, 8-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (28.6 mg, 100%); the major diastereomer was determined to be 95% ee by chiral HPLC analysis (Chiralcel IA, 5% EtOH/hexanes, 1 mL/min, 210 nm, t_r(*anti*, major) = 12.7 min, t_r(*anti*, minor) = 12.2 min, t_r(*syn*, major) = 14.2 min, t_r(*syn*, minor) = 21.1 min); mp 124.0-127.0 °C; $[\alpha]_D^{20}$ -38.4 (*c* 1.2, $CHCl_3$); R_f = 0.32 (20% EtOAc/hexanes); IR (film) 3374, 2977, 1689, 1547, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 6.96 (m, 2H), 5.48 (dd, *J* = 9.2, 5.6 Hz, 1H), 5.31 (d, *J* = 9.2 Hz, 1H), 4.93 (m, 1H) , 1.58 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.7, 139.1, 127.1, 126.0, 125.6, 85.8, 80.8, 53.3, 28.2, 15.5; HRMS (ESI): Exact mass calcd for $C_{12}H_{18}N_2NaO_4S$ $[M+Na]^+$ 309.0885, found 309.0903.



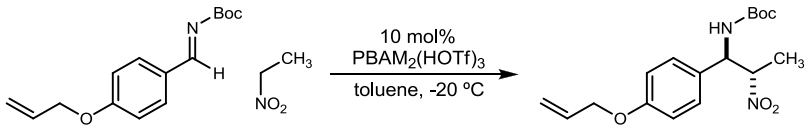
***tert*-Butyl (1*R*,2*S*)-2-nitro-1-(thiophen-3-yl)propylcarbamate (77l).** The imine (21.1 mg, 100 μmol) was treated with nitroethane according to the general procedure. The

reaction was stirred for 24 h and concentrated to a colorless solid determined to be 35:1 dr by GC (major diastereomer: t_r = 12.09 min, minor diastereomer: t_r = 11.83 min). Flash column chromatography (SiO_2, 8-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (26.3 mg, 92%); the major diastereomer was determined to be 91% ee by chiral HPLC analysis (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1 mL/min, 210 nm, t_r(*anti*, major) = 12.7 min, t_r(*anti*, minor) = 12.2 min, t_r(*syn*, major) = 14.2 min, t_r(*syn*, minor) = 21.1 min); mp 145.5-147.0 °C; $[\alpha]_D^{20}$ -38.4 (*c* 1.9, $CHCl_3$); R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3376, 3094, 3009, 2978, 2935, 1682, 1545,1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 4.8, 2.8 Hz, 1H), 7.19 (br s, 1H), 6.98 (d, *J* = 4.4 Hz, 1H), 5.31 (br s, 2H), 4.91 (br s, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.9, 136.9, 126.9, 125.8, 123.0, 85.4, 80.5, 53.5, 28.2, 15.3; HRMS (ESI): Exact mass calcd for $C_{12}H_{18}N_2NaO_4S$ $[M+Na]^+$ 309.0885, found 309.0893.



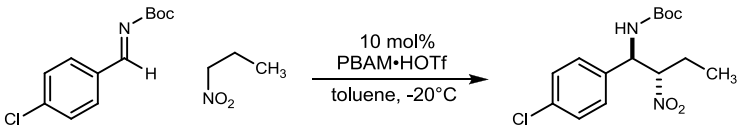
***tert*-Butyl (1*R*,2*S*)-2-nitro-1-(4-(phenylthio)phenyl)propylcarbamate (77m).** The imine (31.3 mg, 100 μmol) was treated with nitroethane according to the general procedure. The reaction was stirred for 24 h and concentrated to a colorless solid (20:1 dr, ^{1}H NMR). Flash column chromatography (SiO_2, 8-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (30.9 mg, 80%); the major diastereomer was determined to be 89% ee by chiral HPLC analysis (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1 mL/min, 230 nm, t_r(*anti*, major) = 17.8 min, t_r(*anti*, minor) = 19.3 min, t_r(*syn*, major) = 22.5 min, t_r(*syn*, minor) = 26.2 min); mp 163.0-165.0 °C; $[\alpha]_D^{20}$ -35.0 (*c* 1.8, $CHCl_3$); R_f =

0.23 (20% EtOAc/hexanes); IR (film) 3376, 2980, 2928, 1680, 1545, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.31 (br s, 1H), 5.15 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.89 (br s, 1H), 1.52 (d, *J* = 6.4 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.8, 137.5, 134.6, 134.1, 132.2, 130.1, 129.4, 127.8, 127.6, 85.6, 80.6, 57.0, 28.2, 15.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4S$ $[M+Na]^+$ 411.1354, found 411.1338.

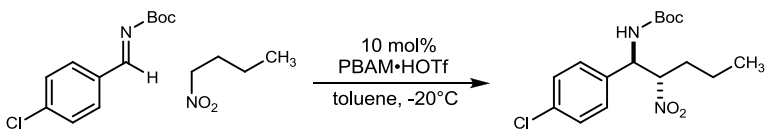


***tert*-Butyl (1*R*,2*S*)-1-(4-(allyloxy)phenyl)-2-nitropropylcarbamate (77n).** The imine (26.1 mg, 100 μmol) was treated with nitroethane according to the general procedure. The reaction was stirred for 24 h and concentrated to a colorless solid determined to be 28:1 dr by GC (major diastereomer: t_r = 15.49 min, minor diastereomer: t_r = 15.27 min). Flash column chromatography (SiO_2, 8-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (30.6 mg, 91%); the major diastereomer was determined to be 89% ee by chiral HPLC analysis (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1 mL/min, 230 nm, t_r(*anti*, major) = 15.8 min, t_r(*anti*, minor) = 17.0 min, t_r(*syn*, major) = 21.4 min, t_r(*syn*, minor) = 17.8 min); mp 109.0-111.0 °C; $[\alpha]_D^{20}$ -30.9 (*c* 1.1, $CHCl_3$); R_f = 0.30 (20% EtOAc/hexanes); IR (film) 3376, 2981, 2926, 1681, 1548, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.03 (dddd, *J* = 17.2, 10.6, 5.3, 5.3 Hz, 1H), 5.39 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.29 (br s, 1H), 5.28 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.10 (dd, *J* = 8.4, 6 Hz, 1H), 4.89 (br s, 1H), 4.51 (d, *J* = 5.2 Hz, 2H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 158.6,

154.9, 132.9, 128.5, 128.0, 117.8, 115.0, 85.9, 80.3, 68.7, 56.9, 28.2, 15.4; HRMS (ESI): Exact mass calcd for $C_{17}H_{24}N_2NaO_5$ $[M+Na]^+$ 359.1583, found 359.1579.

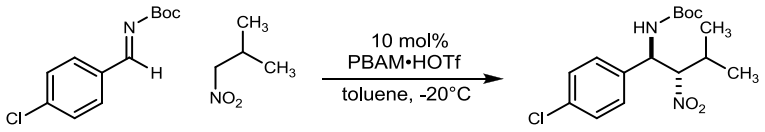


***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitrobutylcarbamate (77o).** The imine (24.0 mg, 100 µmol) was treated with 1-nitropropane according to the general procedure but using PBAM·HOTf as the catalyst. The reaction was stirred for 21 h and concentrated to a colorless solid. Flash column chromatography (SiO_2, 20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (28.3 mg, 86%) that was determined to be 20:1 dr, 91% ee (major diastereomer) by chiral HPLC analysis (Chiralcel AD, 5% EtOH/hexanes, 1 mL/min, t_r(*anti*, major) = 9.4 min, t_r(*anti*, minor) = 13.2 min, t_r(*syn*, major) = 12.1 min, t_r(*syn*, minor) = 17.0 min); mp 155.5-157.5 °C; $[\alpha]_D^{20}$ -35.6 (*c* 1.4, $CHCl_3$); R_f = 0.33 (20% EtOAc/hexanes); IR (film) 3375, 2981, 1677, 1547, 1519, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.17 (br s, 1H), 5.11 (br s, 1H), 4.71 (br s, 1H), 2.03 (m, 1H), 1.87 (m, 1H), 1.42 (s, 9H), 0.98 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.8, 135.2, 134.6, 129.1, 128.2, 92.7, 80.8, 56.2, 28.2, 23.5, 10.4; HRMS (ESI): Exact mass calcd for $C_{15}H_{20}ClN_2O_4$ $[M-H]^-$ 327.1112, found 327.1118.



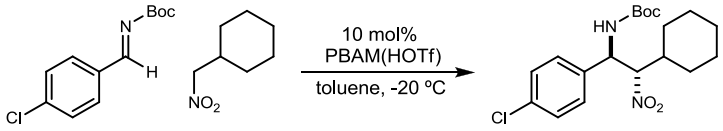
***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitropentylcarbamate (77p).** The imine (24.0 mg, 100 µmol) was treated with 1-nitrobutane according to the general procedure but

using PBAM ·HOTf as the catalyst. The reaction was stirred for 21 h and concentrated to a colorless solid. Flash column chromatography (SiO_2, 20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (28.3 mg, 86%) that was determined to be 23:1 dr, 91% ee (major diastereomer) by chiral HPLC analysis (Chiralcel AD, 5% EtOH/hexanes, 1 mL/min, t_r(*anti*, major) = 9.4 min, t_r(*anti*, minor) = 13.2 min, t_r(*syn*, major) = 12.1 min, t_r(*syn*, minor) = 17.0 min); mp 154.0-155.5 °C; $[\alpha]_D^{20}$ -31.8 (*c* 1.1, $CHCl_3$); R_f = 0.42 (20% EtOAc/hexanes); IR (film) 3378, 2961, 2929, 1680, 1548, 1520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.17 (br s, 1H), 5.11 (br s, 1H), 4.71 (br s, 1H), 2.03 (m, 1H), 1.87 (m, 1H), 1.42 (s, 9H). 1.40-1.25 (m, 2H), 0.98 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.8, 135.2, 134.6, 129.1, 128.2, 92.7, 80.8, 56.2, 28.2, 23.5, 10.4; HRMS (ESI): Exact mass calcd for $C_{16}H_{22}ClN_2O_4$ $[M-H]^-$ 341.1268, found 341.1269.

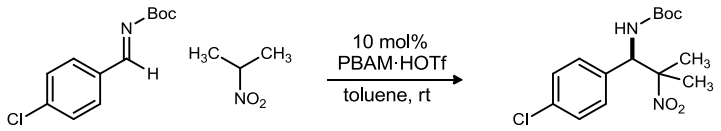


***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-3-methyl-2-nitrobutylcarbamate (77q).** The imine (24.0 mg, 100 μmol) was treated with 2-methyl-1-nitropropane according to the general procedure but using PBAM ·HOTf as the catalyst. The reaction was stirred for 19 h and concentrated to a colorless solid (7:1 dr, ^1H NMR). Flash column chromatography (SiO_2, 4-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (20.8 mg, 61%); the major diastereomer was determined to be 88% ee by chiral HPLC analysis (Chiralcel AD, 2% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 26.9 min, t_r(*anti*, minor) = 30.4 min, t_r(*syn*, major) = 20.6 min, t_r(*syn*, minor) = 18.1 min); mp 149.0-151.0 °C; R_f = 0.23 (10% EtOAc/hexanes); IR (film) 3351, 2975, 1699, 1550, 1494 cm^{-1}; ^1H

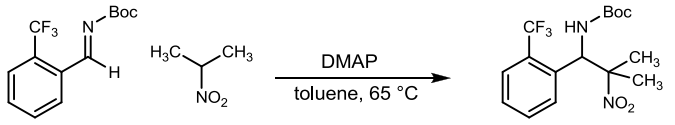
NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.23 (br s, 1H), 4.97 (br s, 1H), 4.72 (br s, 1H), 2.29 (br s, 1H), 1.42 (s, 9H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.6, 135.8, 134.6, 129.1, 128.4, 96.1, 80.8, 53.8, 29.7, 28.7, 28.3, 19.8; HRMS (ESI): Exact mass calcd for $C_{16}H_{22}ClN_2O_4$ $[M-H]^-$ 341.1268, found 341.1274.



***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitropentylcarbamate (77r).** The imine (24.0 mg, 100 μmol) was treated with (nitromethyl)cyclohexane according to the general procedure but using PBAM·HOTf as the catalyst. The reaction was stirred for 43 h and concentrated to a colorless solid (13:1 dr, ^1H NMR). Flash column chromatography (SiO_2, 4-20% ethyl acetate in hexanes) yielded the addition product as a colorless solid (27.7 mg, 72%); the major diastereomer was determined to be 89% ee by chiral HPLC analysis (Chiralcel AD, 5% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 25.8 min, t_r(*anti*, minor) = 15.7 min, t_r(*syn*, major) = 11.5 min, t_r(*syn*, minor) = 20.4 min); mp 165.0-167.0 °C; $[\alpha]_D^{20}$ -58.3 (*c* 1.2, $CHCl_3$); R_f = 0.43 (20% EtOAc/hexanes); IR (film) 2932, 2855, 1683, 1549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.28 (br s, 1H), 4.98 (br s, 1H), 4.71 (br s, 1H), 2.00-1.60 (m, 6H), 1.42 (s, 9H), 1.35-1.00 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.6, 135.7, 134.5, 129.1, 128.4, 95.8, 80.7, 53.0, 38.0, 30.3, 28.2, 26.2, 25.8; HRMS (ESI): Exact mass calcd for $C_{19}H_{27}ClNaN_2O_4$ $[M+Na]^+$ 405.1557, found 405.1540.

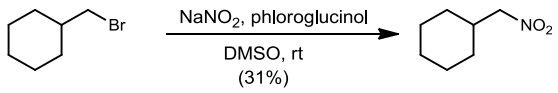


(*R*)-*tert*-Butyl 1-(4-chlorophenyl)-2-methyl-2-nitropropylcarbamate (79). The imine (24.0 mg, 100 μmol) was treated with 2-nitropropane according to the general procedure with the exception that the reaction was carried out at room temperature with PBAM·HOTf as the catalyst. The reaction was stirred for 20 h and concentrated to a colorless solid. Flash column chromatography (SiO_2, 8-25% ethyl acetate in hexanes) yielded the addition product as a colorless solid (22.1 mg, 67%); the major product was determined to be 71% ee by chiral HPLC analysis (Chiralcel AD, 5% ^{i}PrOH/hexanes, 1 mL/min, t_r(major) = 12.2 min, t_r(minor) = 11.2 min; mp 162.0-164.0 °C; $[\alpha]_D^{20}$ -34.0 (*c* 1.0, $CHCl_3$); R_f = 0.31 (20% EtOAc/hexanes); IR (film) 3338, 2980, 2929, 1699, 1543, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 5.84 (d, *J* = 10.0 Hz, 1H), 5.00 (d, *J* = 9.6 Hz, 1H), 1.69 (s, 3H), 1.52 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 135.2, 134.4, 129.1, 128.8, 90.3, 80.5, 60.4, 28.2, 25.1, 23.2; HRMS (ESI): Exact mass calcd for $C_{15}H_{20}ClN_2O_4$ $[M-H]^-$ 327.1112, found 327.1118.

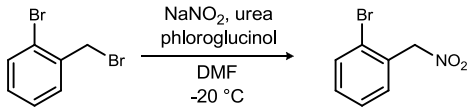


***tert*-butyl 2-methyl-2-nitro-1-(2-(trifluoromethyl)phenyl)propylcarbamate (79b).** The imine (273.3 mg, 1.000 mmol) was dissolved in toluene (1.0 mL). Then DMAP (122.0 mg, 1.000 mmol) and 2-nitropropane (449 μL, 5.00 mmol) were added to the reaction

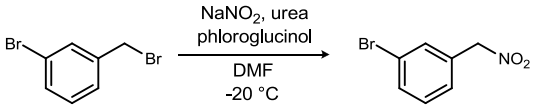
mixture. The reaction was heated to 65 °C and stirred for 3 hours. The reaction mixture was then purified by column chromatography (SiO_2, 7-20% EtOAc/hexanes) to yield a white solid (286.4 mg, 79%). mp 130.5-131.5 °C; R_f = 0.32 (20% EtOAc/hexanes); IR (film) 3267, 3148, 2983, 1698, 1546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 325 K) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.42 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.30 (br s, 1H), 5.88 (br s, 1H), 5.65 (d, *J* = 9.2 Hz, 1H), 1.70 (s, 3H), 1.49 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 325 K) ppm 154.7, 136.2, 132.5, 129.0 (q, $^2J_{CF}$ = 30.0 Hz) 128.5, 127.6, 126.7 (q, $^3J_{CF}$ = 6.0 Hz), 124.1 (q, $^1J_{CF}$ = 273 Hz), 91.2, 80.6, 55.8, 28.2, 25.9, 22.9; HRMS (ESI): Exact mass calcd for $C_{16}H_{22}F_3N_2O_4$ $[M+H]^+$ 363.1526, found 363.1519.



(Nitromethyl)cyclohexane (80). $NaNO_2$ (1.4 g, 20 mmol) and phloroglucinol (1.6 g, 12 mmol) were dispensed into a 100 mL round-bottomed flask with stir bar. DMSO (57 mL) was added and the mixture was stirred at room temperature until homogenous. Bromide (2.0 g, 11 mmol) was added and the reaction mixture was stirred for 25 hours. The mixture was poured into ice water and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (4-8% EtOAc/hexanes) provided a clear oil (500 mg, 31%). R_f = 0.10 (10% EtOAc/hexanes); IR (film) 2930, 2856, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, *J* = 7.2 Hz, 2H), 2.13 (m, 1H), 1.79-1.61 (m, 5H), 1.35-1.21 (m, 2H), 1.21-1.12 (m, 1H), 1.09-0.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 81.7, 36.8, 30.0, 25.7, 25.2; HRMS (CI): Exact mass calcd for $C_7H_{14}NO_2$ $[M+H]^+$ 144.1025, found 144.1014.

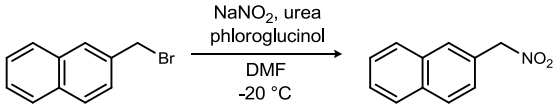


1-Bromo-2-(nitromethyl)benzene (82c). $NaNO_2$ (621.0 mg, 9.000 mmol), urea (721.2 mg, 12.00 mmol), and phloroglucinol (832.3 mg, 6.600 mmol) were dispensed into a 15 mL round bottom flask with a stir bar. DMF (9.1 mL) was added and the reaction mixture was stirred for 20 min at room temperature. The mixture was chilled to -20 °C before the addition of bromide (1.4996 g, 6.0000 mmol). The mixture was stirred for 5 h. The mixture was poured onto ice water and extracted with ether. The combined organic layers were washed with water, dried over MgSO4, filtered, and concentrated. The residue was purified by column chromatography (0-10% EtOAc/hexanes) to provide a slightly golden oil (391.8 mg, 30%). R_f = 0.28 (5% EtOAc/hexanes); IR (film) 3061, 3014, 2964, 2915, 1557 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.44 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.40 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 5.61 (s, 2H) ; ^{13}C NMR (150 MHz, $CDCl_3$) ppm 133.3, 132.7, 131.7, 129.4, 128.0, 125.8, 79.0; HRMS (CI): Exact mass calcd for $C_7H_{10}BrN_2O_2$ $[M+NH_4]^+$ 232.9920, found 232.9921.

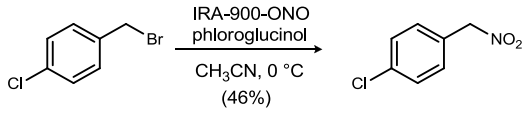


1-Bromo-3-(nitromethyl)benzene (82d). $NaNO_2$ (414.0 mg, 6.000 mmol), urea (721.2 mg, 12.00 mmol), and phloroglucinol (756.7 mg, 6.000 mmol) were stirred with DMF (9.1 mL) at room temperature until homogenous. The reaction mixture was chilled to -20 °C before the addition of bromide (1.4996 g, 6.000 mmol). The mixture was stirred at -20

°C for 5.5 h before pouring into ice water. The mixture was extracted with ether. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0-10% EtOAc/hexanes) provided a clear, slightly green oil (379.9 mg, 29%). R_f = 0.23 (10% EtOAc/hexanes); IR (film) 3064, 2914, 1553 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64-7.61 (m, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 7.8, 7.8 Hz), 5.40 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 133.2, 133.0, 131.4, 130.6, 128.6, 122.9, 79.1; HRMS (CI): Exact mass calcd for $C_7H_6BrNO_2$ $[M]^+$ 214.9576, found 214.9575.

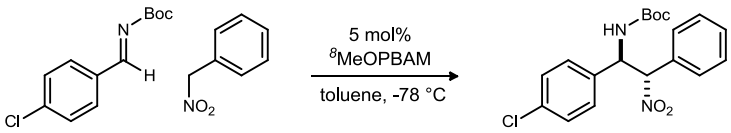


2-(Nitromethyl)naphthalene (82e). $NaNO_2$ (1.035 g, 15.00 mmol), urea (1.202 g, 20.00 mmol), phloroglucinol (1.261 g, 10.00 mmol), and bromide (2.211 g, 10.00 mmol) were reacted according to the aforementioned procedure but with a reaction time of 5 h. Column chromatography (0-3% EtOAc/hexanes) provided a yellow solid (358.4 mg, 19%). Mp 81.5-82.5 °C. R_f = 0.30 (10% EtOAc/hexanes); IR (film) 3060, 2910, 1550 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.94-7.85 (m, 4H), 7.59-7.52 (m, 3H), 5.60 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 133.6, 133.0, 130.0, 129.0, 128.2, 127.8, 127.2, 127.0, 126.8, 126.4, 80.2; HRMS (CI): Exact mass calcd for $C_{11}H_9NO_2$ $[M]^+$ 187.0628, found 187.0634.

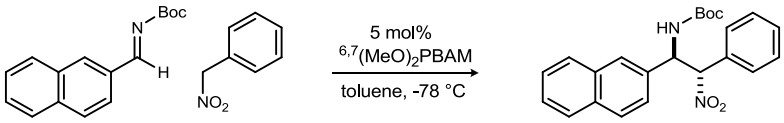


1-Chloro-4-(nitromethyl)benzene (82f). $NaNO_2$ (7.600 g, 109.5 mmol), urea (8.800 g, 146.0 mmol), and phloroglucinol (10.100 g, 80.30 mmol) were stirred with DMF (111 mL) at room temperature until homogenous. The reaction mixture was chilled to -20 °C before the addition of bromide (15.0 g, 73.0 mmol). The mixture was stirred at -20 °C for 3.25 h before pouring into ice water. The mixture was extracted with ether. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0-4% EtOAc/hexanes) provided a clear oil that froze/solidified to a slightly yellow crystalline solid upon storage in a freezer (13.1 g, 45%). Mp 28.0-29.0 °C; R_f = 0.45 (20% EtOAc/hexanes); IR (film) 3095, 3036, 2916, 1555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.35 (m, 4H), 5.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 136.3, 131.4, 129.4, 128.0, 79.1; HRMS (CI): Exact mass calcd for $C_7H_7ClNO_2$ $[M+H]^+$ 172.0160, found 172.0157.

General Procedure for the Synthesis of Adducts 86-86v, 101-101g. Imine (100 μmol) and catalyst (5.0 μmol) were dispensed into a vial with a stir bar. Toluene (1.0 mL) was added, and the reaction was stirred at room temperature until homogenous. The reaction mixture was chilled to -78 °C before nitroalkane (110 μmol) was added. The reaction mixture was stirred for 18-26 h. The chilled mixture was diluted with CH_2Cl_2 and quickly filtered through a pad of silica. The silica pad was flushed with EtOAc. The filtrate was concentrated and purified by column chromatography.

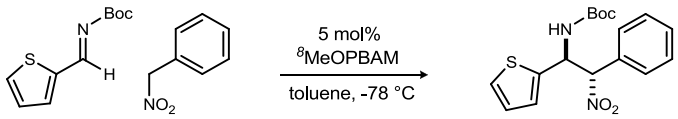


***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitro-2-phenylethylcarbamate (86).** According to the general procedure, purification by column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (36.5 mg, 97%) that was found to be 91% ee and 13:1 dr by chiral HPLC; (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1 mL/min, 230 nm, t_r(*anti*, major) = 20.4 min, t_r(*anti*, minor) = 27.7 min, t_r(*syn*, major) = 24.3 min, t_r(*syn*, minor) = 46.1 min); mp 177.5-178.5 °C; $[\alpha]_D^{20}$ -28.2 (*c* 0.11, $CHCl_3$); R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3386, 2984, 2924, 1683, 1549, 1520 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.6 Hz, 2H), 7.42 (m, 1H), 7.42 (d, *J* = 6.6 Hz, 2H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.76 (br s, 1H), 5.62 (br s, 1H), 4.84 (br s, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 130.4, 129.2, 128.9, 128.6, 128.6, 94.0, 80.6, 56.1, 28.2. HRMS (ESI): Exact mass calcd for $C_{19}H_{21}ClN_2NaO_4$ $[M+Na]^+$ 399.1088, found 399.1070.

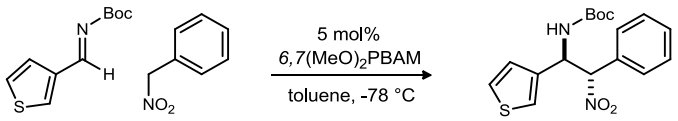


***tert*-Butyl (1*R*,2*S*)-1-(naphthalen-2-yl)-2-nitro-2-phenylethylcarbamate (86c).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (38.9 mg, 99%) that was found to be 91% ee and 25:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 10.6 min, t_r(*anti*, minor) = 13.2 min, t_r(*syn*, major) = 9.2 min, t_r(*syn*, minor) = 17.5

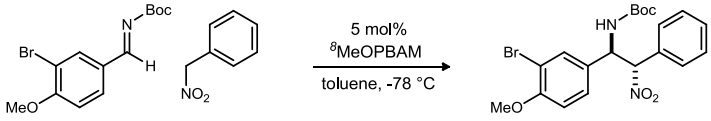
min); Mp 183.0-184.5 °C; $[\alpha]_D^{20}$ -39 (*c* 0.11, $CHCl_3$); R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3403, 2977, 1688, 1547, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.80 (m, 4H), 7.65-7.58 (m, 2H), 7.54-7.48 (m, 2H), 7.48-7.40 (m, 4H), 5.97-5.80 (m, 2H), 4.90 (d, *J* = 8.4 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 134.8, 133.23, 133.16, 131.5, 130.2, 129.1, 128.9, 128.8, 128.1, 127.7, 126.7, 126.6 (2C), 124.4, 94.2, 80.3, 56.7, 28.0; HRMS (ESI): Exact mass calcd for $C_{23}H_{24}N_2NaO_4$ $[M+Na]^+$ 415.1634, found 415.1635.



***tert*-Butyl (1*S*,2*S*)-2-nitro-2-phenyl-1-(thiophen-2-yl)ethylcarbamate (86d).** According to the general procedure, purification by column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (31.2 mg, 90%) that was found to be 87% ee and 21:1 dr by chiral HPLC; (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 33.5 min, t_r(*anti*, minor) = 23.0 min, t_r(*syn*, major) = 22.0 min, t_r(*syn*, minor) = 43.1 min); Mp 169.0-171.0 °C; $[\alpha]_D^{20}$ -33 (*c* 0.10, $CHCl_3$); R_f = 0.34 (20% EtOAc/hexanes); IR (film) 3385, 2979, 1688, 1546, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.46-7.35 (m, 3H), 7.27 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.05 (br d, 1H), 6.95 (dd, *J* = 8.8, 3.6 Hz, 1H), 6.00-5.90 (m, 1H), 5.90-5.80 (m, 1H), 4.98-4.85 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.1, 140.4, 131.4, 130.2, 128.8, 128.6, 127.0, 126.3, 125.7, 94.5, 80.6, 52.5, 28.0; HRMS (ESI): Exact mass calcd for $C_{17}H_{20}N_2NaO_4S$ $[M+Na]^+$ 371.1041, found 371.1026.



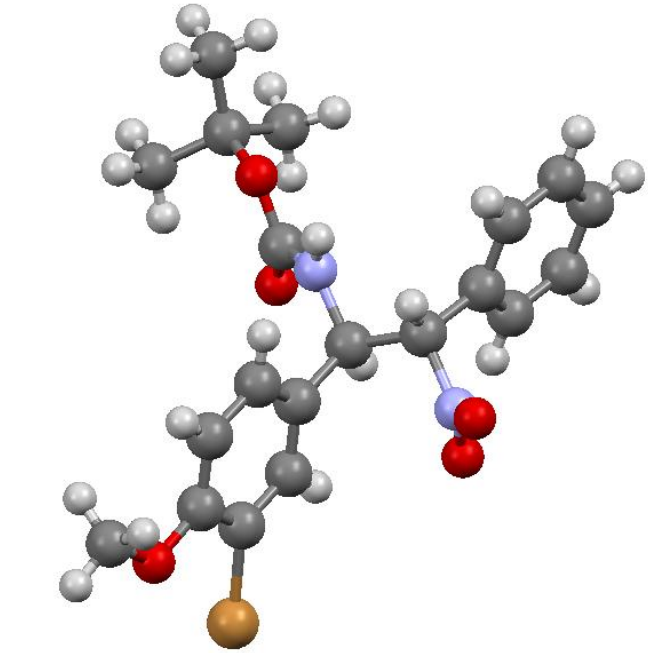
***tert*-butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-(thiophen-3-yl)ethylcarbamate (86e).** According to the general procedure, purification by column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (29.6 mg, 85%) that was found to be 82% ee and 30:1 dr by chiral HPLC; (Chiralcel AD-H, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 19.8 min, t_r(*anti*, minor) = 16.3 min, t_r(*syn*, major) = 15.0 min, t_r(*syn*, minor) = 28.1 min); Mp 174.0-176.0 °C; $[\alpha]_D^{20}$ -35 (*c* 0.11, $CHCl_3$); R_f = 0.34 (20% EtOAc/hexanes); IR (film) 3385, 2977, 2927, 1678, 1547, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.44-7.36 (m, 3H), 7.32 (dd, *J* = 5.2, 2.8 Hz, 1H), 7.28-7.24 (m, 1H), 7.07 (dd, 4.8, 1.2 Hz, 1H), 5.90-5.70 (m, 2H), 4.88 (br s, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 138.1, 131.5, 130.1, 128.8, 128.7, 126.8, 126.1, 123.3, 94.0, 80.4, 52.6, 28.0; HRMS (ESI): Exact mass calcd for $C_{17}H_{20}N_2NaO_4S$ $[M+Na]^+$ 371.1041, found 371.1032.

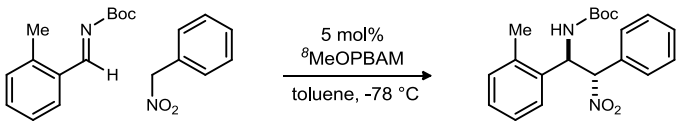


***tert*-Butyl (1*R*,2*S*)-1-(3-bromo-4-methoxyphenyl)-2-nitro-2-phenylethylcarbamate (86g).** This was prepared according to the general procedure with the exception that the scale was 58 μmol (imine) and the reaction was warmed to -20 °C and stirred for one hour before workup. Purification by column chromatography (0-20% ethyl acetate in hexanes) afforded a white solid (20.4 mg, 78%) that was found to be 75% ee and 21:1 dr

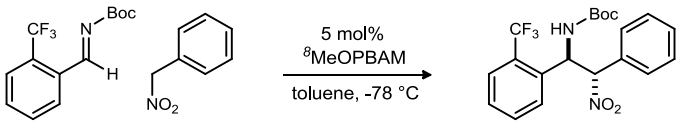
by chiral HPLC; (Chiralcel IA, 5% iPrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 61.8 min, t_r(*anti*, minor) = 29.2 min, t_r(*syn*, major) = 26.8 min, t_r(*syn*, minor) = 49.6 min); Mp 157.0-159.0 °C; R_f = 0.19 (20% EtOAc/hexanes); IR (film) 3387, 2979, 1685, 1553 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.2, 2.0 Hz, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.46-7.38 (m, 3H), 7.30-7.25 (dd, *J* = 8.4, 2.0Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 5.58 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.77 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 156.1, 154.1, 131.9, 131.3, 131.1, 130.3, 128.9 (2C), 128.7 (2C), 127.7, 112.1, 112.0, 94.1, 80.5, 56.2, 55.8, 28.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}BrN_2NaO_5$ $[M+Na]^+$ 473.0688, found 473.0711.

Figure 45. Crystal Structure of Phenylnitromethane Aza-Henry Adduct 86g



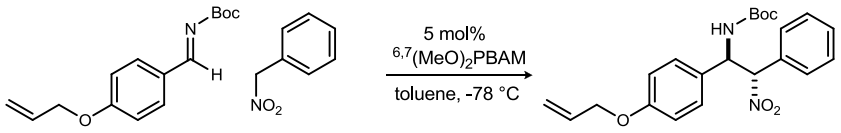


***tert*-Butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-o-tolylethylcarbamate (86h).** Product was prepared according to the general procedure with the exception that the reaction was warmed to -20 °C and stirred for one hour before workup. Purification by column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (31.2 mg, 88%) that was found to be 87% ee and 50:1 dr by chiral HPLC; (Chiralcel AD-H, 5% EtOH/hexanes, 0.7 mL/min, t_r(*anti*, major) 27.2 min, t_r(*anti*, minor) = 14.5 min, t_r(*syn*, major) = 17.0 min, t_r(*syn*, minor) = 15.8 min); Mp 135.0-137.0 °C; $[\alpha]_D^{20}$ -82 (*c* 0.11, $CHCl_3$); R_f = 0.44 (20% EtOAc/hexanes); IR (film) ~3300 (broad), 2978, 2932, 1703, 1555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.46-7.36 (m, 3H), 7.33-7.26 (m, 1H), 7.25-7.18 (m, 3H), 6.12-5.90 (m, 1H), 5.90-5.80 (m, 1H), 4.85-4.60 (m, 1H), 2.53 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.9, 136.1, 131.7, 131.2, 130.1, 128.8, 128.7, 128.5, 126.7, 124.9, 93.4, 80.2, 52.0, 27.9, 19.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4$ $[M+Na]^+$ 379.1634, found 379.1633.

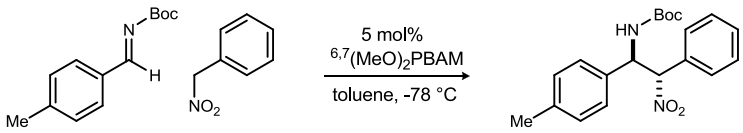


***tert*-butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-(2-(trifluoromethyl)phenyl)ethylcarbamate (86i).** According to the general procedure, column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (35.6 mg, 87%) that was found to be 77% ee and 20:1 dr by chiral HPLC; (Chiralcel IA, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(anti, major) 39.7 min, t_r(anti, minor) = 30.6 min, t_r(syn, major) = 13.4 min, t_r(syn, minor) = 27.8 min); $[\alpha]_D^{20}$ -51.2 (c 1.11, $CHCl_3$) of 62% ee material by HPLC; R_f = 0.25 (20% EtOAc/hexanes); IR (film) 3256, 3137, 2981, 2932, 1700, 1557 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 322 K) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.70-7.50 (m, 4H), 7.48-7.38 (m, 4H), 6.26 (br s, 1H), 5.99 (br s,

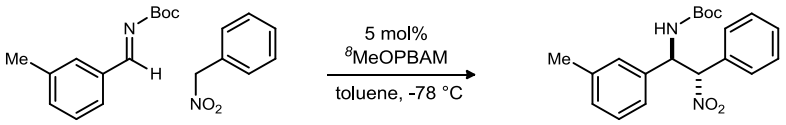
1H), 4.91 (br s, 1H), 1.27 (s, 9H) ; ^{13}C NMR (150 MHz, $CDCl_3$, 322 K) ppm 153.9, 136.0, 132.4, 131.5, 130.2, 128.9 (2C), 128.8 (2C), 128.6 (q, $^2J_{CF}$ = 30 Hz), 127.0 (q, $^3J_{CF}$ = 6.0 Hz), 124.2 (q, $^1J_{CF}$ = 272 Hz), 91.9, 80.6, 53.6, 28.0; ^{19}F NMR (282 MHz, $CDCl_3$) ppm -56.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{21}F_3N_2NaO_4$ $[M+Na]^+$ 433.1351, found 433.1365.



***tert*-Butyl (1*R*,2*S*)-1-(4-(allyloxy)phenyl)-2-nitro-2-phenylethylcarbamate (86j).** Product was prepared according to the general procedure with the exception that the reaction was warmed to -20 °C and stirred for one hour before workup. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (28.0 mg, 79%) that was found to be 87% ee and 131:1 dr by chiral HPLC; (Chiralcel IA, 12% EtOH/hexanes, 0.5 mL/min, t_r(*anti*, major) 14.9 min, t_r(*anti*, minor) = 13.1 min, t_r(*syn*, major) = 13.8 min, t_r(*syn*, minor) = 22.3 min); Mp 174.5-176.0 °C; $[\alpha]_D^{20}$ -42 (*c* 0.16, $CHCl_3$); R_f = 0.21 (20% EtOAc/hexanes); IR (film) 3394, 2981, 2930, 1683, 1549, 1514 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 2H), 7.45-7.37 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.04 (dddd, *J* = 16.8, 10.2, 4.8, 4.8 Hz, 1H), 5.74 (br s, 1H), 5.61 (br s, 1H), 5.41 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.29 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.80 (d, *J* = 7.8 Hz, 1H), 4.52 (d, *J* = 4.8 Hz, 2H) 1.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 158.8, 154.2, 133.0, 131.6, 130.1, 129.7, 128.8 (2C), 128.4, 117.8, 115.1, 94.4, 80.3, 68.8, 56.1, 28.0; HRMS (ESI): Exact mass calcd for $C_{22}H_{26}N_2NaO_5$ $[M+Na]^+$ 421.1739, found 421.1730.

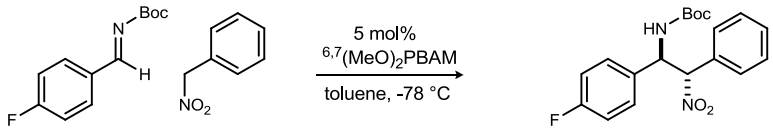


***tert*-Butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-p-tolylethylcarbamate (86k).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (33.0 mg, 93%) that was found to be 91% ee and 38:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 0.7 mL/min, t_r(*anti*, major) 12.1 min, t_r(*anti*, minor) = 13.1 min, t_r(*syn*, major) = 11.2 min, t_r(*syn*, minor) = 20.7 min); Mp 181.0-183.0 °C; $[\alpha]_D^{20}$ -46 (*c* 0.11, $CHCl_3$); R_f = 0.36 (20% EtOAc/hexanes); IR (film) 3393, 2979, 1685, 1549, 1517 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.45-7.37 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 5.75 (br s, 1H), 5.64 (br s, 1H), 4.78 (d, *J* = 9.0 Hz, 1H), 2.34 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 138.6, 134.5, 131.6, 130.1, 129.7, 128.78, 128.76, 127.0, 94.4, 80.2, 56.3, 28.0, 21.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4$ $[M+Na]^+$ 379.1634, found 379.1626.



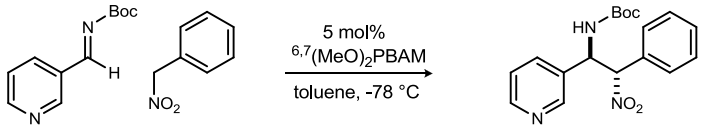
***tert*-butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-*m*-tolylethylcarbamate (86l).** Product was prepared according to the general procedure with the exception that the reaction was warmed to -20 °C and stirred for one hour before workup. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (32.2 mg, 90%) that was found to be

81% ee and 28:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 8.2 min, t_r(*anti*, minor) = 9.3 min, t_r(*syn*, major) = 6.4 min, t_r(*syn*, minor) = 13.1 min); Mp 175.0-177.0 °C; $[\alpha]_D^{20}$ -18 (*c* 0.15, $CHCl_3$); R_f = 0.35 (20% EtOAc/hexanes); IR (film) 3393, 2975, 2922, 1684 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.46-7.37 (m, 3H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.17-7.12 (m, 3H), 5.75 (br s, 1H), 5.66 (br s, 1H), 4.82 (br s, 1H), 2.35 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 138.8, 137.4, 131.6, 130.1, 129.5, 128.9, 128.78, 128.75, 127.9, 124.0, 94.4, 80.3, 56.4, 28.0, 21.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4$ $[M+Na]^+$ 379.1634, found 379.1630.

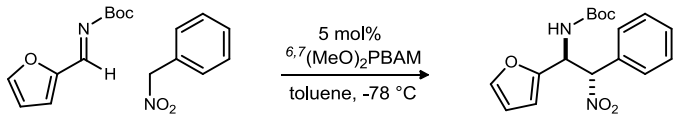


***tert*-Butyl (1*R*,2*S*)-1-(4-fluorophenyl)-2-nitro-2-phenylethylcarbamate (86m).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (35.0 mg, 97%) that was found to be 87% ee and 15:1 dr by chiral HPLC; (Chiralcel IA, 5% EtOH/hexanes, 0.5 mL/min, t_r(*anti*, major) 19.1 min, t_r(*anti*, minor) = 20.5 min, t_r(*syn*, major) = 22.8 min, t_r(*syn*, minor) = 39.9 min); Mp 178.5-180.0 °C; $[\alpha]_D^{20}$ -18 (*c* 0.15, $CHCl_3$); R_f = 0.34 (20% EtOAc/hexanes); IR (film) 3391, 2986, 2925, 1683 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.46-7.39 (m, 3H), 7.34 (dd, *J* = 8.4, 4.8 Hz, 2H), 7.05 (dd, *J* = 8.4, 8.4 Hz, 2H), 5.75 (br s, 1H), 5.64 (br s, 1H), 4.81 (d, *J* = 9.0 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 162.7 (d, $^1J_{CF}$ = 246 Hz), 154.2, 133.4, 131.3, 130.3, 129.0 (d, $^3J_{CF}$ = 9.0 Hz), 128.9, 128.7, 116.0 (d, $^2J_{CF}$ = 23 Hz), 94.2, 80.6, 56.2, 28.0; ^{19}F NMR (376

MHz, $CDCl_3$) ppm -112.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}FN_2NaO_4$ $[M+Na]^+$ 383.1383, found 383.1392.

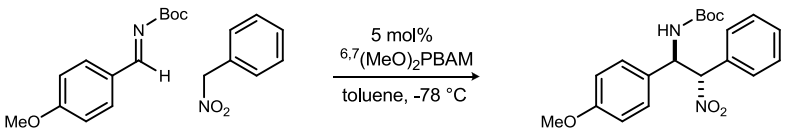


***tert*-butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-(pyridin-3-yl)ethylcarbamate (86n).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (20-40% ethyl acetate in hexanes) afforded a white solid (28.0 mg, 82%) that was found to be 60% ee and 28:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 14.7 min, t_r(*anti*, minor) = 8.6 min, t_r(*syn*, major) = 11.6 min, t_r(*syn*, minor) = 20.0 min); Mp 166.0-168.0 °C; $[\alpha]_D^{20}$ -15 (*c* 0.13, $CHCl_3$); R_f = 0.05 (20% EtOAc/hexanes); IR (film) 3390, 2982, 2927, 1683, 1550, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.0 Hz, 1H), 8.58 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.56-7.51 (m, 2H), 7.48-7.38 (m, 3H), 7.30 (dd, *J* = 7.2, 4.8 Hz, 1H), 5.95-5.80 (m, 1H), 5.70-5.55 (m, 1H), 5.20-5.00 (m, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 150.0, 149.0, 135.0, 133.3, 131.1, 130.5, 129.1, 128.5, 123.7, 93.5, 80.8, 55.0, 28.0; HRMS (ESI): Exact mass calcd for $C_{18}H_{22}N_3O_4$ $[M+H]^+$ 344.1610, found 344.1594.



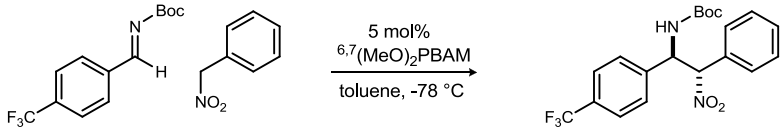
***tert*-butyl (1*S*,2*S*)-1-(furan-2-yl)-2-nitro-2-phenylethylcarbamate (86o).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in

hexanes) afforded a white solid (28.1 mg, 85%) that was found to be 68% ee and 18:1 dr by chiral HPLC; (Chiralcel IA, 5% EtOH/hexanes, 1 mL/min, t_r(*anti*, major) 10.4 min, t_r(*anti*, minor) = 8.0 min, t_r(*syn*, major) = 9.2 min, t_r(*syn*, minor) = 19.0 min); Mp 156.0-158.0 °C; $[\alpha]_D^{20}$ -54 (*c* 0.15, $CHCl_3$); R_f = 0.40 (20% EtOAc/hexanes); IR (film) 3392, 2980, 2933, 1689, 1549, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.45-7.36 (m, 4H), 6.35-6.30 (m, 2H), 5.90-5.75 (m, 2H), 5.00-4.80 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.1, 149.6, 142.8, 131.1, 130.1, 128.73, 128.70, 110.6, 108.7, 92.4, 80.5, 50.4, 28.0; HRMS (ESI): Exact mass calcd for $C_{17}H_{20}N_2NaO_5$ $[M+Na]^+$ 355.1270, found 355.1257.

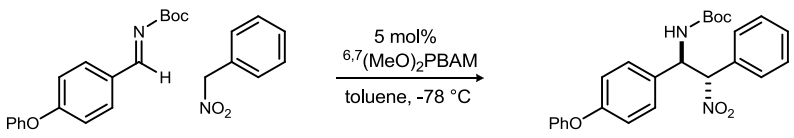


***tert*-Butyl (1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitro-2-phenylethylcarbamate (86p).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (31.0 mg, 83%) that was found to be 85% ee and 81:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 0.5 mL/min, t_r(*anti*, major) 21.3 min, t_r(*anti*, minor) = 23.6 min, t_r(*syn*, major) = 19.8 min, t_r(*syn*, minor) = 37.0 min); Mp 161.0-162.5 °C; $[\alpha]_D^{20}$ -43 (*c* 0.14, $CHCl_3$); R_f = 0.18 (20% EtOAc/hexanes); IR (film) 3390, 2980, 1683, 1548, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.53 (m, 2H), 7.44-7.37 (m, 3H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.75 (d, *J* = 10.0 Hz, 1H), 5.61 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.7, 154.2, 131.6,

130.1, 129.5, 128.8 (2C), 128.4, 114.3, 94.4, 80.3, 56.2, 55.3, 28.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4$ $[M+Na]^+$ 395.1583, found 395.1567.

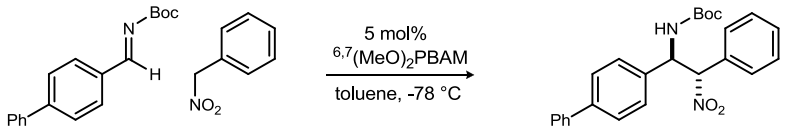


***tert*-Butyl (1*R*,2*S*)-2-nitro-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethylcarbamate (86q).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (40.8 mg, 99%) that was found to be 84% ee and 14:1 dr by chiral HPLC; (Chiralcel IA, 8% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 9.2 min, t_r(*anti*, minor) = 13.9 min, t_r(*syn*, major) = 12.6 min, t_r(*syn*, minor) = 20.0 min); Mp 193.5-194.5 °C; $[\alpha]_D^{20}$ -21 (*c* 0.14, $CHCl_3$); R_f = 0.33 (20% EtOAc/hexanes); IR (film) 3390, 2985, 1683, 1548, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.58-7.53 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.43-7.40 (m, 3H), 5.80 (br s, 1H), 5.71 (br s, 1H), 4.89 (br s, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 141.5, 131.0, 130.9 (q, $^2J_{CF}$ = 32 Hz), 130.5, 129.0, 128.6, 127.7, 126.0 (q, $^3J_{CF}$ = 4.0 Hz), 123.8 (q, $^1J_{CF}$ = 271 Hz), 93.7, 80.8, 56.3, 28.0; ^{19}F NMR (282 MHz, $CDCl_3$) ppm -61.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{21}F_3N_2NaO_4$ $[M+Na]^+$ 433.1351, found 433.1364.

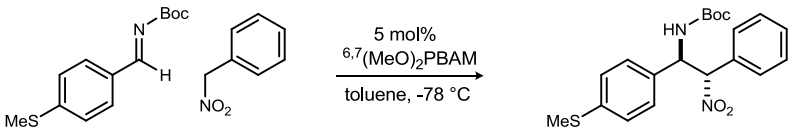


***tert*-butyl (1*R*,2*S*)-2-nitro-1-(4-phenoxyphenyl)-2-phenylethylcarbamate (86r).** According to the general procedure, column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (42.1 mg, 97%) that was found to be 83% ee and 25:1 dr

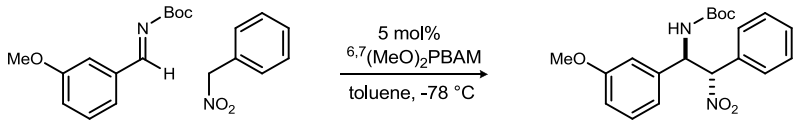
by chiral HPLC; (Chiralcel AD-H, 6% EtOH/hexanes, 1 mL/min, t_r(*anti*, major) 21.3 min, t_r(*anti*, minor) = 23.0 min, t_r(*syn*, major) = 26.1 min, t_r(*syn*, minor) = 35.1 min); Mp 184.0-185.0 °C; $[\alpha]_D^{20}$ -41 (*c* 0.11, $CHCl_3$); R_f = 0.31 (20% EtOAc/hexanes); IR (film) 3391, 2980, 1682, 1550, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2H), 7.45-7.39 (m, 3H), 7.38-7.33 (m, 2H), 7.33-7.28 (m, 2H), 7.16-7.10 (m, 1H), 7.04-7.00 (m, 2H), 7.00-6.95 (m, 2H), 5.76 (d, *J* = 10.0 Hz, 1H), 5.70-5.60 (m, 1H), 4.78 (d, *J* = 9.2 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.8, 156.5, 154.2, 132.0, 131.5, 130.2, 129.9, 128.84, 128.75, 128.7, 123.8, 119.4, 118.8, 94.3, 80.4, 56.3, 28.1; HRMS (ESI): Exact mass calcd for $C_{25}H_{26}N_2NaO_5$ $[M+Na]^+$ 457.1739, found 457.1730.



***tert*-Butyl (1*R*,2*S*)-1-(biphenyl-4-yl)-2-nitro-2-phenylethylcarbamate (86s).** Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 99%) that was found to be 93% ee and 44:1 dr by chiral HPLC; (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 32.6 min, t_r(*anti*, minor) = 23.9 min, t_r(*syn*, major) = 26.1 min, t_r(*syn*, minor) = 28.7 min); Mp 194.0-196.0 °C; $[\alpha]_D^{20}$ -56 (*c* 0.15, $CHCl_3$); R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3398, 2978, 2922, 1686, 1548, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.55 (m, 6H), 7.47-7.40 (m, 7H), 7.39-7.33 (m, 1H), 5.82 (br s, 1H), 5.73 (br s, 1H), 4.90 (br s, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 141.6, 140.3, 136.4, 131.5, 130.2, 128.83, 128.80, 128.76, 127.7, 127.59, 127.56, 127.1, 94.2, 80.4, 56.5, 28.0; HRMS (ESI): Exact mass calcd for $C_{25}H_{26}N_2NaO_4$ $[M+Na]^+$ 441.1790, found 471.1776.

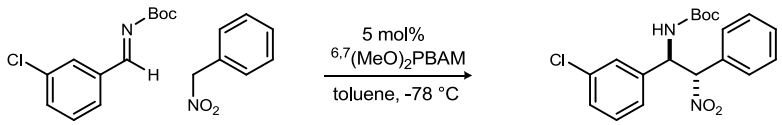


***tert*-butyl (1*R*,2*S*)-1-(4-(methylthio)phenyl)-2-nitro-2-phenylethylcarbamate (86t)**. Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (36.6 mg, 94%) that was found to be 93% ee and 69:1 dr by chiral HPLC; (Chiralcel IA, 18% ^{i}PrOH/hexanes, 0.6 mL/min, t_r(*anti*, major) 13.0 min, t_r(*anti*, minor) = 15.6 min, t_r(*syn*, major) = 14.2 min, t_r(*syn*, minor) = 21.0 min); Mp 185.0-186.0 °C; $[\alpha]_D^{20}$ -54 (*c* 0.13, $CHCl_3$); R_f = 0.23 (20% EtOAc/hexanes); IR (film) 3390, 2978, 2922, 1680, 1549, 1518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.53 (m, 2H), 7.46-7.39 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 5.84-5.69 (m, 1H), 5.62 (br s, 1H), 4.88 (br s, 1H), 2.47 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 139.4, 134.1, 131.4, 130.2, 128.8, 128.7, 127.6, 126.7, 94.1, 80.4, 56.4, 28.0, 15.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4S$ $[M+Na]^+$ 411.1354, found 411.1350.



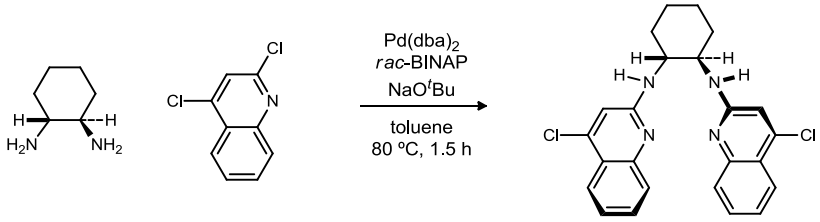
***tert*-butyl (1*R*,2*S*)-1-(3-methoxyphenyl)-2-nitro-2-phenylethylcarbamate (86u).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (32.8 mg, 88%) that was found to be 89%

ee and 38:1 dr by chiral HPLC; (Chiralcel IA, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 48.8 min, t_r(*anti*, minor) = 11.9 min, t_r(*syn*, major) = 14.5 min, t_r(*syn*, minor) = 20.2 min); Mp 181.0-182.0 °C; $[\alpha]_D^{20}$ -44 (*c* 0.12, $CHCl_3$); R_f = 0.22 (20% EtOAc/hexanes); IR (film) 3388, 2978, 2932, 1683, 1549, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, 2H), 7.45-7.37 (m, 3H), 7.28 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.93 (br d, *J* = 7.6 Hz, 1H), 6.90-6.84 (m, 2H), 5.76 (br d, *J* = 9.6 Hz, 1H), 5.66 (br s, 1H), 4.83 (br s, 1H), 3.80 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.9, 154.2, 139.1, 131.5, 130.2, 130.1, 128.8 (2C), 119.1, 114.1, 113.1, 94.2, 80.4, 56.5, 55.3, 28.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_5$ $[M+Na]^+$ 395.1583, found 395.1568.



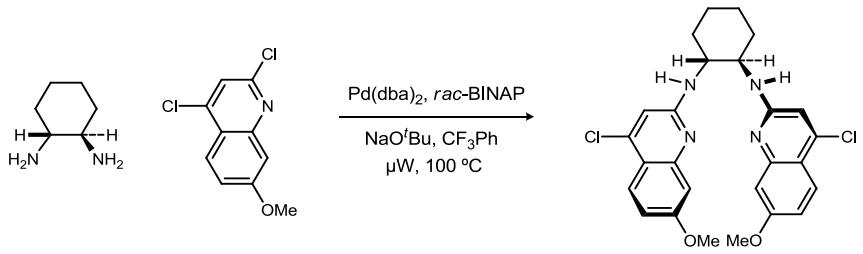
***tert*-butyl (1*R*,2*S*)-1-(3-chlorophenyl)-2-nitro-2-phenylethylcarbamate (86v).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (29.8 mg, 79%) that was found to be 74% ee and 17:1 dr by chiral HPLC; (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 10.8 min, t_r(*anti*, minor) = 9.2 min, t_r(*syn*, major) = 8.1 min, t_r(*syn*, minor) = 12.4 min); Mp 174.0-176.0 °C; $[\alpha]_D^{20}$ -26 (*c* 0.13, $CHCl_3$); R_f = 0.28 (20% EtOAc/hexanes); IR (film) 3393, 2975, 1683, 1544, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.53 (m, 2H), 7.47-7.39 (m, 3H), 7.35 (br s, 1H), 7.34-7.23 (m, 3H), 5.75 (br d, *J* = 10.0 Hz, 1H), 5.64 (br s, 1H), 4.85 (br s, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 139.6,

134.9, 131.2, 130.4, 130.3, 130.0 (2C), 128.6, 127.4, 125.5, 93.9, 80.7, 56.3, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}ClN_2NaO_4$ $[M+Na]^+$ 399.1088, found 399.1087.

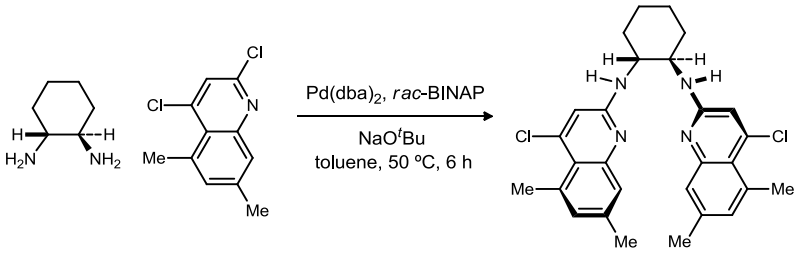


^{4}ClQuinBAM (92).[173] A flame-dried flask was charged with $Pd(dba)_2$ (217 mg, 378 μmol), *rac*-BINAP (235 mg, 378 μmol), sodium *tert*-butoxide (2.180 g, 22.68 mmol), (*R*,*R*)-diaminocyclohexane (865 mg, 7.57 mmol), and 2,4-dichloroquinoline (3.000 g, 15.22 mmol), and the reaction vessel was placed under an argon atomosphere.[174] Toluene (90 mL) was added, and the resulting red-brown solution was heated at 85 °C. The reaction was monitored by TLC; after 3 h, nearly complete conversion was observed. The reaction was cooled to 25 °C, diluted with EtOAc, and washed with satd aq NH_4Cl. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (SiO_2, 10% ethyl acetate in hexanes) of the residue provided the title compound (1.8 g, 54%) as a yellow powder. Mp 236.0-237.0; $[\alpha]_D^{20}$ +508 (*c* 1.0, DMSO); R_f = 0.23 (20% EtOAc/hexanes); IR (film) 3220, 2930, 1601 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.62-7.53 (m, 4H), 7.29-7.20 (m, 4H), 6.84 (s, 2H), 4.05 (br s, 2H), 2.28-2.16 (m, 2H), 1.83-1.67 (m, 2H), 1.50-1.28 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 156.5, 148.5, 140.2, 130.4, 126.0, 123.4, 122.1, 120.3, 112.6, 53.6, 31.7, 24.3; HRMS (CI): Exact mass calcd for $C_{24}H_{23}Cl_2N_4$ $[M+H]^+$ 437.1300, found 437.1294.

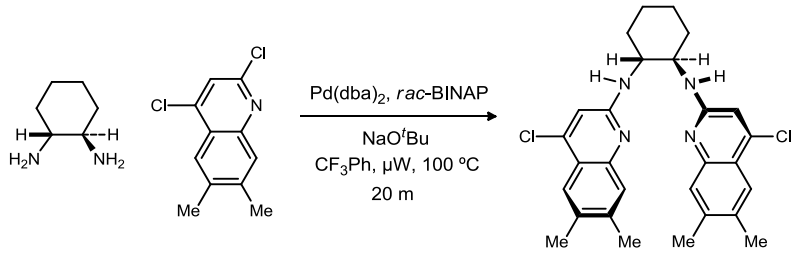
[173] See Appendix for larger scale *Organic Syntheses* manuscript procedure.
[174] Adapted from Wagaw, S.; Rennels, R.; Buchwald, S. *J Am. Chem. Soc*. **1997**, *119*, 8451-8458.



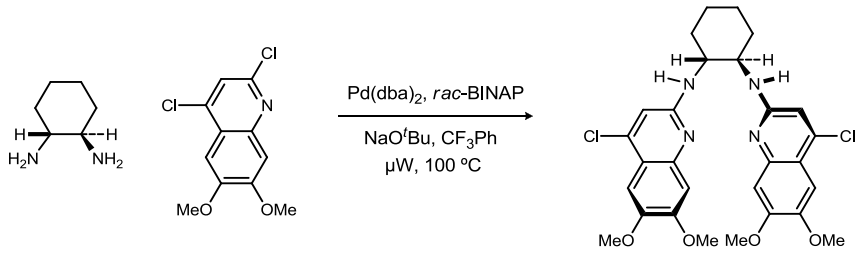
^{4}Cl^{7}MeOQuinBAM (92b). A 2-5 mL μW vial was charged with (*R,R*)-diaminocyclohexane (125.2 mg, 1.096 mmol), 2,4-dichloro-7-methoxyquinoline (500 mg, 2.190 mmol), $Pd(dba)_2$ (12.6 mg, 22.0 μmol), *rac*-BINAP (13.6 mg, 22.0 μmol), and sodium *tert*-butoxide (316.2 mg, 3.290 mmol).[176] Trifluoromethylbenzene (3.8 mL) was added and the resulting suspension was heated at 100 °C and stirred in the microwave for 10 min. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated and washed with CH_2Cl_2 then hexanes to provide a light brown powder (412.9 mg, 76%) that was pure by ^{1}H NMR; $[\alpha]_D^{20}$ +580 (*c* 0.19, $CHCl_3$); R_f = 0.25 (50% EtOAc/hexanes); IR (film) 3220, 2933, 1610, 1510 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 325 K) δ 7.82 (d, *J* = 9.0 Hz, 2H), 7.08 (s, 2H), 6.91 (dd, *J* = 9.0, 2.5 Hz, 2H), 6.31 (br s, 2H), 5.64 (br s, 2H), 4.09 (br s, 2H), 3.94 (s, 6H), 2.41-2.32 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 325 K) ppm 162.0, 157.3, 150.5, 142.3, 125.3, 116.3, 114.4, 109.5, 106.0, 56.1, 55.5, 32.9, 24.9; HRMS (ESI): Exact mass calcd for $C_{26}H_{27}Cl_2N_4O_2$ $[M+H]^+$ 497.1511, found 497.1501.



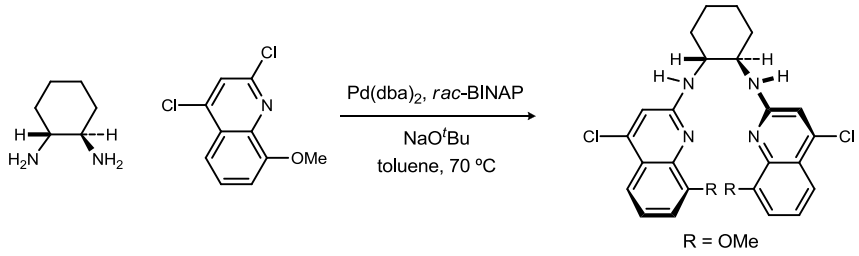
^{4}Cl^{5,7}(Me)$_2$BAM (92c). A 25 mL round bottom flask was charged with $Pd(dba)_2$ (15.9 mg, 27.7 μmol), *rac*-BINAP (34.6 mg, 55.4 μmol), sodium *tert*-butoxide (362.0 mg, 3.76 mmol), (*R*,*R*)-diaminocyclohexane (126.2 mg, 1.106 mmol), and the quinoline (500 mg, 2.21 mmol). Toluene (8 mL) was added, and the reaction mixture was heated at 50 °C and stirred. The reaction mixture was monitored by TLC; after 6 h, complete conversion was observed. The reaction was cooled to room temperature, quenched with sat. aq. NH_4Cl, and extracted with EtOAc. The extract was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (10-25% ethyl acetate in hexanes) provided a yellow solid (265.1 mg, 49%). mp 235.0-237.0 °C; $[\alpha]_D^{20}$ +356 (*c* 1.14, $CHCl_3$); R_f = 0.36 (25% EtOAc/hexanes); IR (film) 3225, 2967, 2938, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 2H), 6.84 (s, 2H), 6.29 (s, 2H), 5.65 (br s, 2H), 4.10-3.90 (m, 2H), 3.08-2.85 (m, 2H), 2.84 (s, 6H), 2.40 (s, 6H), 2.38-2.25 (m, 2H), 1.90-1.70 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.9, 150.6, 142.3, 139.7, 134.9, 128.5, 125.0, 118.4, 112.9, 55.9, 32.8, 24.9, 21.3 (2C); HRMS (ESI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4$ $[M+H]^+$ 493.1926, found 493.1927.



^{4}Cl^{6,7}(Me)$_2$BAM (92d). A 2-5 mL μW vial was charged with $Pd(dba)_2$ (17.8 mg, 31.0 μmol), *rac*-BINAP (19.3 mg, 31.0 μmol), sodium *tert*-butoxide (446.3 mg, 4.644 mmol), (*R*,*R*)-diaminocyclohexane (176.8 mg, 1.548 mmol), and the quinoline (700.0 mg, 3.096 mmol). Trifluorotoluene (5 mL) was added, and the reaction mixture was heated at 100 °C and stirred for 20 min. Complete conversion was observed by TLC. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated to a crude solid that was rinsed with ether to provide a light yellow solid (180.2 mg, 24%). mp >260 °C; $[\alpha]_D^{20}$ +228 (*c* 1.12, $CHCl_3$); R_f = 0.30 (25% EtOAc/hexanes); IR (film) 3219, 2937, 2859, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 2H), 7.50 (s, 2H), 6.37 (s, 2H), 5.69 (br s, 2H), 4.12-3.96 (m, 2H), 2.41 (s, 6H), 2.38 (s, 6H), 2.37-2.29 (m, 2H), 1.89-1.80 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 156.2, 147.3, 141.5, 140.4, 131.9, 126.1, 123.6, 119.7, 111.2, 56.0, 32.8, 24.8, 20.2, 19.7; HRMS (ESI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4$ $[M+H]^+$ 493.1926, found 493.1949.

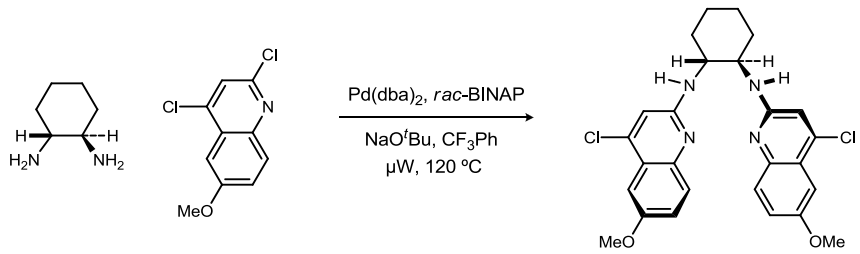


^{4}Cl^{6,7}(MeO)$_2$QuinBAM (92e). A 10-20 mL μW vial was charged with (*R,R*)-diaminocyclohexane (442.4 mg, 3.874 mmol), 2,4-dichloro-6,7-dimethoxyquinoline (2.000 g, 7.749 mmol), $Pd(dba)_2$ (44.5 mg, 77.48 μmol), *rac*-BINAP (48.2 mg, 77.48 μmol), and sodium *tert*-butoxide (1.117 g, 11.62 mmol).[176] Trifluoromethylbenzene (13.4 mL) was added and the resulting suspension was heated at 100 °C and stirred in the microwave for 10 min. The reaction mixture was filtered through celite with CH_2Cl_2 and concentrated. The residue was triturated with ethyl acetate and hexanes to provide a light brown powder (1.4612 g, 68%) that was sufficiently pure by ^{1}H NMR; $[\alpha]_D^{20}$ +410 (*c* 0.10, $CHCl_3$); R_f = 0.15 (50% EtOAc/hexanes); IR (film) 3223, 2930, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 330 K) δ 7.24 (s, 2H), 7.09 (s, 2H), 6.32 (br s, 2H), 5.50 (br s, 2H), 4.02 (s, 6H), 4.00 (br s, 2H), 3.97 (s, 6H), 2.38-2.28 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 330 K) ppm 156.2, 153.2, 147.1, 145.3, 141.0, 115.7, 109.2, 106.6, 103.6, 56.2 (2C), 56.1, 33.0, 24.9; HRMS (CI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4O_4$ $[M+H]^+$ 557.1717, found 557.1717.



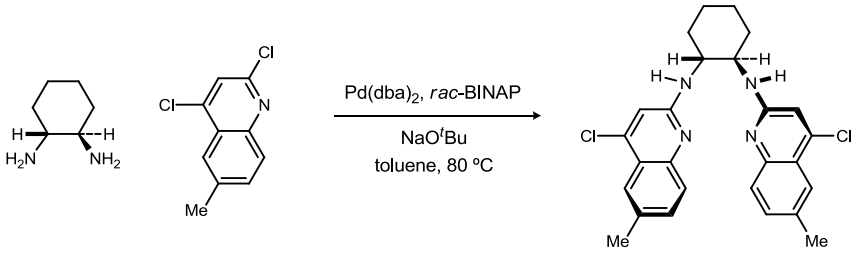
^{4}Cl^{8}MeOQuinBAM (92f). A 100 mL round bottom flask was charged with $Pd(dba)_2$ (25.2 mg, 43.8 μmol), *rac*-BINAP (27.3 mg, 43.8 μmol), sodium *tert*-butoxide (632.0 mg, 6.576 mmol), (*R*,*R*)-diaminocyclohexane (250.3 mg, 2.192 mmol), and the quinoline (1.0000 g, 4.385 mmol).[175] Toluene (22 mL) was added, and the reaction mixture was heated at 70 °C and stirred for 3.5 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and purified by column chromatography (25-50% ethyl acetate in hexanes) to provide a yellow solid (642.6 mg, 62%). $[\alpha]_D^{20}$ +530 (*c* 0.16, $CHCl_3$); R_f = 0.31 (50% EtOAc/hexanes); IR (film) 3240, 2933, 1607, 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.4, 0.8 Hz, 2H), 7.17 (dd, *J* = 7.6, 0.8 Hz, 2H), 7.01 (dd, *J* = 7.6, 0.8 Hz, 2H), 6.59 (s, 2H), 6.38 (br s, 2H), 4.15-3.95 (m, 2H), 4.04 (s, 6H), 2.45-2.30 (m, 2H), 1.85-1.70 (m, 2H), 1.50-1.30 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.9, 153.2, 142.1, 140.0, 122.2, 121.9, 116.2, 112.7, 109.8, 56.6, 56.2, 32.5, 24.7; HRMS (ESI): Exact mass calcd for $C_{26}H_{27}Cl_2N_4O_2$ $[M+H]^+$ 497.1511, found 497.1521.

[175] Adapted from Wagaw, S.; Rennels, R.; Buchwald, S. *J Am. Chem. Soc*. **1997**, *119*, 8451-8458.



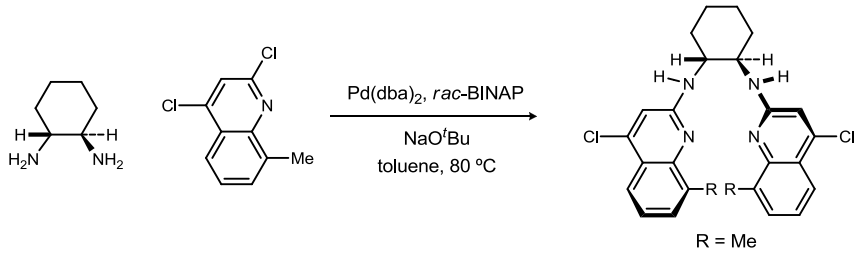
^{4}Cl^{6}MeOQuinBAM (92g). A 2-5 mL μW vial was charged with (*R,R*)-diaminocyclohexane (125.2 mg, 1.096 mmol), 2,4-dichloro-6-methoxyquinoline (500 mg, 2.190 mmol), $Pd(dba)_2$ (12.6 mg, 22.0 μmol), *rac*-BINAP (13.6 mg, 22.0 μmol), and sodium *tert*-butoxide (316.2 mg, 3.290 mmol).[176] Trifluoromethylbenzene (3.8 mL) was added and the resulting suspension was heated at 120 °C and stirred in the microwave for 10 min. The reaction mixture was triturated with CH_2Cl_2 and filtered. The filtrate was concentrated and purified by column chromatography (10-20% ethyl acetate in hexanes) to provide a yellow solid (420.3 mg, 77%) that was pure by ^{1}H NMR; $[\alpha]_D^{20}$ +610 (*c* 0.18, $CHCl_3$); R_f = 0.18 (20% EtOAc/hexanes); IR (film) 3218, 2925, 1605, 1495 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 325 K) δ 7.64 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 3.0 Hz, 2H), 7.25 (dd, *J* = 9.0, 3.0 Hz, 2H), 6.38 (br s, 2H), 5.72 (br s, 2H), 4.05-3.90 (m, 2H), 3.91 (s, 6H), 2.39-2.25 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$, 325 K) ppm 155.5, 155.4, 144.0, 141.4, 127.6, 121.9, 121.8, 111.8, 103.7, 56.1, 55.6, 33.0, 24.9; HRMS (ESI): Exact mass calcd for $C_{26}H_{27}Cl_2N_4O_2$ $[M+H]^+$ 497.1511, found 497.1500.

[176] Adapted from Wagaw, S.; Rennels, R.; Buchwald, S. *J Am. Chem. Soc*. **1997**, *119*, 8451-8458.



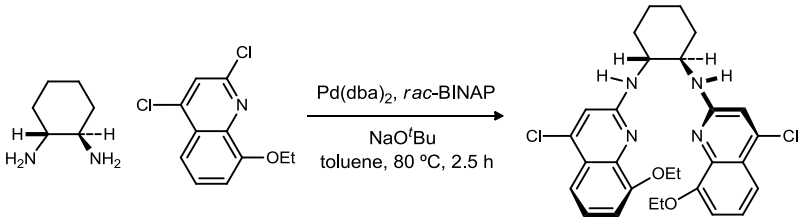
^{4}Cl^{6}MeQuinBAM (92h). A 100 mL round bottom flask was charged with $Pd(dba)_2$ (27.1 mg, 47.2 μmol), *rac*-BINAP (29.4 mg, 47.2 μmol), sodium *tert*-butoxide (679.8 mg, 7.074 mmol), (*R,R*)-diaminocyclohexane (269.2 mg, 2.358 mmol), and the quinoline (1.0000 g, 4.715 mmol).[177] Toluene (27 mL) was added, and the reaction mixture was heated at 80 °C and stirred for 3 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and the resulting solid was washed with CH_2Cl_2 and hexanes to provide a brown powder (802.2 mg, 73%). $[\alpha]_D^{20}$ +310 (*c* 0.11, $CHCl_3$); R_f = 0.16 (5% EtOAc/hexanes); IR (film) 3226, 2929, 2857, 1603 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.43 (dd, *J* = 8.4, 1.8 Hz, 2H), 6.42 (br s, 2H), 5.77 (br s, 2H), 4.08 (br s, 2H), 2.49 (s, 6H), 2.41-2.35 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.38 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 156.1, 146.8, 141.7, 132.4, 132.1, 126.0, 123.2, 121.3, 112.1, 56.1, 32.8, 24.8, 21.3; HRMS (ESI): Exact mass calcd for $C_{26}H_{27}Cl_2N_4$ $[M+H]^+$ 465.1613, found 465.1602.

[177] Adapted from Wagaw, S.; Rennels, R.; Buchwald, S. *J Am. Chem. Soc*. **1997**, *119*, 8451-8458.

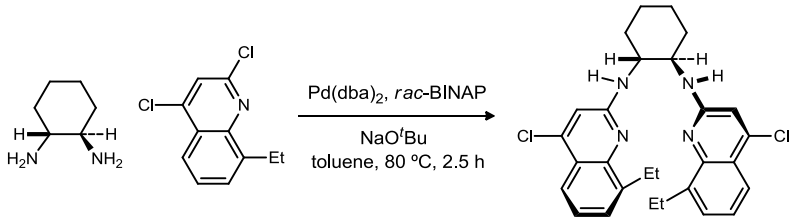


^{4}Cl^{8}MeQuinBAM (92i). A 50 mL round bottom flask was charged with $Pd(dba)_2$ (29.8 mg, 51.9 μmol), *rac*-BINAP (32.3 mg, 51.9 μmol), sodium *tert*-butoxide (747.6 mg, 7.779 mmol), (*R*,*R*)-diaminocyclohexane (296.1 mg, 2.593 mmol), and the quinoline (1.1000 g, 5.187 mmol).[178] Toluene (24 mL) was added, and the reaction mixture was heated at 80 °C and stirred. The reaction mixture was monitored by TLC; after 75 min, complete conversion was observed. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and purified by column chromatography (2-5% ethyl acetate in hexanes) to provide a yellow solid (989.7 mg, 82%). $[\alpha]_D^{20}$ +600 (*c* 0.14, $CHCl_3$); R_f = 0.34 (10% EtOAc/hexanes); IR (film) 3414, 3279, 2932, 2856, 1604, 1525 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.18 (dd, *J* = 7.8, 7.8 Hz, 2H), 6.45 (s, 2H), 5.88 (br s, 2H), 4.15-4.05 (m, 2H), 2.71 (s, 6H), 2.48-2.38 (m, 2H), 1.92-1.82 (m, 2H), 1.55-1.45 (m, 2H), 1.45-1.35 (m, 2H) ; ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.5, 147.2, 142.6, 133.9, 130.7, 122.0, 121.9, 121.1, 111.5, 56.9, 32.8, 25.0, 18.2; HRMS (ESI): Exact mass calcd for $C_{26}H_{27}Cl_2N_4$ $[M+H]^+$ 465.1613, found 465.1606.

[178] Adapted from Wagaw, S.; Rennels, R.; Buchwald, S. *J Am. Chem. Soc*. **1997**, *119*, 8451-8458.

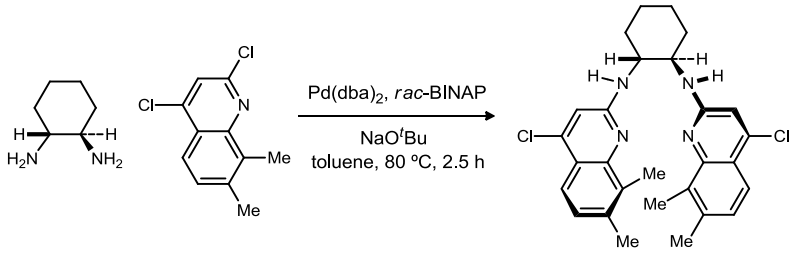


^{4}Cl^{8}OEtQuinBAM (92j). A 50 mL round bottom flask was charged with $Pd(dba)_2$ (23.7 mg, 41.3 μmol), *rac*-BINAP (25.7 mg, 41.3 μmol), sodium *tert*-butoxide (595.3 mg, 6.195 mmol), (*R*,*R*)-diaminocyclohexane (235.8 mg, 2.065 mmol), and the quinoline (1.000 g, 4.131 mmol). Toluene (14 mL) was added, and the reaction mixture was heated at 80 °C and stirred. The reaction mixture was monitored by TLC; after 2.5 h, complete conversion was observed. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and purified by column chromatography (0-20% ethyl acetate in hexanes) to provide a yellow solid (779.2 mg, 72%). mp 102.0-104.0 °C; $[\alpha]_D^{20}$ +590 (*c* 1.27, $CHCl_3$); R_f = 0.38 (25% EtOAc/hexanes); IR (film) 3238, 3069, 2980, 2931, 2859, 1608, 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.0, 0.8 Hz, 2H), 7.15 (dd, *J* = 8.0, 0.8 Hz, 2H), 7.04 (br d, *J* = 7.2 Hz, 2H), 6.59 (s, 2H), 6.57 (s, 2H), 4.27 (qd, *J* = 6.8, 2.0 Hz, 4H), 4.08-3.97 (m, 2H), 2.46-2.35 (m, 2H), 1.86-1.75 (m, 2H), 1.56 (t, *J* = 6.8 Hz, 6H), 1.49-1.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.7, 152.5, 142.0, 140.3, 122.3, 121.9, 116.3, 112.6, 111.8, 64.9, 56.9, 32.6, 24.8, 14.9; HRMS (ESI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4O_2$ $[M+H]^+$ 525.1824, found 525.1813.

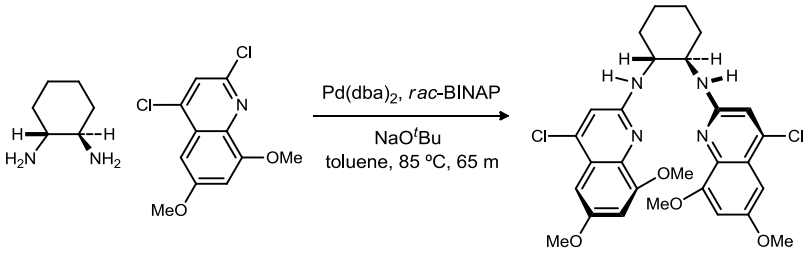


^{4}Cl^{8}EtQuinBAM (92k). A 50 mL round bottom flask was charged with $Pd(dba)_2$ (25.4 mg, 44.2 μmol), *rac*-BINAP (27.5 mg, 44.2 μmol), sodium *tert*-butoxide (637.4 mg, 6.633 mmol), (*R*,*R*)-diaminocyclohexane (252.5 mg, 2.211 mmol), and the quinoline (1.000 g, 4.423 mmol).[179] Toluene (15 mL) was added, and the reaction mixture was heated at 80 °C and stirred. The reaction mixture was monitored by TLC; after 2.5 h, complete conversion was observed. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and purified by column chromatography (0-2% ethyl acetate in hexanes) to provide a light yellow solid (660.6 mg, 61%). mp 74.0-76.0 °C; $[\alpha]_D^{20}$ +611 (*c* 1.08, $CHCl_3$); R_f = 0.53 (10% EtOAc/hexanes); IR (film) 3414, 3282, 2931, 2858, 1606, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.49 (d, *J* = 6.4 Hz, 2H), 7.23 (dd, *J* = 8.0, 7.2 Hz, 2H), 6.47 (s, 2H), 5.76 (br s, 2H), 4.16-4.04 (m, 2H), 3.29 (dq, *J* = 14.8, 7.6 Hz, 2H), 3.11 (dq, *J* = 14.8, 7.2 Hz, 2H), 2.52-2.40 (m, 2H), 1.95-1.83 (m, 2H), 1.55-1.46 (m, 2H), 1.46-1.36 (m, 2H), 1.41 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.5, 146.7, 142.7, 139.7, 129.1, 122.2, 121.9, 121.3, 111.6, 56.8, 33.1, 25.01, 24.97, 14.7; HRMS (ESI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4$ $[M+H]^+$ 493.1926, found 493.1947.

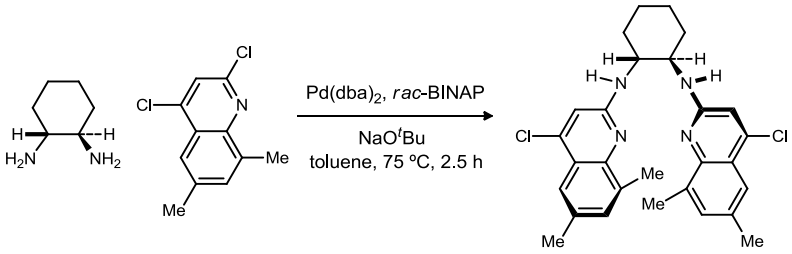
[179] Adapted from Wagaw, S.; Rennels, R.; Buchwald, S. *J Am. Chem. Soc*. **1997**, *119*, 8451-8458.



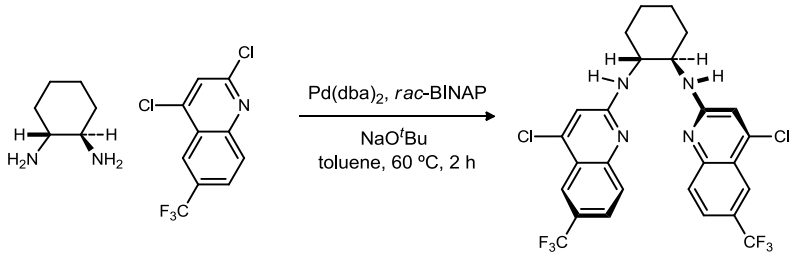
^{4}Cl^{7,8}(Me)$_2$QuinBAM (92l). A 50 mL round bottom flask was charged with Pd(dba)$_2$ (25.4 mg, 44.2 μmol), *rac*-BINAP (27.5 mg, 44.2 μmol), sodium *tert*-butoxide (637.4 mg, 6.663 mmol), (*R,R*)-diaminocyclohexane (252.5 mg, 2.211 mmol), and the quinoline (1.000 g, 4.423 mmol). Toluene (15 mL) was added, and the reaction mixture was heated at 80 °C and stirred. The reaction mixture was monitored by TLC; after 2.5 h, complete conversion was observed. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through silica gel. The filtrate was concentrated and the crude solid was rinsed with EtOAc/hexanes to provide a light yellow solid (723.8 mg, 66%). mp >260 °C; $[\alpha]_D^{20}$ +702 (*c* 1.18, $CHCl_3$); R_f = 0.49 (10% EtOAc/hexanes); IR (film) 3413, 3279, 2931, 2857, 1607, 1527 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.38 (s, 2H), 5.81 (br s, 2H), 4.17-4.03 (m, 2H), 2.66 (s, 6H), 2.50-2.39 (m, 2H), 2.47 (s, 6H), 1.95-1.80 (m, 2H), 1.55-1.46 (m, 2H), 1.46-1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.6, 147.1, 142.5, 138.4, 131.3, 125.0, 120.8, 119.5, 110.6, 56.9, 32.9, 25.1, 20.8, 13.5; HRMS (ESI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4$ $[M+H]^+$ 493.1926, found 493.1942.



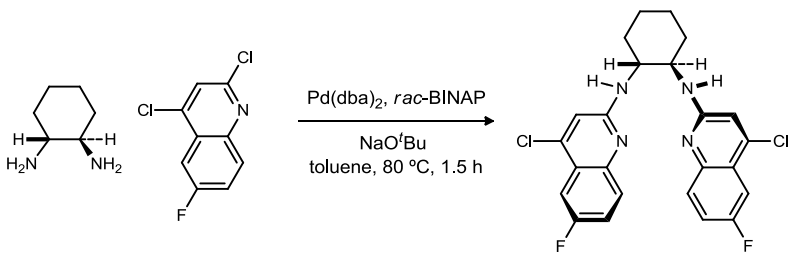
^{4}Cl^{6,8}(MeO)$_2$QuinBAM (92m). A 25 mL round bottom flask was charged with Pd(dba)$_2$ (22.3 mg, 38.7 μmol), *rac*-BINAP (24.1 mg, 38.7 μmol), sodium *tert*-butoxide (558.4 mg, 5.811 mmol), (*R,R*)-diaminocyclohexane (221.2 mg, 1.937 mmol), and the quinoline (1.000 g, 3.874 mmol). Toluene (13 mL) was added, and the reaction mixture was heated at 85 °C and stirred. The reaction mixture was monitored by TLC; after 65 min, complete conversion was observed. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and purified by column chromatography (25-30% ethyl acetate in hexanes) to provide a yellow/orange solid (775.7 mg, 72%). mp 120.0-122.0 °C; $[\alpha]_D^{20}$ +434 (*c* 1.28, $CHCl_3$); R_f = 0.09 (25% EtOAc/hexanes); IR (film) 3245, 2934, 2856, 1606, 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 2.4 Hz, 2H), 6.68 (d, *J* = 2.4 Hz, 2H), 6.57 (s, 2H), 6.09 (s, 2H), 4.01 (s, 6H), 3.98-3.90 (m, 2H), 3.88 (m, 6H), 2.42-2.28 (m, 2H), 1.86-1.70 (m, 2H), 1.52-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 154.7, 154.2, 141.2, 136.0, 122.1, 112.6, 102.2, 94.7, 56.6, 56.2, 55.4, 32.5, 24.7; HRMS (ESI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4O_4$ $[M+H]^+$ 557.1722, found 557.1738.



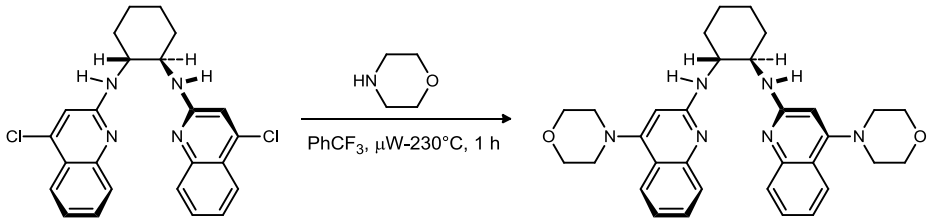
^{4}Cl^{6,8}(Me)$_2$QuinBAM (92n). A 50 mL round bottom flask was charged with Pd(dba)$_2$ (25.4 mg, 44.2 μmol), *rac*-BINAP (27.5 mg, 44.2 μmol), sodium *tert*-butoxide (637.4 mg, 6.663 mmol), (*R,R*)-diaminocyclohexane (252.5 mg, 2.211 mmol), and the quinoline (1.000 g, 4.423 mmol). Toluene (15 mL) was added, and the reaction mixture was heated at 75 °C and stirred for 2.5 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and purified by column chromatography (0-2% ethyl acetate in hexanes) to provide a yellow/brown solid (681.0 mg, 62%). mp 192.0-194.0 °C; $[\alpha]_D^{20}$ +530 (*c* 1.08, $CHCl_3$); R_f = 0.52 (10% EtOAc/hexanes); IR (film) 3414, 3279, 2926, 2857, 1604, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 2H), 7.31 (s, 2H), 6.43 (s, 2H), 5.81 (br s, 2H), 4.12-4.00 (m, 2H), 2.67 (s, 6H), 2.48-2.40 (m, 2H), 2.44 (s, 6H), 1.93-1.80 (m, 2H), 1.53-1.45 (m, 2H), 1.45-1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.1, 145.6, 142.0, 133.7, 132.8, 131.4, 121.03, 120.96, 111.5, 56.9, 32.9, 25.1, 21.3, 18.1; HRMS (ESI): Exact mass calcd for $C_{28}H_{31}Cl_2N_4$ $[M+H]^+$ 493.1926, found 493.1945.



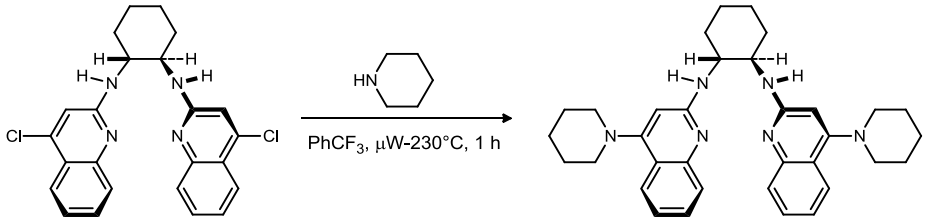
^{4}Cl^{6}CF$_3$QuinBAM (92o). A 25 mL round bottom flask was charged with $Pd(dba)_2$ (14.0 mg, 24.4 μmol), *rac*-BINAP (15.2 mg, 24.4 μmol), sodium *tert*-butoxide (352.3 mg, 3.666 mmol), (*R,R*)-diaminocyclohexane (139.5 mg, 1.222 mmol), and the quinoline (650.0 g, 2.443 mmol). Toluene (12 mL) was added, and the reaction mixture was heated at 60 °C and stirred. The reaction mixture was monitored by TLC; after 2 h, complete conversion was observed. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and purified by column chromatography (0-10% ethyl acetate in hexanes) to provide a yellow solid (285.7 mg, 41%). mp 169.0-171.0 °C; $[\alpha]_D^{20}$ +458 (*c* 1.17, $CHCl_3$); R_f = 0.16 (10% EtOAc/hexanes); IR (film) 3222, 2936, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 2H), 7.75 (s, 4H), 6.47 (s, 2H), 5.97 (br s, 2H), 4.25-4.00 (m, 2H), 2.45-2.25 (m, 2H), 1.95-1.80 (m, 2H), 1.60-1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.5, 150.1, 142.8, 126.8, 126.5, 124.4 (q, $^{2}J_{CF}$ = 33 Hz), 124.3 (q, $^{1}J_{CF}$ = 270 Hz), 122.2, 120.7, 113.2, 56.1, 32.6, 24.7; ^{19}F NMR (282 MHz, $CDCl_3$) ppm -59.8; HRMS (ESI): Exact mass calcd for $C_{26}H_{21}Cl_2F_6N_4$ $[M+H]^+$ 573.1047, found 573.1064.



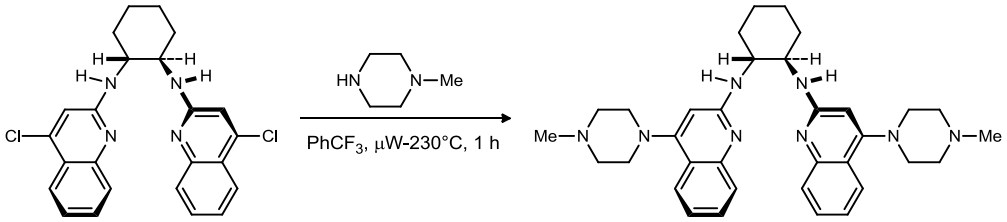
^{4}Cl^{6}FQuinBAM (92p). A 25 mL round bottom flask was charged with $Pd(dba)_2$ (14.0 mg, 24.4 μmol), *rac*-BINAP (15.2 mg, 24.4 μmol), sodium *tert*-butoxide (352.3 mg, 3.666 mmol), (*R,R*)-diaminocyclohexane (139.5 mg, 1.222 mmol), and the quinoline (527.8 mg, 2.443 mmol). Toluene (12 mL) was added, and the reaction mixture was heated at 80 °C and stirred. The reaction mixture was monitored by TLC; after 1.5 h, complete conversion was observed. The reaction was cooled to room temperature, diluted with CH_2Cl_2, and filtered through celite. The filtrate was concentrated and washed with CH_2Cl_2/hexanes to provide a yellow solid (279.6 mg, 48%). mp 210.0 °C (decomp.); $[\alpha]_D^{20}$ +330 (*c* 0.20, $CHCl_3$); R_f = 0.14 (10% EtOAc/hexanes); IR (film) 3217, 2928, 1607 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 2H), 7.57 (br d, *J* = 7.0 Hz, 2H), 7.34 (ddd, *J* = 8.5, 8.5, 2.5 Hz, 2H), 6.44 (s, 2H), 5.70 (s, 2H), 4.15-3.95 (m, 2H), 2.40-2.25 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 158.3 (d, $^{1}J_{CF}$ = 239 Hz), 156.1, 145.3, 141.5, 128.1, 121.8, 119.8 (d, $^{2}J_{CF}$ = 25 Hz), 112.9, 108.3 (d, $^{2}J_{CF}$ = 25 Hz), 56.1, 32.8, 24.8; HRMS (ESI): Exact mass calcd for $C_{24}H_{21}Cl_2F_2N_4$ $[M+H]^+$ 473.1111, found 473.1126.



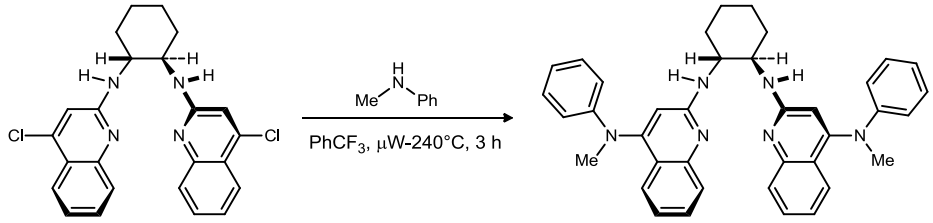
MorphoBAM (94a). A 2-5 mL microwave vial was charged with ^{4}ClBAM (94.0 mg, 214 μmol), morpholine (370 μL, 4.28 mmol), and trifluoromethylbenzene (1.4 mL). This suspension was heated at 230 °C and stirred in the microwave for 1 aAlh. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (85.6 mg, 74%). mp 254.0-256.0 °C; $[\alpha]_D^{20}$ +361 (*c* 1.08, $CHCl_3$); R_f = 0.29 (10% MeOH/0.5% AcOH/CH_2Cl_2);); IR (film) 3290, 2929, 2855, 1609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.65 (dd, *J* = 8.0, 0.8 Hz, 2H), 7.45 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 2H), 7.09 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 2H), 5.97 (br s, 2H), 5.46 (s, 2H), 4.24-4.10 (m, 2H), 3.83-3.70 (m, 8H), 2.92-2.80 (m, 4H), 2.55-2.45 (m, 4H), 2.37-2.27 (m, 2H), 1.92-1.80 (m, 2H), 1.58-1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.1, 156.5, 149.2, 129.0, 126.4, 123.2, 120.7, 119.0, 99.8, 66.8, 56.4, 52.1, 33.1, 25.0; HRMS (ESI): Exact mass calcd for $C_{32}H_{39}N_6O_2$ $[M+H]^+$ 539.3134, found 539.3114.



PipeBAM (94b). A 2-5 mL microwave vial was charged with ^{4}ClBAM (100.0 mg, 227.6 μmol), piperidine (449 μL, 4.55 mmol), and trifluoromethylbenzene (1.5 mL). This suspension was heated at 230 °C and stirred in the microwave for 1h. The reaction was then concentrated and purified by column chromatography (3-20% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (90.2 mg, 74%). mp 225.5-227.5 °C; $[\alpha]_D^{20}$ +362 (*c* 1.12, $CHCl_3$); R_f = 0.31 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3288, 2933, 2854, 1607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.62 (m, 4H), 7.42 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 2H), 7.08 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 2H), 5.80 (br s, 2H), 5.46 (s, 2H), 4.24-4.10 (m, 2H), 2.89-2.70 (m, 4H), 2.58-2.46 (m, 4H), 2.35-2.25 (m, 2H), 1.90-1.80 (m, 2H), 1.72-1.40 (m, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.4, 157.9, 149.2, 128.7, 126.3, 123.6, 120.4, 119.7, 99.6, 56.4, 53.0, 33.2, 26.0, 25.1, 24.4; HRMS (ESI): Exact mass calcd for $C_{34}H_{43}N_6$ $[M+H]^+$ 535.3549, found 535.3543.

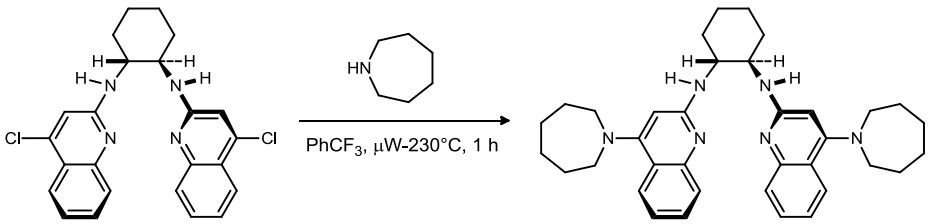


MPZBAM (94c). A 2-5 mL microwave vial was charged with ^{4}ClBAM (60.0 mg, 137 μmol), *N*-methylpiperizine (303 μL, 2.73 mmol), and trifluoromethylbenzene (900 μL). This suspension was heated at 230 °C and stirred in the microwave for 1 h. The reaction was then concentrated and diluted with CH_2Cl_2. The solution was washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (65.3 mg, 85%). mp 234.0-235.0 °C; $[\alpha]_D^{20}$ +297 (*c* 1.07, $CHCl_3$); R_f = 0.02 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3284, 2935, 2846, 2800, 1608 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (br d, *J* = 7.6 Hz, 2H), 7.66 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.43 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 2H), 7.08 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 2H), 5.94 (br s, 2H), 5.59 (s, 2H), 4.17-4.04 (m, 2H), 3.10-2.85 (m, 4H), 2.73-2.62 (m, 4H), 2.61-2.42 (m, 8H), 2.38-2.28 (m, 2H), 2.33 (s, 6H), 1.89-1.77 (m, 2H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.1, 156.7, 149.2, 128.9, 126.3, 123.3, 120.6, 119.3, 99.8, 56.5, 55.0, 51.5, 46.0, 33.1, 25.0; HRMS (ESI): Exact mass calcd for $C_{34}H_{45}N_8$ $[M+H]^+$ 565.3767, found 565.3746.



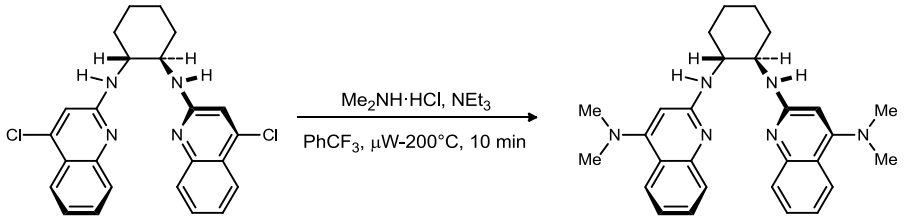
MANBAM (94d). A 2-5 mL microwave vial was charged with ^{4}ClBAM (150.0 mg, 341.0 μmol), *N*-methylaniline (1.48 mL, 13.6 mmol), and trifluoromethylbenzene (2.3

mL). This suspension was heated at 240 °C and stirred in the microwave for 3 h. The reaction was then concentrated and purified by column chromatography (0-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (111.7 mg, 57%).mp 205.0-207.0 °C; $[\alpha]_D^{20}$ +349 (*c* 1.14, $CHCl_3$); R_f = 0.30 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3405, 3266, 3059, 2930, 2857, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.4, 0.8 Hz, 2H), 7.43-7.35 (m, 4H), 7.11 (dd, *J* = 8.4, 7.2 Hz, 4H), 6.96 (ddd, *J* = 6.8, 6.8, 1.2 Hz, 2H), 6.84 (dd, *J* = 7.2, 7.2 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 4H), 6.08 (s, 2H), 5.84 (br s, 2H), 4.23-4.11 (m, 2H), 3.08 (s, 6H), 2.45-2.30 (m, 2H), 1.90-1.80 (m, 2H), 1.60-1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.2, 153.8, 149.54, 149.48, 129.3, 129.0, 126.2, 124.4, 121.2, 120.4, 120.3, 118.1, 106.4, 56.3, 41.0, 33.1, 25.0; HRMS (ESI): Exact mass calcd for $C_{38}H_{39}N_6$ $[M+H]^+$ 579.3236, found 579.3256.



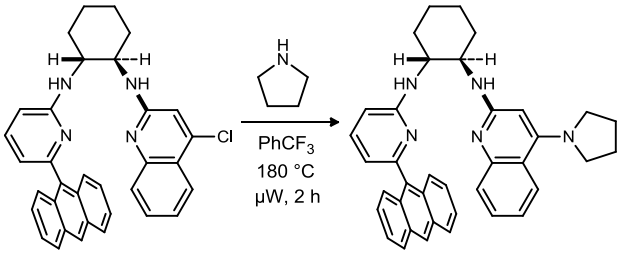
HomopipeBAM (94h). A 2-5 mL microwave vial was charged with ^{4}ClBAM (60.0 mg, 137 μmol), homopiperidine (308 μL, 2.73 mmol), and trifluoromethylbenzene (910 μL). This suspension was heated at 230 °C and stirred in the microwave for 1 h. The reaction was then concentrated and purified by column chromatography (5-10% methanol in

dichloromethane w/ 0.5% AcOH) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (62.0 mg, 81%). mp 186.0-188.0 °C; $[\alpha]_D^{20}$ +330 (*c* 0.50, $CHCl_3$); R_f = 0.31 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3303, 2928, 2854, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (br d, *J* = 8.0 Hz, 2H), 7.66 (br d, *J* = 8.4 Hz, 2H), 7.42 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 2H), 7.07 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 2H), 5.65 (br s, 2H), 5.54 (s, 2H), 4.22-4.05 (m, 2H), 3.12-3.02 (m, 4H), 2.95-2.82 (m, 4H), 2.35-2.20 (m, 2H), 1.90-1.78 (m, 2H), 1.78-1.58 (m, 16 H), 1.55-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.4, 158.3, 149.5, 128.5, 126.3, 124.2, 120.1, 119.9, 98.8, 56.4, 54.2, 33.3, 28.6, 27.3, 25.1; HRMS (ESI): Exact mass calcd for $C_{36}H_{47}N_6$ $[M+H]^+$ 563.3862, found 563.3844.



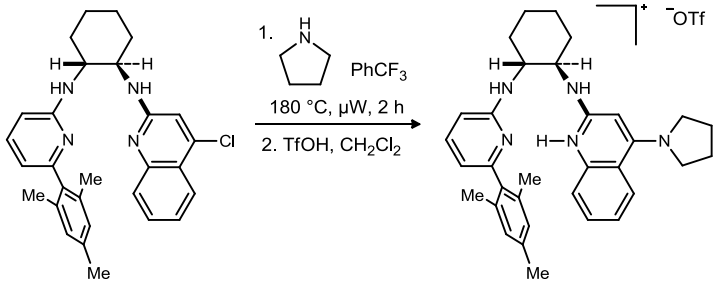
^{4}(Me$_2$N)BAM (94i). A 0.5-2.0 mL microwave vial was charged with the corresponding ^{4}ClBAM (200.0 mg, 457.3 μmol), $Me_2NH{\cdot}HCl$ (372.9 mg, 4.573 mmol), triethylamine (1.0 mL, 7.1 mmol) and trifluoromethylbenzene (1 mL). This suspension was heated at 200 °C and stirred in the microwave for 10 min. The reaction was then concentrated and purified by column chromatography (2-5% MeOH/CH_2Cl_2 w/ 0.5% AcOH). This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an off white powder (74.5 mg, 36%). mp 216.0-217.5 °C; $[\alpha]_D^{20}$ +529 (*c* 1.01, $CHCl_3$); R_f = 0.40 (10%

MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3262, 2931, 2855, 1604, 1534 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.44 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 2H), 7.10 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 2H), 5.77 (br s, 2H), 5.55 (s, 2H), 4.20-4.07 (m, 2H), 2.61 (s, 12 H), 2.47-2.37 (m, 2H), 1.89-1.78 (m, 2H), 1.55-1.39 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 158.2, 157.7, 149.4, 128.7, 126.3, 124.1, 120.4, 119.3, 98.6, 56.4, 43.5, 33.3, 25.1; HRMS (CI): Exact mass calcd for $C_{28}H_{35}N_6$ $[M+H]^+$ 455.2918, found 455.2914.



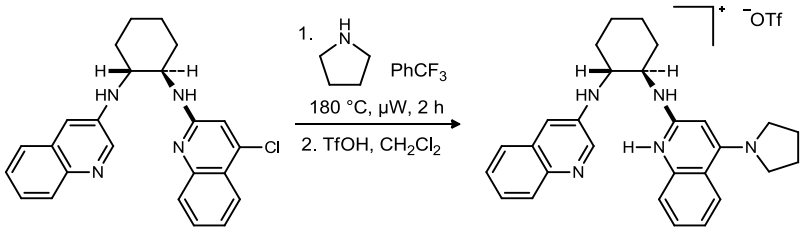
(^{6}(^{9}Anth)^{2}Pyr)-PBAM (98). A 2-5 mL microwave vial was charged with the corresponding ^{4}ClBAM (355.0 mg, 672.2 μmol), pyrrolidine (552 μL, 6.72 mmol), and trifluoromethylbenzene (3.4 mL). This suspension was heated at 180 °C and stirred in the microwave for 2 h. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane w/ 0.5% AcOH) to provide a yellow solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (285 mg, 75%). mp 151.0-153.0 °C; $[\alpha]_D^{20}$ +257 (*c* 1.09, $CHCl_3$); R_f = 0.33 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3255, 3052, 2928, 2856, 1590, 1524 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.90-7.80 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.50-7.38 (m, 4H), 7.38-7.30 (m, 2H), 7.08 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.62 (d, *J* = 7.0 Hz, 1H), 6.45-6.25 (m,

2H), 5.58 (s, 1H), 4.75-4.55 (m, 1H), 4.20-4.00 (m, 1H), 3.78-3.68 (m, 1H), 3.52-3.42 (m, 4H), 2.45-2.35 (m, 1H), 2.20-2.10 (m, 1H), 1.98-1.88 (m, 4H), 1.75-1.65 (m, 2H), 1.48-1.30 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 158.7, 157.7, 155.4, 153.6, 149.5, 136.6, 136.5, 131.4, 131.3, 129.9, 129.7, 128.8, 128.2, 128.1, 126.8, 126.6, 125.14, 125.07, 124.9 (2C), 124.8, 119.6, 118.4, 114.9, 107.1, 91.7, 56.7, 54.2, 51.8, 32.5, 32.3, 25.6, 24.8, 24.1 (1 carbon overlapping); HRMS (CI): Exact mass calcd for $C_{38}H_{38}N_5$ $[M+H]^+$ 564.3122, found 564.3120.



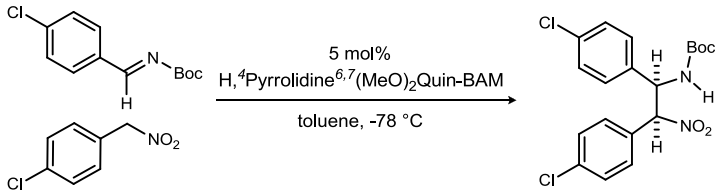
(^{6}Mes^{2}Pyr)-PBAM·HOTf (99·HOTf). A 0.5-2.0 mL microwave vial was charged with the corresponding ^{4}ClBAM (95.0 mg, 202 μmol), pyrrolidine (166 μL, 2.02 mmol), and trifluoromethylbenzene (200 μL). This suspension was heated at 180 °C and stirred in the microwave for 2 h. The reaction was then concentrated and purified by column chromatography (5-15% methanol in dichloromethane w/ 0.5% AcOH). This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a light brown powder (106.5 mg, >99%). mp 108.0-110.0 °C; $[\alpha]_D^{20}$ +8.3 (*c* 0.58, $CHCl_3$); R_f = 0.35 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3298, 2934, 2866, 1646, 1608 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$,325K) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.76 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.56-7.46 (m, 2H), 7.25-7.18 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.82 (s, 2H), 6.37 (d, *J* = 7.2

Hz, 1H), 5.78 (s, 1H), 3.93-3.80 (m, 2H), 3.79-3.64 (m, 4H), 2.26 (s, 3H), 2.15-2.05 (m, 1H), 2.06 (s, 6H), 1.90-1.40 (11H), 2NH, HOTf *not observed*; ^{13}C NMR (150 MHz, $CDCl_3$, 325 K) ppm 176.7, 155.5, 155.3, 151.9, 142.3, 139.1, 138.5, 135.8, 131.9, 128.5, 125.8, 123.5, 122.9, 120.4 (q, $^1J_{CF}$ = 317 Hz), 118.6, 115.7, 113.7, 108.2, 85.1, 57.2, 56.6, 53.0, 32.01, 31.97, 25.8, 24.5, 24.3, 21.0, 19.5, 1C *broadened/overlapping*; ^{19}F NMR (282 MHz, $CDCl_3$) ppm -76.6; HRMS (ESI): Exact mass calcd for $C_{33}H_{40}N_5$ [M-CF_3SO_3]$^+$ 506.3284, found 506.3267.



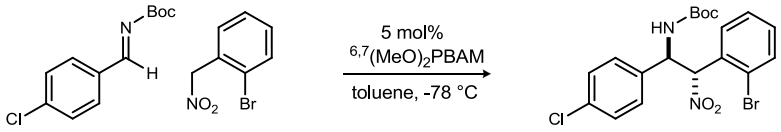
^{3}QuinPBAM·HOTf (100·HOTf). A 0.5-2.0 mL microwave vial was charged with the corresponding ^{4}ClBAM (71.4 mg, 177 μmol), pyrrolidine (146 μL, 1.77 mmol), and trifluoromethylbenzene (830 μL). This suspension was heated at 180 °C and stirred in the microwave for 2 h. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane w/ 0.5% AcOH) to provide a light brown solid (50.0 mg, 65%). To a stirring CH_2Cl_2 solution of this material was added 1 equivalent of triflic acid. The solution was concentrated to leave a yellow/brown solid. Mp 131.0-133.0 °C; $[\alpha]_D^{20}$ +170 (*c* 0.55, $CHCl_3$); R_f = 0.34 (10% MeOH/0.5% AcOH/CH_2Cl_2); IR (film) 3309, 2938, 2865, 1643, 1610, 1525 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.78 (br s, 1H), 8.40 (d, *J* = 1.2 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.55 (br d, *J* = 7.2 Hz, 1H), 7.41-7.32 (m, 2H), 7.29 (dd, *J* = 7.2 Hz, 1H), 7.27-7.21 (m, 2H), 7.10 (dd, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.55 (br s, 1H), 4.85 (br s,

1H), 3.90-3.70 (m, 1H), 3.70-3.30 (m, 5H), 2.12-2.01 (m, 2H), 1.94-1.80 (m, 4H), 1.80-1.70 (m, 2H), 1.68-1.54 (m, 2H), 1.48-1.30 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.4, 151.8, 142.0, 139.6, 137.8, 137.2, 131.5, 129.8, 127.6, 126.6, 126.0, 125.7, 124.6, 122.8, 120.3 (q, $^1J_{CF}$ = 318 Hz), 118.1, 115.4, 114.5, 85.8, 57.02, 56.97, 52.6, 32.3, 31.7, 25.6, 24.6, 24.4; ^{19}F NMR (282 MHz, $CDCl_3$) ppm -76.4; HRMS (ESI): Exact mass calcd for $C_{28}H_{32}N_5$ $[M\text{-}CF_3SO_3]^+$ 438.2658, found 438.2649.

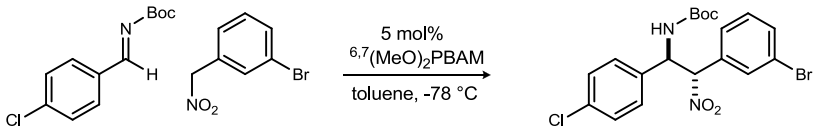


***tert*-Butyl (1*R*,2*S*)-1,2-bis(4-chlorophenyl)-2-nitroethylcarbamate (101).** Imine (1.5000 g, 6.2580 mmol) and H,^{4}Pyrrolidine^{6,7}(MeO)$_2$Quin-BAM (196.1 mg, 312.9 μmol) were dispensed into a 100 mL round bottom flask equipped with stir bar. Toluene (63 mL) was added and the mixture was chilled to -78 °C before addition of the nitroalkane **9** (1.1810 g, 6.8840 mmol). The reaction was stirred at -78 °C for 24 h. The reaction was kept at the reaction temperature and filtered directly through a pad of silica gel with CH_2Cl_2. The filtrate was concentrated to give 2.2772 g of a white solid that was 6:1 *anti*:*syn*. A portion (1.1000 g) of this material was recrystallized from toluene to provide colorless crystals. The crystalline material (586.8 mg) was separated from the mother liquor and found to be >200:1 dr, 97% ee by chiral HPLC; (Chiralcel AD-H, 12% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) = 30.5 min, t_r(*anti*, minor) = 12.8 min, t_r(*syn*, major) = 14.9 min, t_r(*syn*, minor) = 45.6 min). Mp 172.0-174.0 °C; $[\alpha]_D^{20}$ -150 (*c* 0.13, $CHCl_3$); R_f = 0.24 (20% EtOAc/hexanes); IR (film) 3381, 2982, 1682, 1551, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.35 (d,

J = 8.4 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 5.76 (d, *J* = 9.6 Hz, 1H), 5.58 (dd, *J* = 9.6, 9.6 Hz, 1H), 4.78 (d, *J* = 9.6 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 136.6, 135.6, 134.9, 130.1, 129.7, 129.3, 129.1, 128.6, 93.2, 80.8, 56.1, 28.0; HRMS (CI): Exact mass calcd for $C_{19}H_{21}Cl_2N_2O_4$ $[M+H]^+$ 411.0873, found 411.0865.

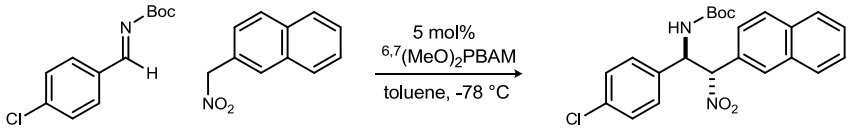


***tert*-butyl (1*R*,2*S*)-2-(2-bromophenyl)-1-(4-chlorophenyl)-2-nitroethylcarbamate (101b).** According to the general procedure, column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (41.4 mg, 91%) that was found to be 76% ee and 4:1 dr by chiral HPLC; (Chiralcel AD-H, 10% *i*PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 8.7 min, t_r(*anti*, minor) = 16.8 min, t_r(*syn*, major) = 14.5 min, t_r(*syn*, minor) = 25.1 min); Mp 143.0-145.0 °C; R_f = 0.46 (20% EtOAc/hexanes); IR (film) 3500-3250 (broad), 2979, 2930, 1704, 1556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.40 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.38-7.26 (m, 5H), 6.44 (d, *J* = 10.4 Hz, 1H), 5.70 (br s, 1H), 4.92 (br s, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 153.9, 135.8, 134.8, 133.0, 131.5, 131.0, 129.3, 128.9, 128.6, 128.2, 125.5, 91.6, 80.5, 56.2, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M+Na]^+$ 477.0193, found 477.0169.



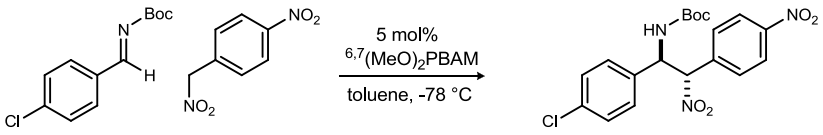
***tert*-Butyl (1*R*,2*S*)-2-(3-bromophenyl)-1-(4-chlorophenyl)-2-nitroethylcarbamate (101c).** According to the general procedure, column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 91%) that was found to be 89% ee

and 13:1 dr by chiral HPLC; (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 29.7 min, t_r(*anti*, minor) = 14.6 min, t_r(*syn*, major) = 13.4 min, t_r(*syn*, minor) = 17.2 min); Mp 178.0-179.0 °C; $[\alpha]_D^{20}$ -39 (*c* 0.15, $CHCl_3$); R_f = 0.40 (20% EtOAc/hexanes); IR (film) 3388, 2982, 1681, 1549, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.58 (ddd, *J* = 8.0, 1.6, 0.8 Hz, 1H), 7.52 (br d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.29 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 5.75 (br s, 1H), 5.56 (br m, 1H), 4.87 (br s, 1H), 1.29 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) ppm 154.2, 135.6, 134.9, 133.5, 133.3, 131.8, 130.4, 129.3, 128.6, 127.2, 122.8, 93.1, 80.8, 56.3, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M+Na]^+$ 477.0193, found 477.0197.

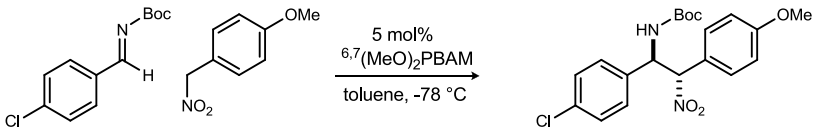


***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-(naphthalen-2-yl)-2-nitroethylcarbamate (101d).** According to the general procedure, column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (42.1 mg, 99%) that was found to be 80% ee and 10:1 dr by chiral HPLC; (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 53.9 min, t_r(*anti*, minor) = 18.0 min, t_r(*syn*, major) = 16.7 min, t_r(*syn*, minor) = 26.3 min); Mp 185.5-187.0 °C; $[\alpha]_D^{20}$ -27 (*c* 0.15, $CHCl_3$); R_f = 0.32 (20% EtOAc/hexanes); IR (film) 3388, 2980, 1683, 1550, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.92-7.85 (m, 3H), 7.65 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.59-7.52 (m, 2H), 7.38-7.32 (m, 4H), 5.95 (br d, *J* = 8.8 Hz, 1H), 5.72 (br dd, *J* = 9.2, 9.2 Hz, 1H), 4.86 (d, *J* = 8.8 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.1, 134.7, 134.0, 132.8, 129.3, 129.2, 129.0, 128.7, 128.6, 128.3, 127.7, 127.4, 126.9, 124.6,

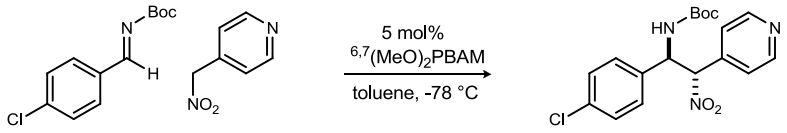
94.2, 80.7, 56.0, 28.0; HRMS (ESI): Exact mass calcd for $C_{23}H_{23}ClN_2NaO_4$ $[M+Na]^+$ 449.1244, found 449.1256.



***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitro-2-(4-nitrophenyl)ethylcarbamate (101e).** According to the general procedure, column chromatography (15-30% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 99%) that was found to be 76% ee and 2:1 dr by chiral HPLC; (Chiralcel IA, 10% EtOH/hexanes, 1 mL/min, t_r(*d*$_1$, major) 9.8 min, t_r(*d*$_1$, minor) = 12.6 min, t_r(*d*$_2$, major) = 21.5 min, t_r(*d*$_2$, minor) = 52.8 min); Mp 165.5-166.0 °C; R_f = 0.07 (10% EtOAc/hexanes); IR (film) 3405, 2981, 2926, 1681, 1551, 1522 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) ***d*$_1$** δ 8.35 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 11.2 Hz, 1H), 5.57 (dd, *J* = 10.8, 10.8 Hz, 1H), 1.14 (s, 9H); ***d*$_2$** δ 8.13 (d, *J* = 8.8 Hz, 2H), 8.13-8.07 (1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.20 (d, *J* = 11.2 Hz, 1H), 5.69 (dd, *J* = 10.4, 10.4 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 154.5, 154.2, 148.5, 148.3, 138.3, 137.9, 136.9, 136.1, 133.2, 132.6, 130.3, 130.2, 129.8, 129.6, 128.8, 128.5, 123.9, 123.7, 92.2, 91.9, 78.9 (2C), 56.3, 55.6, 28.0, 27.7. HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClN_3NaO_6$ $[M+Na]^+$ 444.0938, found 444.0952.

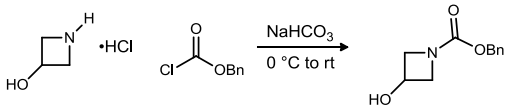


***tert*-Butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-(4-methoxyphenyl)-2-nitroethylcarbamate (101f).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (36.5 mg, 90%) that was found to be 86% ee and 17:1 dr by chiral HPLC; (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major) 27.6 min, t_r(*anti*, minor) = 14.3 min, t_r(*syn*, major) = 16.7 min, t_r(*syn*, minor) = 37.9 min); Mp 165.0-166.0 °C; $[\alpha]_D^{20}$ -9.1 (*c* 0.11, $CHCl_3$); R_f = 0.27 (20% EtOAc/hexanes); IR (film) 3385, 2981, 1683, 1552, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.68 (br s, 1H), 5.58 (br s, 1H), 4.85 (br s, 1H), 3.82 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 161.1, 154.3, 136.2, 134.6, 130.1, 129.1, 128.6, 123.2, 114.3, 93.6, 80.6, 56.1, 55.4, 28.1. HRMS (ESI): Exact mass calcd for $C_{20}H_{23}ClN_2NaO_5$ $[M+Na]^+$ 429.1193, found 429.1211.

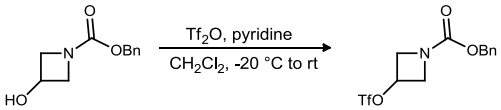


***tert*-butyl (1*R*,2*S*)-1-(4-chlorophenyl)-2-nitro-2-(pyridin-4-yl)ethylcarbamate (101g).** According to the general procedure, column chromatography (7-25% ethyl acetate in hexanes) afforded a yellow solid (21.7 mg, 57%) that was found to be 71% and 67% ee (major and minor diastereomer respectively) and 1.4:1 dr by chiral HPLC; (Chiralcel AD-H, 10% EtOH/hexanes, 1 mL/min, t_r(*anti*, major) 13.3 min, t_r(*anti*, minor) = 9.0 min, t_r(*syn*, major) = 19.1 min, t_r(*syn*, minor) = 39.4 min); Mp 145.0-146.5 °C; R_f = 0.10 (40%

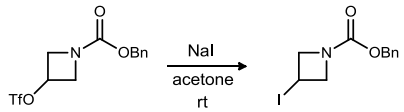
EtOAc/hexanes); IR (film) 3300, 2979, 2932, 1710, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) ***d₁*** δ 8.70 (br s, 2H), 7.48 (br s, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.81 (br s, 1H), 5.58 (br s, 1H), 4.95 (br s, 1H), 1.26 (s, 9H); ***d₂*** δ 8.63 (br s, 1H), 7.32-7.25 (m, 4H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.89 (br s, 1H), 5.67 (br s, 1H), 5.60-5.50 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.1 (2C), 150.5, 150.4, 139.7, 139.6, 135.1, 135.0, 134.6 (2C), 129.4, 129.3, 128.6, 128.1, 123.2, 122.2, 92.8, 92.6, 81.0 (2C), 56.7, 56.3, 28.1, 28.0.



Benzyl 3-hydroxyazetidine-1-carboxylate (112). 3-Hydroxyazetidine hydrochloride (5.000 mg, 45.64 mmol) was dissolved in 50 mL of deionized water. Sodium bicarbonate (17.43 g, 207.5 mmol) was added at room temperature. The stirring mixture was chilled to 0 °C, then benzylchloroformate (7.078 g, 41.49 mmol) was added. The reaction mixture was allowed to warm gradually to room temperature overnight. The reaction mixture was diluted with water before extraction with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated to a slightly golden oil (8.208 g, 95%). R_f = 0.14 (50% EtOAc/hexanes); IR (film) 3405, 2951, 2881, 1683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.08 (s, 2H), 4.58 (br s, 1H), 4.20 (dd, *J* = 10.0, 6.5 Hz, 2H), 3.87 (dd, *J* = 10.0, 4.5 Hz, 2H), 3.04 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 156.5, 136.5, 128.5, 128.1, 127.9, 66.8, 61.7, 59.1; HRMS (EI): Exact mass calcd for $C_{11}H_{13}NO_3$ $[M]^+$ 207.0890, found 207.0884.

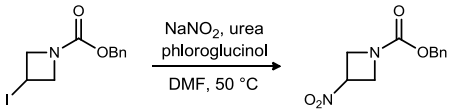


Benzyl 3-(trifluoromethylsulfonyloxy)azetidine-1-carboxylate (112b). The following is modified from the procedure of Watanabe *et al*., *Tetrahedron*, **2008**, *64*, 4072. To a stirring solution of benzyl 3-hydroxyazetidine-1-carboxylate (1.000 g, 4.826 mmol), pyridine (778 μL, 9.652 mmol), and CH_2Cl_2 (24 mL) was added trifluoromethanesulfonic anhydride (974 μL, 5.791 mmol) dropwise at -20 °C. The reaction was allowed to gradually warm to room temperature while stirring. The reaction mixture was concentrated then dissolved in ethyl acetate. The organic solution was washed with water, then sat aq $NaHCO_3$, then brine before drying with $MgSO_4$. A golden oil was obtained (1.539 g, 94%). R_f = 0.30 (20% EtOAc/hexanes); IR (film) 3354, 3262, 2958, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.47-5.40 (m, 1H), 5.11 (s, 3H), 4.41 (ddd, *J* = 11.2, 6.8, 0.8 Hz, 2H), 4.25 (ddd, *J* = 10.8, 4.0, 0.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 155.9, 135.9, 128.5, 128.3, 128.1, 118.3 (q, *J* = 319.5 Hz), 74.3, 67.3, 56.5; HRMS (EI): Exact mass calcd for $C_{12}H_{12}F_3NO_5S$ $[M]^+$ 339.0383, found 339.0389.

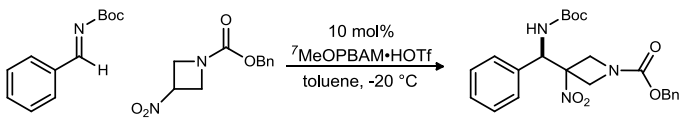


Benzyl 3-iodoazetidine-1-carboxylate (114). The triflate (142.2 mg, 419 μmol) was dissolved in acetone (1 mL) in a vial equipped with a stir bar. Sodium iodide (125.6 mg, 838 μmol) was then added and the reaction was stirred at room temperature for 2 h. The reaction was then filtered through silica with CH_2Cl_2. The filtrate was filtered to remove the precipitated solid. That precipitated solid was washed with CH_2Cl_2 and the combined organic layers were concentrated to a red oil (118.2 mg, 89%); R_f = 0.25 (20%

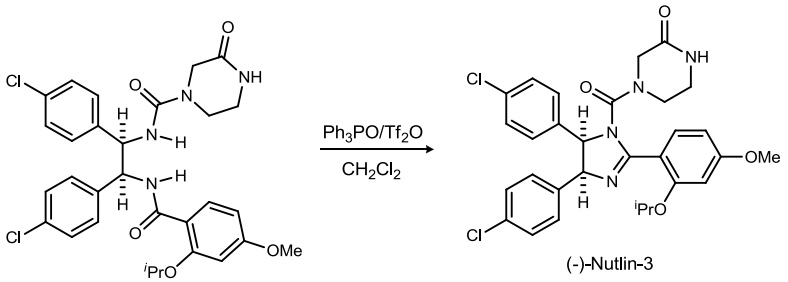
EtOAc/hexanes); IR (film) 2953, 2884, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 5.10 (s, 2H), 4.73 (dd, *J* = 9.2, 7.6 Hz, 2H), 4.50 (tt, *J* = 7.6, 5.2 Hz, 1H), 4.36 (dd, *J* = 10.4, 5.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 155.7, 136.2, 128.5, 128.2, 128.0, 67.0, 61.6; HRMS (ESI): Exact mass calcd for $C_{11}H_{12}INNaO_2$ $[M+Na]^+$ 339.9811, found 339.9821.



Benzyl 3-nitroazetidine-1-carboxylate (116). To a solution of the iodide (457.3 mg, 1.442 mmol) in DMF (7.2 mL) was added urea (173.3 mg, 2.884 mmol), then phloroglucinol (181.8 mg, 1.442 mmol), then sodium nitrite (497.6 mg, 7.211 mmol). The reaction was then heated to 50 °C and stirred for 19 h. The reaction was then poured onto water and extracted with ethyl acetate, and the combined organic layers were then washed with water, dried over $MgSO_4$, and concentrated. The resulting oil was purified by column chromatography (10-20% ethyl acetate in hexanes) to provide the nitro azetidine as a white solid (136.4 mg, 40%). Mp 90.0-92.0 °C; R_f = 0.35 (40% EtOAc/hexanes); IR (film) 2959, 1713, 1557 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.19-5.12 (m, 1H), 5.13 (s, 2H), 4.49 (dd, *J* = 10.4, 4.8 Hz, 2H), 4.42 (dd, *J* = 10.4, 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 155.8, 135.9, 128.5, 128.3, 128.1, 71.6, 67.3, 54.1; HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_2O_4$ $[M]^+$ 236.0792, found 236.0784.



(*R*)-benzyl 3-((*tert*-butoxycarbonylamino)(phenyl)methyl)-3-nitroazetidine-1-carboxylate (117). Imine (20.5 mg, 100 μmol) and ^{7}MeOPBAM·HOTf (7.2 mg, 10 μmol) were dispensed into a flame dried vial with a stir bar. The two compounds were then stirred in toluene (100 μL) at room temperature until homogeneous. The reaction mixture was chilled to -20 °C before the nitroazetidine (23.6 mg, 100 μmol) was added. The reaction was stirred for 20 h, and then filtered through a pad of silica gel using CH_2Cl_2 and EtOAc and concentrated. Flash column chromatography (SiO_2, 12-20% ethyl acetate in hexanes) of the residue yielded the addition product as a colorless solid (19.2 mg, 87%); the major product was determined to be 92% ee by chiral HPLC analysis (Chiralcel IA, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(major) = 17.8 min, t_r(minor) = 15.4 min; mp 134.0-136.0 °C; $[\alpha]_D^{20}$ +6.82 (*c* 1.10, $CHCl_3$); R_f = 0.24 (20% EtOAc/hexanes); IR (film) 3325, 2978, 2932, 1714, 1549 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.30 (m, 8H), 7.20-7.10 (m, 2H), 5.76 (br s, 1H), 5.50 (d, *J* = 9.5 Hz, 1H), 5.11 (s, 2H), 4.57 (d, *J* = 10.5 Hz, 1H), 4.47 (d, *J* = 10.0 Hz, 1H), 4.42 (d, *J* = 10.5 Hz, 1H), 4.37 (d, *J* = 10.5 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.9, 155.2, 135.8, 134.6, 129.1, 129.0, 128.5, 128.3, 128.1, 126.4, 85.9, 81.0, 67.4, 57.4, 56.7, 28.2; HRMS (ESI): Exact mass calcd for $C_{23}H_{27}N_3NaO_6$ $[M+Na]^+$ 464.1798, found 464.1776.



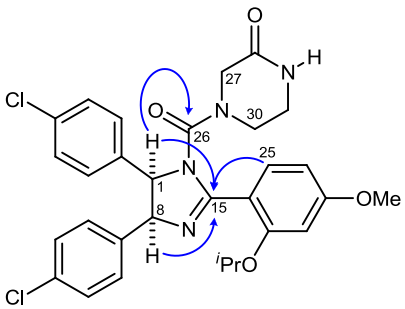
(-)-Nutlin-3 (124).[180] Tf_2O (28.1 μL, 166.8 μmol) was added to a stirred solution of Ph_3PO (92.8 mg, 333.6 μmol) in CH_2Cl_2 (500 μL) at 0 °C. The mixture was stirred for 10 min before urea (50.0 mg, 83.4 μmol) was added as a solution in CH_2Cl_2 (600 μL), and the reaction was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature before addition of aq. $NaHCO_3$. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Column chromatography (0-4% methanol in dichloromethane) of the residue provided the compound as a white solid (42.5 mg, 88%). Mp 127.0-129.0 °C; $[\alpha]_D^{20}$ -150 (*c* 0.13, $CHCl_3$); R_f = 0.24 (5% MeOH/CH_2Cl_2); IR (film) 3229, 2980, 2935, 2247, 1678, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 6.54 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.47 (br s, 1H), 5.55 (d, *J* = 9.6 Hz, 1H), 5.47 (d, *J* = 9.6 Hz, 1H), 4.60 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.75 (d, *J* = 18.0 Hz, 1H), 3.62 (d, *J* = 18.0 Hz, 1H), 3.40-3.31 (m, 1H), 3.23-3.13 (m, 1H), 2.97 (br s, 2H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.0, 160.2, 157.0, 154.7, 136.0, 135.0, 133.1, 132.8, 132.1, 129.2, 128.4, 128.1, 127.9, 113.4, 104.6, 100.1, 71.7, 70.9, 69.1, 55.5, 49.4, 41.8,

[180] Adapted from Pemberton, N.; Pinkner, J. S.; Edvinsson, S.; Hultgren, S. J.; Almqvist, F. *Tetrahedron* **2008**, *64*, 9368-9376.

40.3, 20.03, 20.01; HRMS (CI): Exact mass calcd for $C_{30}H_{31}Cl_2N_4O_4$ $[M+H]^+$ 581.1717, found 581.1705.

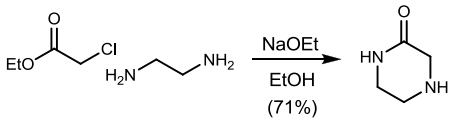
This enantiomer corresponded to "enantiomer-a" using the HPLC conditions as described previously.[181] The compound was found to be 99% ee; (Chiralcel OD, 30% iPrOH/hexanes, 1 mL/min, t_r(major) = 8.6 min, t_r(minor) = *not observed*). Additionally, the (+)-enantiomer was prepared using an identical procedure with (*S*,*S*)-H,[4]PyrrolidineQuin-BAM to form compound **7** (84% ee), which was converted to (+)-Nutlin-3. This compound correlated with "enantiomer-b". and was found to be 85% ee; (Chiralcel OD, 30% iPrOH/hexanes, 1 mL/min, t_r(major) = 10.5 min, t_r(minor) = 8.6 min).

Figure 46. Nutlin-3 HMBC Correlations (600 MHz)

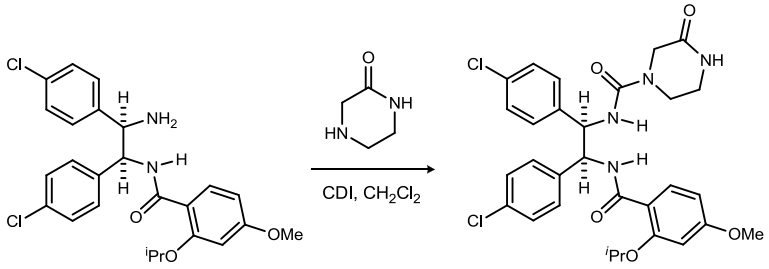


Further evidence supporting the structural assignment includes an HMBC (Figure 46), which clearly showed the anticipated couplings for Nutlin-3. C26 (155 ppm) Showed correlations to H27/H27` and H30/H30' and to H1 (but not H8). C15 (160 ppm) Showed correlations to both of the imidazoline methines (H1 and H8) and also to the H25.

[181] Wang, Z.; Jonca, M.; Lambros, T.; Ferguson, S.; Goodnow, R. *J. Pharm. Biomed. Anal.* **2007**, *45*, 720-729.



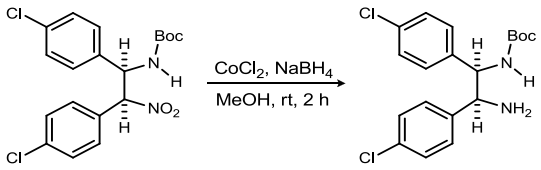
2-Oxo-piperazine (134)[182]. The resulting orange oil was purified by column chromatography (10% MeOH in CH_2Cl_2 w/ 1% NH_4OH). A yellow solid (2.8634 g, 71%) was obtained that was sufficiently pure by ^1H NMR. R_f = 0.07 (10% MeOH/CH_2Cl_2 w/ 1% NH_4OH); IR (film) 3400, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (br s, 1H), 3.46 (s, 2H), 3.35-3.28 (m, 2H), 2.98 (t, *J* = 5.5 Hz, 2H), 1.89 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.4, 49.6, 42.7, 42.2; HRMS (CI): Exact mass calcd for $C_4H_9N_2O$ $[M+H]^+$ 101.0709, found 101.0714.



***N*-((1*R*,2*S*)-1,2-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carbox-amide (135).** Amine (100.0 mg, 211.2 μmol) was dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature. CDI (41.1 mg, 253.5 μmol) was added and the reaction was stirred for 1 h. 2-Oxo-piperazine (42.3 mg, 422.4 μmol) was added, and the reaction mixture was stirred for an additional 4 hours. The reaction mixture was concentrated and purified by column chromatography (0-2-5% methanol in dichloromethane) to provide a white solid (119.6 mg, 94%). $[\alpha]_D^{20}$ +110 (*c* 0.14, $CHCl_3$);

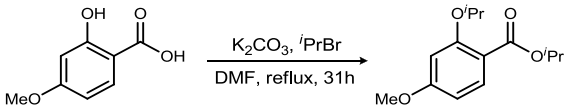
[182] Elmaleh, D. R.; Choi, S.-W. U.S. Patent 6,835,371, December 28, 2004.

R_f = 0.34 (10% MeOH/CH_2Cl_2); IR (film) 3369, 2978, 2932, 2243, 1634, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 4.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.62 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.15 (br s, 1H), 5.77 (dd, *J* = 7.6, 2.0 Hz, 1H), 5.10 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.66 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.15 (d, *J* = 2.4 Hz, 2H), 3.86 (s, 3H), 3.73 (ddd, *J* = 13.2, 5.6, 4.4 Hz, 1H), 3.60 (ddd, *J* = 13.2, 6.4, 4.4 Hz, 1H), 3.46-3.35 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.0, 167.0, 163.0, 157.2, 155.9, 136.7, 136.6, 134.3, 133.8, 133.2, 129.4, 128.6, 128.4, 128.0, 113.5, 105.4, 100.3, 71.4, 61.6, 57.5, 55.5, 47.4, 40.9, 39.9, 21.9, 21.5; HRMS (CI): Exact mass calcd for $C_{30}H_{33}Cl_2N_4O_5$ $[M+H]^+$ 599.1823, found 599.1814.



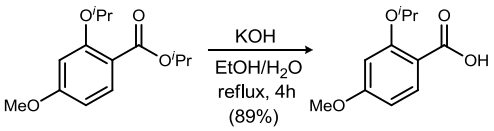
***tert*-Butyl (1*R*,2*S*)-2-amino-1,2-bis(4-chlorophenyl)ethylcarbamate (136).** The nitroalkane (411.3 mg, 1.000 mmol) was dissolved in MeOH (4.0 mL) at room temperature. $CoCl_2$ (129.8 mg, 1.000 mmol) was added and the reaction mixture was chilled to 0 °C before $NaBH_4$ (567.6 mg, 15.00 mmol) was added in three portions over 40 min. The reaction mixture was stirred at 0 °C for an additional 30 min before the mixture was quenched with sat. aq. NH_4Cl. The reaction mixture was adjusted to pH 10 with conc. aq. NH_4OH. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Column chromatography (25-45% ethyl acetate in hexanes) of the residue afforded the product as a white solid (251.7 mg, 66%). Mp 149.0-150.0 °C; $[\alpha]_D^{20}$

+67 (*c* 0.12, $CHCl_3$); R_f = 0.12 (50% EtOAc/hexanes); IR (film) 3377, 2981, 1683, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.49 (d, *J* = 7.6 Hz, 1H), 4.79 (br s, 1H), 4.23 (br s, 1H), 1.50 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 140.3 (2C), 133.3, 133.2, 128.7, 128.4, 128.2 (2C), 79.8, 59.5, 59.1, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{23}Cl_2N_2O_2$ $[M+H]^+$ 381.1137, found 381.1147.

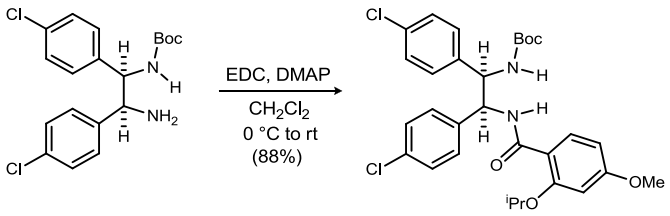


Isopropyl 2-isopropoxy-4-methoxybenzoate (137).[183] Isopropyl bromide (2.926 g, 23.79 mmol) was added to a stirred mixture of 4-methoxysalicylic acid (1.000 g, 5.947 mmol), K_2CO_3 (3.286 g, 23.79 mmol), and dry DMF (30 mL) at room temperature. The mixture was allowed to stir for 20 min before heating to reflux for 31 h. The reaction mixture was cooled to room temperature, treated with KI (98.7 mg, 595 μmol) and stirred for 17 h. The reaction was quenched with 1 M aq HCl then extracted with diethyl ether. The combined organic layers were washed with 1 M aq Na_2CO_3, water, then brine before drying over $MgSO_4$. Concentration of the dried organic layers resulted in a bronze oil (1.0549 g, 70%) that was pure by ^1H NMR. R_f = 0.16 (5% EtOAc/hexanes); IR (film) 2979, 2936, 1721, 1694, 1608, 1575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 1H), 6.49-6.43 (m, 2H), 5.20 (heptet, *J* = 6.4 Hz, 1H), 4.55 (heptet, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 1.36 (d, *J* = 6.0 Hz, 6H), 1.33 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.8, 163.5, 159.3, 133.4, 114.9, 104.9, 101.8, 71.5, 67.5, 55.4, 22.0 (2C); HRMS (CI): Exact mass calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1434, found 253.1431.

[183]Adapted from: Hattori, T.; Shimazumi, Y.; Goto, H.; Yamabe, O.; Morohashi, N.; Kawai, W.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2099-2108.

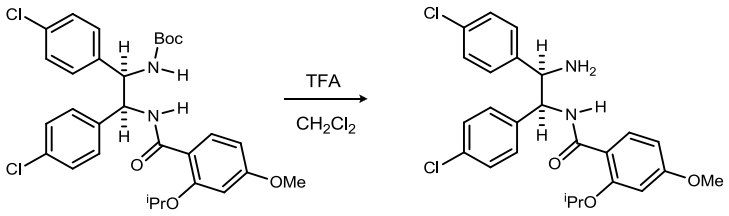


2-Isopropoxy-4-methoxybenzoic acid (138).[135] Ester (985.0 mg, 3.904 mmol) was boiled with KOH (703.8 mg, 12.54 mmol) in a mixture of ethanol (11.7 mL) and water (2.3 mL) for 4 h. EtOH was then removed by evaporation. The remaining material was diluted with water and treated with 3 M HCl until precipitation occurred. The suspension was then extracted with diethyl ether. The combined organic layers were washed with brine before drying over $MgSO_4$. The solution was concentrated to a red oil (733.2 mg, 89%) that was pure by ^{1}H NMR. R_f = 0.33 (50% EtOAc/hexanes); IR (film) 3261, 2981, 1730, 1608 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.91 (br s, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 6.62 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 4.81 (heptet, *J* = 6.5 Hz, 1H), 3.86 (s, 3H), 1.47 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.5, 164.9, 157.8, 135.4, 111.4, 106.8, 100.7, 73.9, 55.7, 21.9; HRMS (ESI): Exact mass calcd for $C_{11}H_{14}NaO_4$ $[M+Na]^+$ 233.0790, found 233.0795.



***tert*-Butyl (1*R*,2*S*)-1,2-bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethylcarbamate (139).** The amine (170.0 mg, 445.8 μmol) and carboxylic acid (93.7 mg, 445.8 μmol) were dissolved in CH_2Cl_2 (2.2 mL) at room temperature. The solution was chilled to 0 °C and EDC (111.1 mg, 579.6 μmol) and DMAP (5.4 mg, 44.6 μmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 16 h, the reaction mixture was diluted with

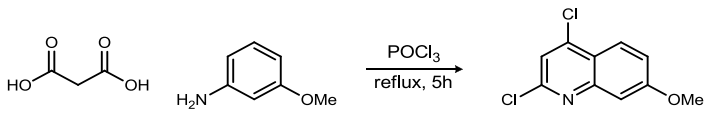
water and extracted with CH_2Cl_2. The combined organic layers were washed once with water, dried over $MgSO_4$, and concentrated. The resulting white solid was washed with CH_2Cl_2 and hexanes, leaving a white solid (224.5 mg, 88%) that was pure by NMR. Mp 239.0-241.0 °C (decomp.); $[\alpha]_D^{20}$ -29 (*c* 0.13, $CHCl_3$); R_f = 0.13 (20% EtOAc/hexanes); IR (film) 3355, 2976, 1680, 1629, 1607, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.2 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.59 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.91 (br s, 1H), 5.78 (br s, 1H), 5.07 (br s, 1H), 4.75-4.60 (m, 1H), 3.84 (s, 3H), 1.38 (s, 9H), 1.30-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.6, 163.6, 157.2, 155.0, 136.9, 136.7, 134.2, 133.6, 133.3, 128.6 (2C), 128.5, 128.3, 114.1, 105.2, 100.2, 79.9, 71.4, 59.5, 56.6, 55.5, 28.3, 22.0, 21.6; HRMS (ESI): Exact mass calcd for $C_{30}H_{34}Cl_2N_2NaO_5$ $[M+Na]^+$ 595.1742, found 595.1743.



***N*-((1*S*,2*R*)-2-Amino-1,2-bis(4-chlorophenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (140).** Amide (180.0 mg, 313.9 μmol) was dissolved in CH_2Cl_2 (3.1 mL). TFA (932 μL, 12.6 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into satd. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered,

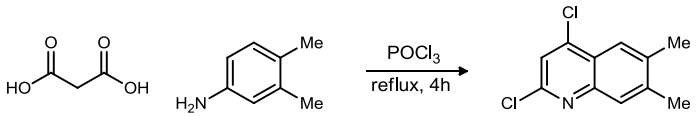
and concentrated to a light brown foam (130.3 mg, 88%). $[\alpha]_D^{20}$ -140 (*c* 0.11, $CHCl_3$); R_f = 0.46 (10% MeOH/CH_2Cl_2); IR (film) 3376, 2925, 2853, 1644, 1605, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.56 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 5.43 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.75 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.41 (d, *J* = 4.8 Hz, 1H), 3.83 (s, 3H), 1.45 (d, *J* = 5.6 Hz, 3H), 1.44 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.7, 163.3, 157.2, 140.7, 136.8, 134.1, 133.2, 133.1, 129.1, 128.4, 128.3, 128.2, 115.0, 105.1, 100.3, 71.5, 59.0, 58.6, 55.5, 22.2, 22.0; HRMS (ESI): Exact mass calcd for $C_{25}H_{27}Cl_2N_2O_3$ $[M+H]^+$ 473.1399, found 473.1400.

2,4-Dichloroquinoline (160). *See Appendix for large scale Organic Syntheses manuscript procedure.*



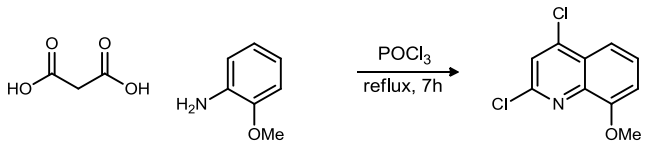
2,4-Dichloro-7-methoxyquinoline (160b). Phosphorus(V) oxychloride (20 mL, 1.3 M) was added through a running condenser into a 3-neck round bottom flask equipped with a stir bar containing malonic acid (2.710 g, 26.00 mmol) at room temperature. While stirring, *m*-anisidine (4.000 g, 32.48 mmol) was added in small portions over a period of 15 minutes through an open neck of the round bottom flask. The reaction mixture was heated and stirred at reflux for 5 hours. The reaction mixture was allowed to cool to room temperature before it was poured over crushed ice (~350 mL). The pH of the resulting

aqueous solution was adjusted to 10 with concentrated ammonium hydroxide. The aqueous suspension was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and filtered before concentration to provide a 2.2:1 mixture (^{1}H NMR) of the 7-methoxy and 5-methoxy regioisomers. Purification by column chromatography (0-8% ethyl acetate in hexanes) yielded a white solid (3.181 g, 54%) that was recrystallized from ethyl acetate and hexanes to provide the 7-methoxy isomer. Mp 131.5-132.5 °C; R_f = 0.18 (5% EtOAc/hexanes); IR (film) 3092, 2982, 1623, 1572, 1559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.2 Hz, 1H), 7.32 (s, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 9.2 ,2.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.2, 150.2, 150.0, 143.9, 125.2, 120.7, 120.1, 119.5, 107.1, 55.7; HRMS (ESI): Exact mass calcd for $C_{10}H_8Cl_2NO$ $[M+H]^+$ 227.9977, found 227.9973.

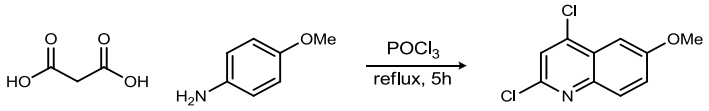


2,4-Dichloro-6,7-dimethylquinoline (160d). Compound was prepared using 3,4-dimethylaniline (10.0 g, 82.5 mmol), malonic acid (6.88 g, 66.0 mmol), and $POCl_3$ (50 mL) according to the general procedure. The reaction time was 4 hours. The crude solid was purified by column chromatography (0-2% Et_2O/hexanes) to produce a white solid (8.104 g, 54%). This material was subjected to column chromatography a second time (0-2% Et_2O/hexanes) and enriched fractions were concentrated to provide 3.095 g of a 2:1 mixture of regioisomers. This material was recrystallized twice from ethyl acetate and hexanes to provide 819 mg of a 44:1 mixture of regioisomers (GC) favoring the desired compound. Mp 95.5-96.5 °C; R_f = 0.34 (10% EtOAc/hexanes); IR (film) 2947, 2917, 1547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.72 (s, 1H), 7.35 (s, 1H), 2.44 (s,

6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.7, 147.1, 143.1, 142.1, 138.1, 128.3, 123.5, 123.2, 120.8, 20.3, 20.2; HRMS (CI): Exact mass calcd for $C_{11}H_{10}Cl_2N$ $[M+H]^+$ 226.0185, found 226.0179.

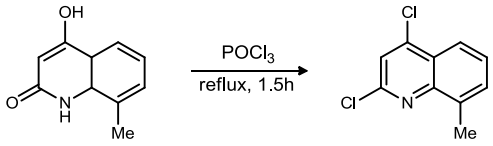


2,4-Dichloro-8-methoxyquinoline (160f). Compound was prepared using *o*-anisidine (14.1 mL, 125 mmol), malonic acid (13.0 g, 125 mmol), and $POCl_3$ (50 mL) according to the general procedure. The reaction time was 7 hours. Soxhlet extraction of the crude solid with hexanes for ~24 h followed by cooling of the obtained extract yielded a yellow solid precipitate (2.6135 g, 9%) that was pure by ^{1}H NMR. Mp 127.5-128.5 °C; R_f = 0.08 (10% EtOAc/hexanes); IR (film) 3097, 3008, 1576, 1561 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 1H), 7.57 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.55 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.8, 148.9, 144.3, 139.9, 128.1, 126.4, 122.7, 115.6, 109.8, 56.3; HRMS (CI): Exact mass calcd for $C_{10}H_7Cl_2NO$ $[M+H]^+$ 226.9899, found 226.9890.

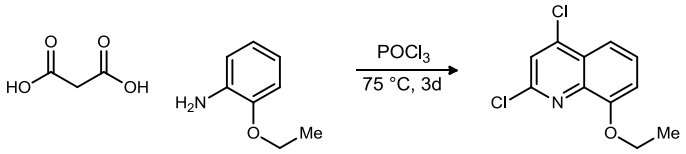


2,4-Dichloro-6-methoxyquinoline (160g). Phosphorus(V) oxychloride (40 mL, 1.5 M) was added through a condenser into a 3-neck round bottom flask containing malonic acid (6.244 g, 60.00 mmol) and a stir bar at room temperature. While stirring, *p*-anisidine (9.236 g, 75.00 mmol) was added in small portions over a period of 15 minutes through an open neck of the round bottom flask. The reaction mixture was heated and stirred at

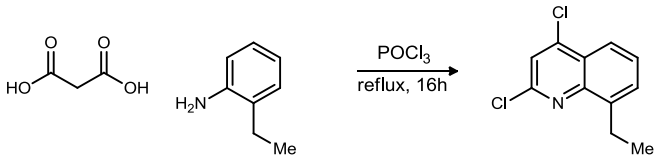
reflux for 5 hours. The reaction mixture was allowed to cool to room temperature before it was poured over crushed ice (~700 mL). The pH of the resulting aqueous solution was then adjusted to 10 with concentrated ammonium hydroxide (~85 mL). The aqueous suspension was extracted with dichloromethane. The combined organic layers were then dried over $MgSO_4$ before concentration. Purification by column chromatography (0-5% ethyl acetate in hexanes) yielded the title compound as a slightly yellow solid (4.7812 g, 35%). Mp 170.5-171.5 °C; R_f = 0.27 (2% EtOAc/hexanes); IR (film) 3084, 3013, 2982, 1623, 1562, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 9.0 Hz, 1H), 7.45 (s, 1H), 7.40 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.36 (d, *J* = 3.0 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 158.9, 147.0, 144.0, 142.6, 130.4 126.3, 124.1, 122.0, 101.9, 55.7; HRMS (CI): Exact mass calcd for $C_{10}H_8Cl_2NO$ $[M+H]^+$ 227.9977, found 227.9974.



2,4-Dichloro-8-methylquinoline (160i). Compound was prepared using 4-hydroxy-8-methylquinolinone (3.400 g, 19.19 mmol) and $POCl_3$ (20 mL) according to the general procedure. The reaction time was 2 hours. Column chromatography (0-2% EtOAc/hexanes) yielded the title compound as a white solid (2.2274 g, 55%). Mp 81.0-81.5 °C; R_f = 0.52 (5% EtOAc/hexanes); IR (film) 3085, 2960, 2922, 1566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 7.49 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.45 (s, 1H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.5, 147.2, 144.3, 137.2, 131.6, 127.4, 125.1, 121.9, 121.6, 18.1; HRMS (ESI): Exact mass calcd for $C_{10}H_8Cl_2N$ $[M+H]^+$ 212.0034, found 212.0033.

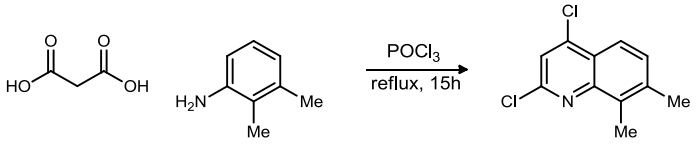


2,4-Dichloro-8-ethoxyquinoline (160j). Compound was prepared using 2-ethoxyaniline (6.5 mL, 50 mmol), malonic acid (5.2 g, 50 mmol), and $POCl_3$ (20 mL) according to the general procedure. The reaction was run at 75 °C for 3 days. Column chromatography (0-10% EtOAc/hexanes) yielded the title compound as a light brown solid (1.8714 g, 15%). Mp 59.5-60.5 °C; R_f = 0.16 (5% EtOAc/hexanes); IR (film) 3081, 2982, 2932, 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.55-7.49 (m, 1H), 7.50 (s, 1H), 7.12 (br d, *J* = 8.0 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.58 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.1, 148.7, 144.1, 140.1, 128.0, 126.4, 122.5, 115.4, 110.8, 64.8, 14.4; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}Cl_2NO$ $[M+H]^+$ 242.0139, found 242.0137.

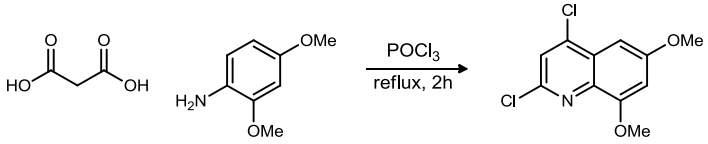


2,4-Dichloro-8-ethylquinoline (160k). Compound was prepared using 2-ethylaniline (6.2 mL, 50 mmol), malonic acid (5.2 g, 50 mmol), and $POCl_3$ (20 mL) according to the general procedure. The reaction time was 16 hours. Column chromatography (0-2% EtOAc/hexanes) provided the title compound as a white solid (2.626 g, 23%). Mp 40.0-41.0 °C; R_f = 0.61 (5% EtOAc/hexanes); IR (film) 3096, 3075, 2969, 2919, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.61 (br d, *J* = 6.8 Hz, 1H), 7.53 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.45 (s, 1H), 3.24 (q, *J* = 7.6 Hz, 2H), 1.36 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.5, 146.7, 144.3, 142.9, 129.9, 127.6, 125.1,

121.8, 121.6, 24.5, 14.8; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}Cl_2N$ $[M+H]^+$ 226.0190, found 226.0196.

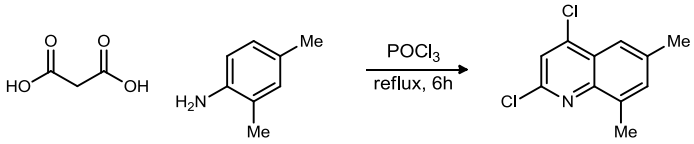


2,4-Dichloro-7,8-dimethylquinoline (160l). Compound was prepared using 2,3-dimethylaniline (6.1 mL, 50 mmol), malonic acid (5.2 g, 50 mmol), and $POCl_3$ (20 mL) according to the general procedure. The reaction time was 15 hours. Purification by column chromatography (100% hexanes) yielded the title compound as a white solid (4.1165 g, 36%). Mp 68.0-69.0 °C; R_f = 0.56 (5% EtOAc/hexanes); IR (film) 3094, 2952, 1608, 1578, 1558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.33 (s, 1H), 2.64 (s, 3H), 2.46 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.3, 147.0 , 144.0, 139.6, 134.4, 130.3, 123.3, 120.7, 120.4, 20.7, 13.5; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}Cl_2N$ $[M+H]^+$ 226.0190, found 226.0187.

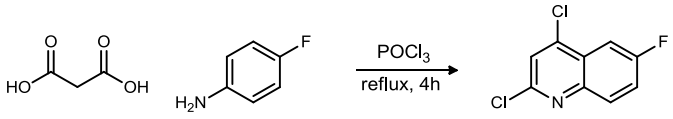


2,4-Dichloro-6,8-dimethoxyquinoline (160m). Compound was prepared using 6,8-dimethoxyaniline (10.0 g, 65.3 mmol), malonic acid (6.79 g, 65.3 mmol), and $POCl_3$ (26 mL) according to the general procedure. The reaction time was 2 hours. The crude solid was soxhlet extracted with hexanes for 3 d to provide the title compound as a greenish-brown solid (1.376 g, 8%). Mp 183.5-184.5 °C; R_f = 0.09 (10% EtOAc/hexanes); IR (film) 3080, 2964, 1615, 1562 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 4.03 (s, 1H), 3.95 (s, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) ppm 159.4, 155.8, 146.1, 142.7, 136.6, 127.1, 122.9, 103.0, 93.7, 56.3, 55.7; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}Cl_2NO_2$ $[M+H]^+$ 258.0089, found 258.0094.

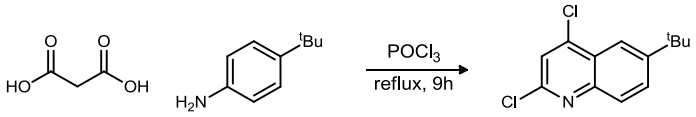


2,4-Dichloro-6,8-dimethylquinoline (160n). Compound was prepared using 2,4-dimethylaniline (6.2 mL, 50 mmol), malonic acid (5.2 g, 50 mmol), and $POCl_3$ (20 mL) according to the general procedure. The reaction time was 6 hours. Precipitation from acetone yielded the title compound as a yellow solid (3.1786 g, 28%). Mp 101.0-103.0 °C; R_f = 0.59 (5% EtOAc/hexanes); IR (film) 3091, 2960, 2921, 1566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 2.71 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 147.6, 145.9, 143.5, 137.6, 136.8, 133.8, 125.1, 121.6, 120.9, 21.7, 18.0; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}Cl_2N$ $[M+H]^+$ 226.0190, found 226.0198.

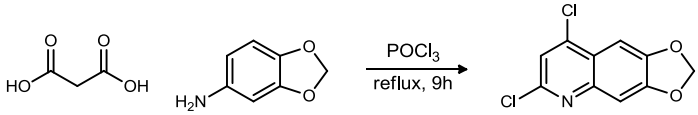


2,4-Dichloro-6-fluoroquinoline (160p). Compound was prepared using 4-fluoroaniline (5.556 g, 50 mmol), malonic acid (5.203 g, 50 mmol), and $POCl_3$ (20 mL) according to the general procedure. The reaction time was 4 hours. The crude solid was soxhlet extracted with hexanes for 6 hours to provide a yellow solid (1.9382 g, 18%). Mp 88.0-90.0 °C; R_f = 0.31 (5% EtOAc/hexanes); IR (film) 3063, 1626, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 9.2, 5.2 Hz, 1H), 7.79 (dd, J = 9.2, 5.2 Hz, 1H), 7.54 (ddd, J = 9.2, 8.0, 2.8 Hz, 1H), 7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.2 (d, $^1J_{CF}$ =

250 Hz), 149.2 (d, $^4J_{CF}$ = 3.0 Hz), 145.1, 143.5 ($^4J_{CF}$ = 6.0 Hz), 131.6 (d, $^3J_{CF}$ = 9.0 Hz), 126.2 (d, $^3J_{CF}$ = 11 Hz), 122.6, 121.7 (d, $^2J_{CF}$ = 25 Hz), 108.2 (d, $^2J_{CF}$ = 25 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) ppm -107.9; HRMS (EI): Exact mass calcd for $C_9H_4Cl_2FN$ $[M]^+$ 214.9699, found 214.9708.

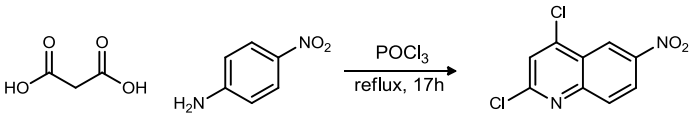


2,4-Dichloro-6-*tert*-butylquinoline (160q). Compound was prepared using 4-*tert*-butylaniline (5.000 g, 33.56 mmol), malonic acid (3.492 g, 33.56 mmol), and $POCl_3$ (20 mL) according to the general procedure. The reaction time was 9 hours. Soxhlet extraction of the crude solid with hexanes for ~48 h yielded the title compound as orange solid (2.872 g, 34%). Mp 43.5-44.5 °C; R_f = 0.48 (5% EtOAc/hexanes); IR (film) 2964, 2869, 1568, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 2.0 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.87 (dd, *J* = 8.8, 2.4Hz, 1H), 7.46 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 151.1, 149.0, 146.6, 144.2, 130.4, 128.5, 124.7, 121.7, 119.1, 35.3, 31.1; HRMS (ESI): Exact mass calcd for $C_{13}H_{14}Cl_2N$ $[M+H]^+$ 254.0503, found 254.0501.



2,4-Dichloro-6,7(methylenedioxy)quinoline (160r). Compound was prepared using 3,4(methylenedioxy)aniline (7.805 g, 75.00 mmol), malonic acid (10.29 g, 75.00 mmol), and $POCl_3$ (30 mL) according to the general procedure. The reaction time was 9 hours. The crude solid was soxhlet extracted with hexanes for 17 hours. Upon cooling, solid precipitated from the extract. This solid was of exceptional purity. The concentrated extract contained product of slightly lower purity. The crude solid was soxhlet extracted

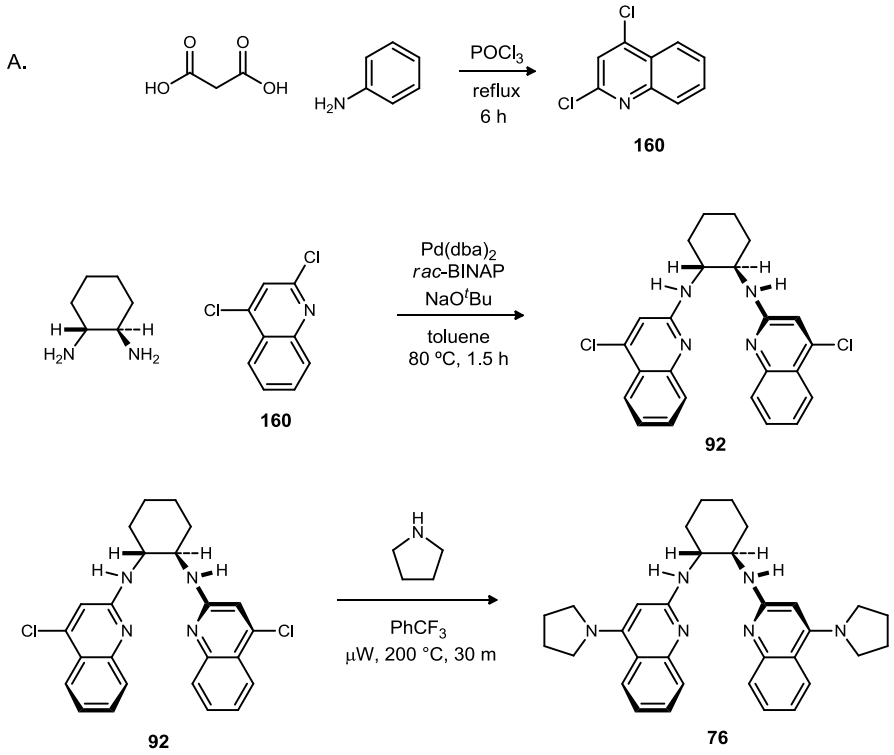
with hexanes for three additional days to recover more of the desired compound. The material was combined to provide 6.103 g (34%). Mp 170.0-171.0 °C; R_f = 0.18 (5% EtOAc/hexanes); IR (film) 3092, 2924, 1614, 1568, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.33 (s, 1H), 7.27 (s, 1H), 6.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 152.1, 149.1, 147.7, 146.6, 142.5, 122.2, 120.0, 105.6, 102.4, 99.8; HRMS (CI): Exact mass calcd for $C_{10}H_6Cl_2NO_2$ $[M+H]^+$ 241.9770, found 241.9769.



2,4-Dichloro-6-nitroquinoline (160s). Compound was prepared using 4-nitroaniline (6.9 g, 50 mmol), malonic acid (5.2 g, 50 mmol), and $POCl_3$ (20 mL) according to the general procedure. The reaction time was 17 hours. The crude solid was soxhlet extracted with hexanes for 18 h to provide a yellow solid (761.4 mg, 6%). Mp 187.0-188.0 °C; R_f = 0.28 (10% EtOAc/hexanes); IR (film) 3092, 3062, 2962, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 2.4 Hz, 1H), 8.56 (d, *J* = 9.2, 2.4 Hz, 1H), 8.18 (d, *J* = 9.2 Hz, 1H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 153.8, 150.1, 146.3, 146.0, 131.0, 125.1, 124.7, 123.9, 121.2; HRMS (EI): Exact mass calcd for $C_9H_4Cl_2N_2O_2$ $[M]^+$ 241.9644, found 241.9654.

APPENDIX

PREPARATION H,[4]PYRROLIDINEQUIN-BAM (PBAM)



Submitted by

Tyler A. Davis, Mark C. Dobish, Ken E. Schwieter, Aspen C. Chun and Jeffrey N. Johnston[184]

1. Procedure

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Caution! Part A of this procedure must be carried out in a well-ventilated hood and the apparatus must be equipped with a hydrogen chloride (HCl) trap to avoid exposure to HCl gas.

A. 2,4-Dichloroquinoline ***(160)***. A 250 mL, 3-neck, round-bottomed flask is equipped with a stir bar (38 x 17 mm) and charged with malonic acid (26.0 g, 250 mmol, Note 1).[185] A rubber septum is connected to one of the side arms and a condenser is attached to the middle neck. That condenser is equipped with a line that runs to an HCl trap (Note 2). The flask is lowered into an ice water bath and $POCl_3$ (100 mL, Note 3) is poured into the open side arm. That open side arm is sealed with a rubber septum. A slight positive flow of nitrogen gas is introduced into the system through a needle inserted into one of the side arm septa (Note 4). Aniline (22.8 mL, 250 mmol, Note 5) is added slowly to the stirring mixture by syringe through a side arm septum over a period of 20 minutes. The flask is then removed from the ice water bath, allowed to stir for 10 minutes, and placed into an oil bath (~110 °C). The mixture is stirred at reflux for 6 hours. The flask was removed from the oil bath and allowed to cool for 5 minutes. The mixture was slowly and carefully poured onto crushed ice (~ 1 L in 2 L beaker) while intermittently stirring with a spatula. The residual material in the 3-neck round-bottomed flask was removed by carefully adding water (100 mL) to the flask and scraping out with a spatula. The aqueous mixture is vigorously stirred by hand with a spatula. The 2 L quench beaker is placed into a bucket of ice. 6 M aq NaOH (475 mL) is added slowly (over a period of 25 min, keeping the temperature ≤ 50 °C) while intermittently stirring. The pH of the solution

[185] A modification of the procedure reported by Jones: Jones, K.; Roset, X.; Rossiter, S.; Whitfield, P. *Org. Biomol. Chem.* **2003**, *1*, 4380-4383.

was ~7 (Note 6). The beaker was removed from the ice bath and the suspension was allowed to cool to rt and age with stirring (stir bar) for 12 h (Note 7). The suspension was then vacuum filtered through a Buchner funnel (12 cm diameter). Water (150 mL) was used to rinse the residual material from the beaker. The filtered red solid was rinsed with water (150 mL) on the filter. After drying on the filter (1 h), the solid was transferred into 2 cellulose thimbles (33 mm x 94 mm, int. diam. x ext. length). Each thimble was Soxhlet extracted with hexanes (300 mL) for 16 h. The hexanes extract was concentrated (Note 8) by rotary evaporation (30 °C, 23 mm Hg) and further dried under vacuum (0.1 mm Hg) to leave a yellow solid (16.5-18.0 g, 33-36%, Note 9) that was used in step B without further purification.

The crude material can be further purified by recrystallization. The crude solid (5.0 g) was dispensed into a 50 mL Erlenmeyer flask and dissolved in 20 mL of a 3:1 mixture of hexanes and toluene with heating in a ~70 °C water bath. The solution was allowed to slowly cool to room temperature (Note 10) before it was placed in an ice-water bath. After 2 hours, the mother liquor was decanted. The recrystallization flask was kept in the ice-water bath while the crystals were rinsed with ice-cold hexanes (5 mL). The rinsate was decanted. Residual solvent was removed by vacuum (0.1 mm Hg) to leave a yellow crystalline solid (2.99-3.17 g, 60-63% recovery, Note 11).

B. H,^{4}ClQuin-BAM ***(92)***. A 100-mL, round-bottomed flask (24/40 joint) equipped with a stir bar (32 x 15 mm), rubber septum and argon inlet needle (Note 12) was first charged with (*R*,*R*)-diaminocyclohexane (1.63 g, 14.3 mmol, Note 13). Then (Note 14) $Pd(dba)_2$ (164 mg, 285 μmol), *rac*-BINAP (356 mg, 572 μmol), sodium *tert*-butoxide (4.12 g, 42.9

mmol), and 2,4-dichloroquinoline (**160**) (5.66 g, 28.6 mmol) were added and the reaction vessel was placed under an argon atmosphere.[186] Toluene (35 mL, Note 15) was dispensed into the flask, and the resulting red-brown solution was placed into an oil bath heated to 80 °C with stirring (Note 16). The reaction was monitored by TLC (Note 17); after 1.5 h, nearly complete conversion was observed. The reaction was cooled to 25 °C, and saturated NH_4Cl (10 mL) and water (10 mL) were added to the flask. The suspension was stirred for 5 min and cooled to 0 °C for 10 m. The reaction mixture was filtered through a Buchner funnel (9 cm diameter) and washed with water (50 mL) and hexanes (150 mL, Note 18) to afford a light yellow solid. This crude solid was transferred to a pre-weighed 100 mL (24/40 joint) round-bottomed flask and dried under vacuum (0.1 mm Hg) for at least 10 h to leave 4.10-4.68 g of a light yellow solid (65-75%, Note 19), which was used in step C without further purification.

C. H,^{4}PyrrolidineQuin-BAM (PBAM) ***(76)***. A 10-20 mL microwave vial equipped with a stir bar (12 x 8 mm) was charged with H,^{4}ClQuin-BAM (**92**) (4.30 g, 9.83 mmol), pyrrolidine (3.23 mL, 39.3 mmol, Note 20), and trifluoromethylbenzene (3.3 mL, Note 21). The vial was sealed, and this suspension was heated with stirring at 200 °C in the microwave for 30 m (Note 22). The reaction mixture was diluted and transferred with 20 mL of dichloromethane to a 500 mL round-bottomed flask for evaporation (Note 23). The reaction was then concentrated by rotary evaporation (80 °C, 23 mm Hg), redissolved in dichloromethane (50 mL), transferred to a 125 mL separatory funnel, and washed with 3M NaOH (50 mL) and water (4 x 50 mL). The resulting organic layer was dispensed into a 125 mL Erlenmeyer flask and dried ($MgSO_4$, 2 g). The solution was filtered (flask

[186] Adapted from Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451-8458.

and filter were rinsed with an extra 25 mL of dichloromethane) into a 250 mL round-bottomed flask and concentrated by rotary evaporation (30 °C, 23 mm Hg) and high vacuum (0.1 mm Hg, 1h) to provide a light brown powder (Note 24).

As much of the material as possible was transferred as a solid from the round-bottomed flask to a pre-weighed 250 mL Erlenmeyer flask. The remaining solid was dissolved and transferred into a 25 mL pear-shaped flask with 10 mL of dichloromethane and concentrated by rotary evaporation (30 °C, 23 mm Hg) and high vacuum (0.1 mm Hg, 1 h). This material was then added to the 250 mL Erlenmeyer flask. The material was dissolved in a 90:10 mixture of acetone and toluene (20 mL/g crude product) with heating in a water bath (70 °C) (Note 25). The solution was removed from heat and placed on the bench for 1 hour to cool to room temperature. The flask was placed in an ice bath for 3 h or until no further crystallization was observed. The mother liquor was decanted leaving crystals that were washed with ice-cold acetone (2 x 10 mL). Residual solvent was removed from the crystals by placing the Erlenmeyer flask under vacuum (0.1 mm Hg) for a period of 5-10 m (Note 26). The crystalline material was transferred to a pre-weighed 20 mL glass scintillation vial and dried for ~14 h in a drying pistol (0.1 mm Hg) over refluxing toluene. The vial was temporarily removed from the drying pistol, and the material was thoroughly pulverized with a spatula and returned to the drying pistol for 6 additional h. The dried material was a white powder (3.12-3.35 g, 63-67% yield) (Note 27).

2. Notes

1. Malonic acid (99%) was purchased from Sigma-Aldrich and used as received.

2. The reflux condenser is fitted with an outlet that is connected with Tygon tubing to two 250 mL bubblers, the first emply, and the second filled with water to serve as the HCl trap.

3. $POCl_3$ (99%) was purchased from Aldrich and used as received.

4. The gas flow should be monitored by constantly checking the bubbler during the aniline addition to prevent the development of negative pressure in the system.

5. Aniline (99.9%) was purchased from Fisher Scientific Company and used as received.

6. This workup procedure should fully hydrolyze all P-Cl bonds leaving phosphoric acid as the byproduct of $POCl_3$ quenching.[187]

7. This served to fully quench the suspension and to produce a finer crude solid with fewer chunks. This facilitated transfer into the soxhlet thimble and allowed for a more efficient extraction due to increased surface area of the solid.

8. It may be necessary to filter the extract if red solid precipates from the solution.

9. The crude 2,4-dichloroquinoline (**160**) exhibited the following: mp 62.0-63.0 (uncorrected); R_f = 0.43 (10% EtOAc/hexanes); IR (film) 3065, 1570, 1554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, *J* = 8.4 Hz, 1H), 7.98 (br d, *J* = 8.4 Hz, 1H), 7.75 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H), 7.60 (ddd, *J* = 8.0, 6.8, 0.8 Hz, 1H), 7.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 149.7, 148.0, 144.2, 131.4, 128.8, 127.8, 125.0, 124.0, 121.8. This data matched the values given in the literature.[185]

[187] Achmatowicz, M. M.; Thiel, O. R.; Colyer, J. T.; Hu, J.; Elipe, M. V. S.; Tomaskevitch, J.; Tedrow, J. S.; Larsen, R. D. *Org. Process Res. Dev.* **2010**, *14*, 1490-1500.

10. If a precipitate forms when the solution is cooled to room temperature, the solution should be filtered before cooling in an ice-water bath.

11. The melting point range of the recrystallized 2,4-dichloroquinoline (**1**) was 63.0-63.5 °C (uncorrected). Material that was purified by column chromatography (0-4% EtOAc/hexanes) exhibited a melting point of 64.0-64.5 °C (uncorrected).

12. The apparatus was flame-dried under reduced pressure (0.1 mm Hg) and then maintained under an atmosphere of argon during the course of reaction.

13. (1*R*,2*R*)-(−)-1,2-Diaminocyclohexane was resolved from a *trans*/*cis* mixture (60/40) using the protocol of Jacobsen[188] with L-(+)-tartaric acid. The salt was then dissolved in 10 M NaOH and continuously extracted using benzene in a liquid/liquid extractor for 5 days. Alternatively, the diamine (98%, optical purity ee: 99%) can be purchased from Sigma-Aldrich. This diamine is stored in a freezer and weighed directly into the 100 mL round-bottomed flask. This diamine is a white solid but becomes a viscous oil as it warms to room temperature. To avoid difficulties in transfer, the diamine is weighed in the reaction vessel without allowing the diamine to warm to room temperature.

14. Bis(dibenzylideneacetone)palladium, 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene and sodium *tert*-butoxide were dispensed into a flame-dried vial in a glovebox under an argon atmosphere. This vial was removed from the glovebox and its contents were then transferred into the round-bottomed flask. Bis(dibenzylideneacetone)palladium was prepared according to the procedure of Rettig and Maitlis.[189] Alternatively, it can be purchased from a commercial supplier. (±)-2,2′-Bis(diphenylphosphino)-1,1′-

[188] Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939-1942.
[189] Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 134-137.

binaphthalene (97%) and sodium *tert*-butoxide (97%) were purchased from Aldrich Chemical Co and were used as received.

15. Toluene (ACS grade) was purchased from Fisher and was dried by passage through a column of activated alumina as described by Grubbs.[190]

16. After 5-10 minutes a solid forms and is manually dispersed by vigorously swirling the flask by hand.

17. Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates from Sorbent Technologies. UV light was used to visualize the product. With 20% ethyl acetate/hexanes, the starting material has R_f = 0.59 and the product has R_f = 0.23. Upon reaction completion, there may still be a relatively faint spot visible of the same R_f as the starting material.

18. Hexanes (ACS grade) was purchased from Fisher Scientific Company and used as received.

19. We have found this material to be of sufficient purity for use as a reactant to make **92**. It can be further purified by column chromatography (10% ethyl acetate in hexanes). This crude material exhibited some variation from batch to batch in terms of melting point. A range of 235-245 °C is observed, but individual samples exhibit a routinely narrow (≤ 2 °C) melting point range. The melting point of material purified by column chromatography is 236.0-237.0 °C. H,^{4}ClQuin-BAM (**2**) exhibited the following: mp 236.0-237.0; $[\alpha]_D^{20}$ +508 (*c* 1.0, DMSO); R_f = 0.23 (20% EtOAc/hexanes); IR (film) 3220, 2930, 1601 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.62-7.53 (m, 4H), 7.29-7.20 (m, 4H), 6.84 (s, 2H), 4.05 (br s, 2H), 2.28-2.16 (m, 2H), 1.83-

[190] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

1.67 (m, 2H), 1.50-1.28 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 156.5, 148.5, 140.2, 130.4, 126.0, 123.4, 122.1, 120.3, 112.6, 53.6, 31.7, 24.3; HRMS (CI): Exact mass calcd for $C_{24}H_{23}Cl_2N_4$ $[M+H]^+$ 437.1300, found 437.1294. We have found H,^{4}ClQuin-BAM to be a bench stable solid. No decomposition of this compound has been observed after years of storage on the benchtop in a screw cap vial.

20. Pyrrolidine (99%) was purchased from Alfa Aesar and was used as received.

21. Trifluoromethyl benzene (99+%) was purchased from Acros and was used as received.

22. The reaction was performed in a Biotage Initiator EXP US 355302 microwave reactor set at a constant temperature of 200 °C. This reaction takes place in a sealed vial. This microwave system monitors the pressure and heat inside the sealed vial and shuts off for safety purposes when 20 bar or 250 °C is reached. Usually, the pressure inside the vial will exceed 15 bar at the initial stages of heating then stabilize. Due to the heat of dissolution in some cases, the pressure may exceed the set safety parameters. When this occurs, the heating protocol is restarted and no further temperature or pressure variations are observed. Confirmation of consumption of starting material can be made by TLC with UV visualization (10% methanol/0.5% acetic acid/89.5% dichloromethane, starting material R_f = 0.79, product R_f = 0.38).

23. Dichloromethane (ACS grade) was purchased from Fisher Scientific Company and used as received. The contents of the microwave vial will congeal upon cooling, but the use of 20 mL of dichloromethane will sufficiently dissolve and transfer the mixture. It might be necessary to stir the contents of the vial with the added dichloromethane for several minutes to get this congealed mixture to dissolve for transfer. The use of an

abnormally large flask (500 mL for less than 30 mL of solution) is necessary because this viscous mixture foams upon concentration by rotavap. The extra headspace is needed to prevent the crude product from foaming out of the flask and into the rotavap bump trap.

24. The material at this stage can be dried by subjecting the material to a drying pistol heated by refluxing toluene for 24-48 h. We have found this dried material without further purification to give the same performance (stereoselection) as a catalyst as material further purified (column chromatography or recrystallization).

25. Acetone (ACS grade) was purchased from Sigma-Aldrich and used as received. The crude material might fully dissolve and crystallize in a matter of seconds upon addition of the solvent mixture at room temperature. These crystals may not fully redissolve upon heating and swirling, but the recrystallization will still work when the solution is cooled.

26. Vacuum was applied with a needle through a septum secured to the top of the flask. The goal of this manipulation is merely to obtain a free-flowing solid.

27. The mother liquor and crystal washings were concentrated and subjected to the same recrystallization procedure to produce an additional 800 mg of product to raise the yield for the last step to 81-85%. During the determination of the melting point, the material gradually turns from white to slightly brown between 200 °C and the melting point. Despite this appearance change, the melting point observed is consistent at 243-245 °C. We have noticed some variation in the melting point range (241-246 °C), but individual samples exhibit a routinely narrow (≤ 2 °C) melting point. PBAM (**92**) exhibited the following: mp 243.0-245.0; $[\alpha]_D^{20}$ +406 (*c* 1.2, $CHCl_3$); R_f = 0.38 (10% MeOH/CH_2Cl_2 with 0.5% acetic acid); IR (film) 3259, 3056, 2927, 2855, 2935, 1591, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.40 (dd, *J*

= 7.2, 7.2 Hz, 2H), 7.01 (dd, *J* = 7.2, 7.2 Hz, 2H), 5.70 (br s, 2H), 5.28 (s, 2H), 4.09 (br s, 2H), 3.35-3.22 (m, 4H), 3.16-3.05 (m, 4H), 2.37-2.23 (m, 2H), 1.90-1.75 (m, 10H), 1.58-1.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.4, 153.2, 149.9, 128.3, 126.4, 124.7, 119.1, 118.7, 93.0, 56.3, 51.5, 33.4, 25.5, 25.1; HRMS (ESI): Exact mass calcd for $C_{32}H_{39}N_6[M+H]^+$ 507.3236, found 507.3250. Anal. calcd for $C_{32}H_{38}N_6$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.80; H, 7.72; N, 16.45. PBAM purified by column chromatography has been stable upon storage in a screw cap vial on the benchtop for several years without sign of decomposition.