Enantioselective Reaction Development using Chiral Bifunctional Brønsted Acid/Base Organocatalysis and Applications to Target Molecule Synthesis

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Acknowledgments

This is not merely the work of a single individual, but a culmination of accomplishments from my friends, colleagues, teachers, and family, nearly all of whom have motivated, inspired, and supported me throughout graduate school and in life from the very beginning.

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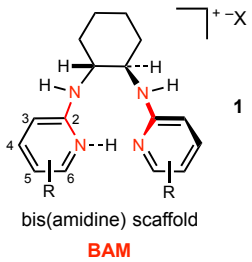
1.1 Previous Developments in Enantioselective, Bis(Amidine) Organocatalysis and the aza-Henry Reaction

The 1990's witnessed a massive influx of asymmetric reaction methods development, particularly in the budding field of organocatalysis, which has since become a staple in the organic chemistry community. In addition to the benefits asymmetric catalysis brings to chemical synthesis, organocatalysis brings the desire to use "greener" organic materials that do not involve the use of toxic metal-based Lewis acids closer to fruition. Another longstanding driving force in the field is curiosity, and the myriad of unique and novel modes of organocatalyst activation of small molecules and reagents to be uncovered – hydrogen-bonding catalysis, covalent-enamine catalysis, Brønsted base catalysis, and Brønsted acid catalysis are just a handful of the many activation modes popularized over the years.

Central to my dissertation work has been the *implementation* of asymmetric, organocatalysis towards target synthesis and the mechanistic understanding of catalyst-substrate interactions. While the discovery and invention of new catalysts has not been a direct primary

Figure 1. The Brønsted basic *bis*(amidine) scaffold.



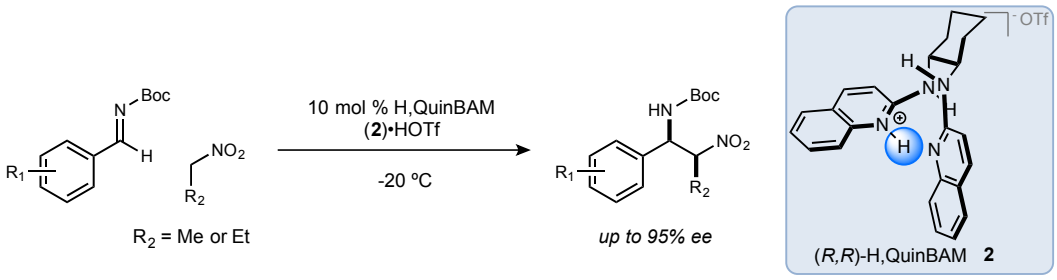
goal, the drive to develop innovative and valuable asymmetric reactions has necessitated the exploration of more selective and robust organocatalyst systems, as detailed herein.

Adding to the many modes of organocatalyst activation in the field, "chiral proton catalysis" has been coined by the Johnston Group since the seminal publication of H,QuinBAM•HOTf (**2**•HOTf) and its use in the asymmetric aza-Henry (or nitro-Mannich) reaction in 2004. Brønsted basic *bis*(amidine) (BAM) ligands of the general structure **1** were envisioned to be employed in such reactions. From the chiral *trans*-1,2-cyclohexanediamine backbone, an array of basic appendages can be joined, where upon Brønsted acid protonation forms the active BAM^{+}–H complex (Figure 1). Central to this plan was the idea that the acidic proton of the chiral catalyst complex would be an electrophilic "chiral proton", functioning as a Brønsted (or Lewis) acid. This came to be the case as catalyst **2** was able to promote asymmetric aza-Henry reactions with good to excellent diastereo- and enantioselectivity (Scheme 1).[1]

Through much optimization of catalyst structure, certain aspects of BAM catalysts were identified as key control elements – perhaps the most critical finding was that the *polar-ionic* hydrogen bond nature of the catalyst, the amidinium (RX^{+}–H, Y^{-}), was essential to selectivity in nonpolar solvents. Also, the more sterically encumbered quinoline heterocycle was found to be

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

Scheme 1. Seminal report implementing chiral proton catalysis in the enantioselective aza-Henry reaction using **2**•HOTf.

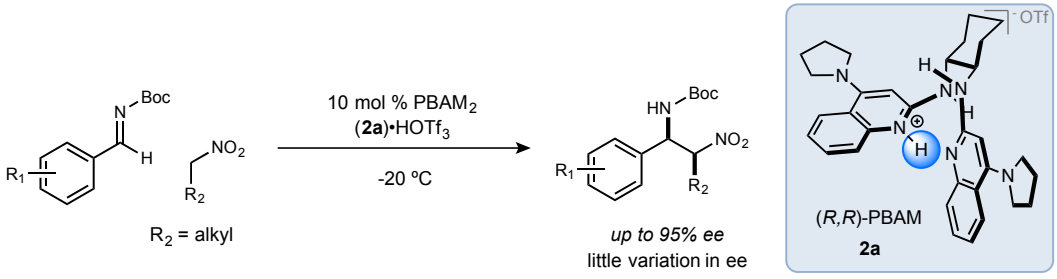


beneficial over substituted pyridines. Importantly, chiral induction comes from a readily obtainable (and common) chiral building block.[2]

This seminal report[1] focused on the additions of nitromethane and nitroethane into electron deficient, Boc-protected aryl aldimines (aza-Henry reaction) facilitated by the triflic acid (HOTf) salt of H,QuinBAM (**2**) to generate enantioenriched β-amino nitroalkanes (Scheme 1). Enantio- and diastereoselection varied greatly in this early report, yet up to 95% ee could be obtained with nitromethane. The nitroalkane in this report was employed as the solvent in order to observe appreciable reactivity.

After several years of experimental optimization and catalyst iterations to improve

Scheme 2. The advancement of BAM catalyst design to PBAM (**2a**), affording aza-Henry products in higher yields and consistent stereoselection.



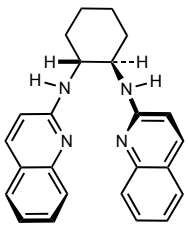
reactivity while maintaining high levels of stereoselection,[3] it was ultimately found that the

[2] Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466.

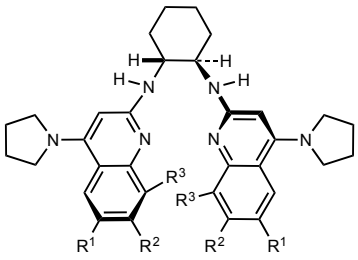
addition of pyrrolidine to the 4-position of the quinoline ring dramatically enhanced reactivity, dubbed pyrrolidine *bis*(amidine) – PBAM (**2a**), due to increased Brønsted basicity as studies within the group have shown. The classic aza-Henry reaction was reexamined in 2010 using this catalyst system.[4] The protonation state of the Brønsted basic ligand **2a** was critical to high stereocontrol and a wider range of nitroalkanes and aryl Boc-imines were now tolerated (Scheme 2). These early reports materialized the notion that the Brønsted acid/Brønsted base catalyst system behaves as a *bifunctional organocatalyst* – the acid portion may activate the Lewis basic imine (or electrophile) while the basic amidine can deprotonate the pronucleophile and generate the active nitronate (nucleophile) species.

In order to achieve these higher levels of stereoselection and reactivity, a library of chiral BAM ligands containing various quinoline derivatives were synthesized by my predecessor Tyler Davis (and others) and assessed under various reaction conditions (Chart 1). These BAM catalysts contain a variety of substituted quinolines rationally designed to alter the steric and electronic nature of the Brønsted basic amidine ligands. Many catalysts have proved fruitful

Chart 1. Bis(amidine) H,QuinBAM (**2**) and common pyrrolidine bis(amidine) (PBAM) chiral catalysts developed in the group.



H,QuinBAM **2**



PBAM **2a**

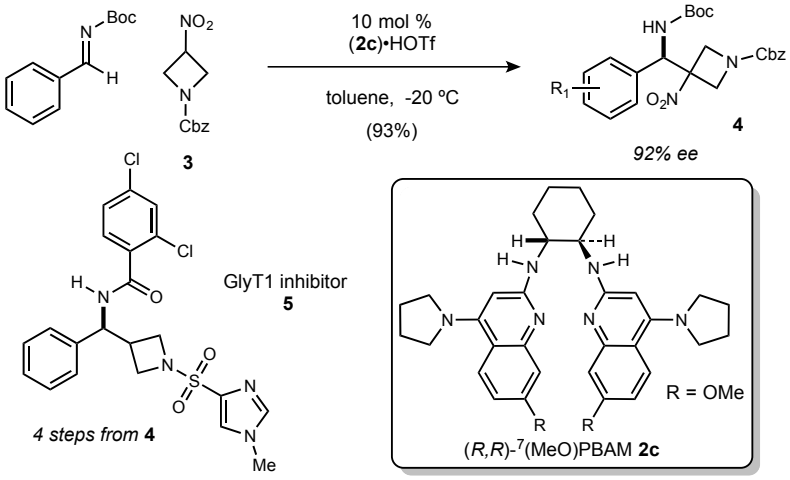
	Substitution	*Common Name*
2a	R^1, R^2, R^3 = H	PBAM
2b	R^1, R^2 = OMe, R^3 = H	$^{6,7}(MeO)_2$PBAM
2c	R^1, R^3 = H, R^2 = OMe	^{7}(MeO)PBAM
2d	R^1, R^2 = H, R^3 = OEt	^{8}(EtO)PBAM
2e	R^1, R^3 = OMe, R^2 = H	$^{6,8}(MeO)_2$PBAM
2f	R^1, R^2 = H, R^3 = OMe	^{8}(MeO)PBAM

[3] Davis, T. A. *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.* Ph. D. Thesis, Vanderbilt University. **2011**.
[4] Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880.

across a range of asymmetric reactions over the years and will be instrumental to the work presented here.

With the stronger and more reactive Brønsted basic catalyst **2a** in hand, a wider array of nucleophile and electrophile counterparts has been explored in the group since 2009. Various pronucleophiles such as bromonitromethane have emerged as very useful preliminary reagents in the aza-Henry reaction – β-amino-α-bromonitroalkanes can ultimately be employed in Umpolung Amide Synthesis (UmAS) for the synthesis of enantioenriched peptides.[5,6]

Scheme 3. Synthesis of GlyT1 inhibitor **5** and the use of 2º nitroalkane **3** in the aza-Henry reaction.



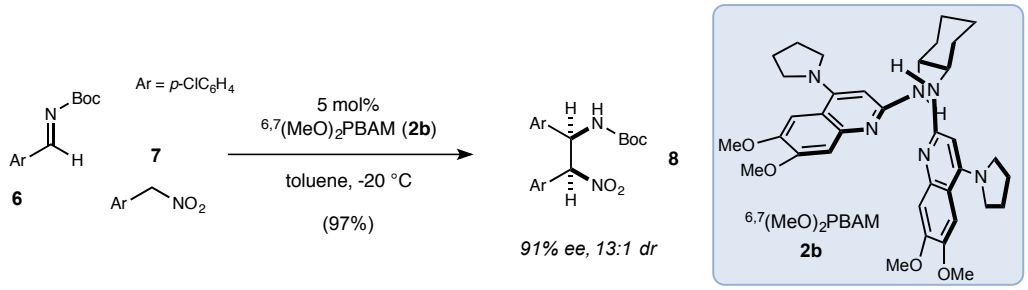
Moving away from simple nitroalkanes, sterically-challenging 2º nitroalkanes (**3**) were explored in the enantioselective aza-Henry reaction en route to the synthesis of a glycine transport 1 (GlyT1) inhibitor (**5**).[7] Again the 1:1 triflic acid salt of the catalyst was found to be optimal – ^{7}(MeO)PBAM (**2c**)•HOTf in this particular case afforded slightly higher levels of enantioselection as compared to **2a**•HOTf (Scheme 3).

[5] Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027.
[6] Shackleford, J. P.; Shen, B.; Johnston, J. N. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 44.
[7] Davis, T. A.; Danneman, M. W.; Johnston, J. N. *Chem. Commun.* **2012**, *48*, 5578.

1.2 The First Enantioselective Synthesis of (–)-Nutlin-3 via the aza-Henry Reaction

In 2011, we reported the use of *aryl* nitromethanes as pronucleophile surrogates in the aza-Henry reaction. Up until this report, aryl nitromethanes had been employed in asymmetric reactions on only two prior occasions, and generally resulted in much lower enantioselection and dr (≤2:1 dr).[8] When screening for optimal conditions in this reaction, the library of BAM catalysts in Chart 1 was readily employed, and surprisingly the *free base* catalyst, $^{6,7}(MeO)_2$PBAM (**2b**), generated β-amino nitroalkane **8** in > 90% ee.[9] This of course was in stark contrast to the previous reports from our group detailing the importance of the "chiral proton" and the added advantage of employing the Brønsted acidic 1:1 catalyst salt. Due to the enhanced

Scheme 4. Aryl nitromethane **7** in the aza-Henry reaction. The free base bis(amidine) catalyst **2b** was employed.



Brønsted acidity of the aryl nitromethanes, however, the authors posited the 1:1 Brønsted acid:BAM salt may still assemble in the reaction, but as the nitronate:BAM salt – no additional acid is needed for high stereocontrol in this reaction (Scheme 4).

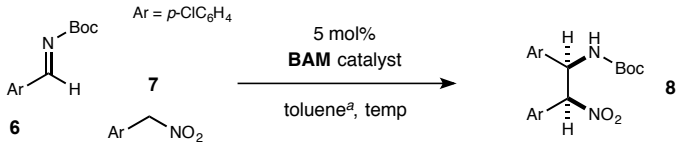
Table 1 details the dramatic effects observed when PBAM-derived catalysts, free base and Brønsted acid salt, were employed in this reaction with aryl nitromethane **7**. The protonated

[8] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992.
[9] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.

BAM catalysts saw little benefit to enantioselection in this system, and the free base of the catalysts actually improved diastereoselection in many cases (entries 1-7, Table 1).

The value of this work additionally lies in its ability to furnish unsymmetrical *cis*-stilbene diamine derivatives from the enantioenriched β-amino nitroalkanes, and is further grounded by the development of the first fully stereocontrolled synthesis of the potent p53/MDM2 inhibitor (–)-Nutlin-3 (**9**, Figure 2) discovered by Hoffmann-La Roche (HLR). This synthesis has paved the way to access *cis*-imidazolines more broadly – a challenging 1,2-diamine motif to access in asymmetric fashion.

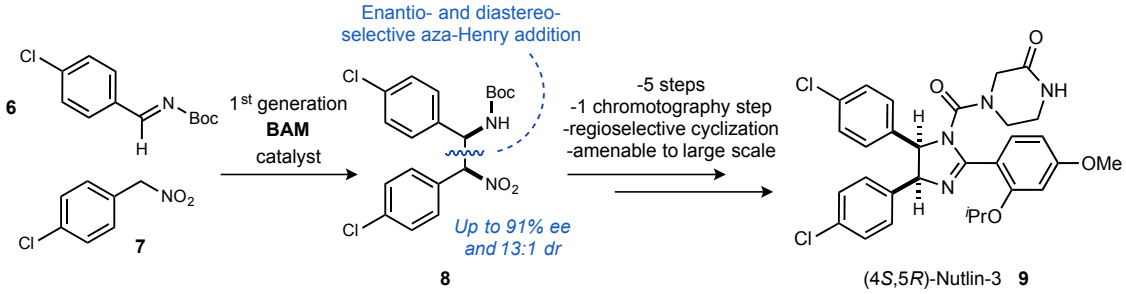
Table 1. Diastereo- and enantioselective BAM-catalyzed aza-Henry reaction using aryl nitromethane **7**. Table adopted from *Chem. Sci.* article.[9]



entry	BAM	temp. (ºC)	TfOH (equiv.)	dr	ee (%)	yield[b] (%)
1	**2**[c]	-20	1	13:1	64	81
2	**2**[c]	-20	0	10:1	65	99
3	6-Me **2a**	-20	1	5:1	58	95
4	6-Me **2a**[c]	-20	0	6:1	63	96
5	**2a**	-78	1	5:1	85	99
6	**2a**	-78	0	9:1	86	97
7	**2a**	-20[d]	0	6:1	83	99
8	**2c**	-78	0	13:1	87	99
9	**2f**	-78	0	16:1	89	99
10	**2b**	**-78**	**0**	**13:1**	**91**	**97**

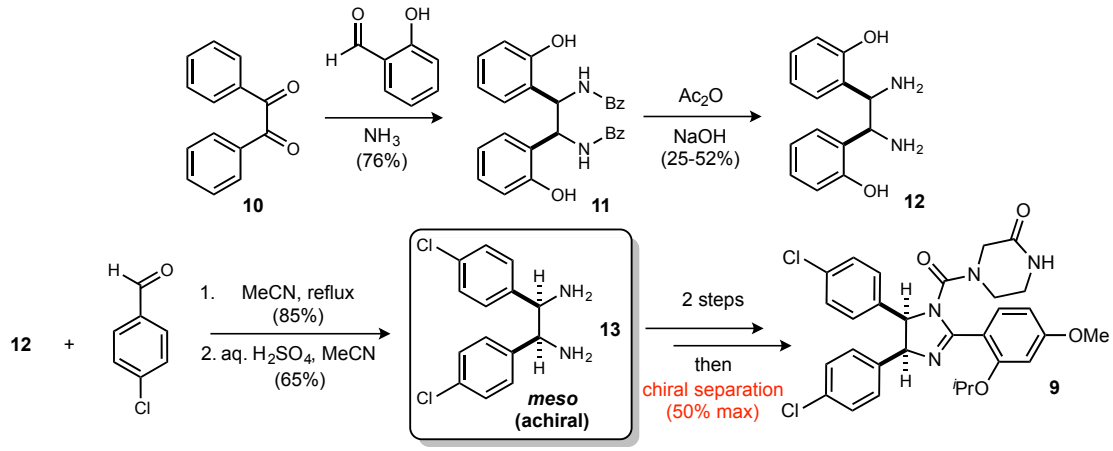
[a]All reactions used 1.1 equiv. of nitroalkane **7** in toluene (0.1M) with 24 h reaction time unless otherwise noted. Configuration assigned by analogy to a previous adduct assigned by X-ray crystallography. dr and ee determined by HPLC using a chiral stationary phase. [b]Isolated yield after column. [c]10mol% catalyst used, 48 h reaction time. [d]2 h reaction time.

Figure 2. The key asymmetric aza-Henry reaction to access masked the *cis*-stilbene diamine intermediate **8** which can be transformed to (–)-Nutlin-3.



Central to the efficiency of this asymmetric (–)-Nutlin-3 synthesis was the orthogonal protection of the enantioenriched β-amino nitroalkane adduct **8**.[9] Conceptually, it would be disadvantageous to reduce the nitro group in **8** to the amine and remove the Boc group, as this would produce a *meso* 1,2-diamine intermediate (achiral). In fact, this is the same *meso* intermediate used in the original HLR patent synthesis[10] of (–)-Nutlin-3 (Scheme 5). The use of *meso*-diamine **13** in the HLR synthesis required expensive intermediates (i.e., **12**) and forced a chiral separation of *rac*-**9** to generate enantiopure (–)-Nutlin-3 (**9**) while discarding the unwanted

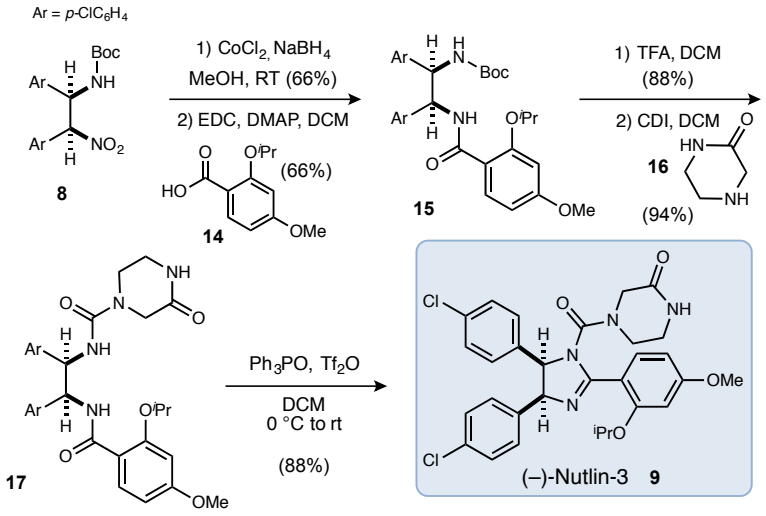
Scheme 5. HLR synthesis to access the *meso*-1,2-stilbene diamine **13** en route to **9**. In a final step 50% material is lost to chiral separation.



[10] N. Kong, E. A. Liu.; Vu, B. T.; **2003**, WO 03/051360 A1.

enantiomer (50% loss of material in final step). This approach on preparative scale is relatively expensive and presents various disadvantages.

Scheme 6. Enantioselective preparation of (–)-Nutlin-3.



The enantioselective synthesis of **9** begins from the β-amino nitroalkane **8**, whereupon nitro group reduction to the amine, amidation with benzoic acid derivative **14** generates amide **15** in good yield. Boc deprotection followed by formation of urea also proceeded in good yield to access the penultimate urea compound **17**. This amide urea was primed for a highly regioselective, dehydrative cyclization using Hendrickson's reagent[11] (Ph_3PO and Tf_2O) generating the *cis*-imidazoline core of (–)-Nutlin-3 (**9**). From aza-Henry adduct **8** (which can be recrystallized), enantiopure **9** was accessed in only five synthetic steps in good overall yield, and presented a significant improvement compared to the Hoffmann-La Roche synthesis. Additionally, the developed synthesis is amenable to large-scale preparation[12] and involves only one chromatographic purification step.

[11] Hendrickson, J. B.; Schwartzman, S. M. *Tet. Lett.* **1975**, 277. Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, *54*, 1144. Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1987**, *52*, 4137.
[12] Davis, T. A.; Vilgelm, A. E.; Richmond, A.; Johnston, J. N. *J. Org. Chem.* **2013**, *78*, 10605.

This work set the stage for future manipulations of the Nutlin framework to access enantioenriched derivatives that may help researchers better understand how p53 binds MDM2 (and its sister complex MDMX), and perhaps apply the synthesis to develop useful analogues and future therapeutics. Most notably, this convergent asymmetric synthesis allows for the preparation of *unsymmetrical* Nutlin derivatives or *cis*-imidazolines for the first time.

1.3 The Nutlin Class of MDM2-p53 Inhibitors

The transcription factor, p53, is a tumor suppressor protein primarily responsible for mediating cell-cycle progression by activating the transcription of certain genes. Its function is essential in depressing genetic mutations and malignancies via controlled cell death (apoptosis), and is often referred to as the "gatekeeper of the genome". Since the seminal discovery of p53 in the late 1970's, extensive studies across many scientific fields have shown that p53, in addition to its ability to bind DNA and activate genes encoding for other pro-apoptotic proteins (such as p21 and BAX), can itself carryout tumor suppressor function.[13] In fact, p53 is so essential in stabilizing cell-cycle equilibria while silencing mutations that wild-type (WT) p53 knockout mice were shown to be highly susceptible to spontaneous tumor growth, metastasis, and early death.[14]

[13] Danovi, D.; Meulmeester, E.; Pasini, D.; Migliorini, D.; Capra, M.; Frenk, R.; de Graaf, P.; Francoz, S.; Gasparini, P.; Gobbi, A.; Helin, K.; Pelicci, P. G.; Jochemsen, A. G.; Marine, J. C. *Mol. Cell Biol.* **2004**, *24*, 5835. Levine, A. J.; Oren, M. *Nat. Rev. Cancer.* **2009**, *9*, 749. Vousden, K. H.; Lane, D. P. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 275.

[14] 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.

Dysregulation of the p53 pathway, including mutations of the p53 gene (*p53* or *TP53*), however, is the most common alteration in human cancers.[15] When the cell senses direst or internal stress, wild-type p53 is upregulated via post-transcriptional modification promoting downstream tumor cell destruction. Under normal, non-stressed conditions, p53 levels within the nucleus are kept at a low basal state, which is the result from a very well studied autoregulatory negative feedback loop. This critical governing event of nuclear p53 levels is controlled by a regulatory binding protein known as MDM2 (or HMD2 in humans). p53-MDM2 binding is a reversible protein-protein interaction which culminates in p53 extrusion from the nucleus and subsequent degradation via the ubiquitin pathway – more formally, MDM2 functions as a p53-specific E3 ubiquitin ligase.[16]

Additionally, overexpression of the MDM2 gene (*mdm2*) has also been shown in nearly 50% of human tumors. This is relevant because MDM2 binds p53 with very high affinity, effectively shutting down p53's primary role in tumor suppression and apoptosis.[17] For these reasons, activation of WT p53 is a popular therapeutic approach in fighting a variety of human cancers.[18] Some other common approaches attempt to promote MDM2 degradation and/or *mdm2* down-regulation.[19] The critical and dynamic relationship that exists between p53 and its binding protein, MDM2, is a highly investigated field in cancer biology and has been increasing dramatically for the past decade, all in hopes of uncovering new cancer therapeutics.

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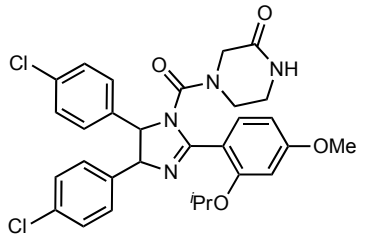
[15] Jaiswal, P. K.; Goel, A.; Mittal, R. D. *Biosci. Trends* **2011**, *5*, 205.
[16] Ashcroft, M.; Vousden, K. H. *Oncogene* **1999**, *18*, 7637.
[17] Allen, J. G.; Bourbeau, M. P.; Wohlhieter, G. E.; Bartberger, M. D.; Michelsen, K.; Hungate, R.; Gadwood, R. C.; Gaston, R. D.; Evans, B.; Mann, L. W.; Matison, M. E.; Schneider, S.; Huang, X.; Yu, D. Y.; Andrews, P. S.; Reichelt, A.; Long, A. M.; Yakowec, P.; Yang, E. Y.; Lee, T. A.; Oliner, J. D. *J. Med. Chem.* **2009**, *52*, 7044.
[18] For an recent review of MDM2-p53 inhibitors in preclinical and clinical trials see the following: Khoury, K.; Popowicz, G. M.; Holak, T. A.; Domling, A. *Medchemcomm* **2011**, *2*, 246.
[19] Levine, A. J.; Oren, M. *Nat. Rev. Cancer.* **2009**, *9*, 749.

Figure 3. MDM2-p53 inhibitor, *rac*-Nutlin-3 (structure depicted in original report).



(±)-Nutlin-3 (±)-**9**

Targeting protein-protein interactions (PPI) in the realm of drug discovery has gained much recent attention as a promising philosophy for discovering new small molecule and biological therapeutics. Traditionally, targeting non-enzymatic PPI has proven challenging due to complex binding modes, but this notion is perhaps more pronounced in p53-MDM2, due to higher relative levels of structural mutations.[20] In 2004, Hoffmann-La Roche (HLR) identified a potent and selective small molecule inhibitor of p53-MDM2, a *cis*-imidazoline derivative known as Nutlin-3 (named after the HLR research site in Nutley, New Jersey), shown to effectively bind MDM2 and free p53 (Figure 3).[14]

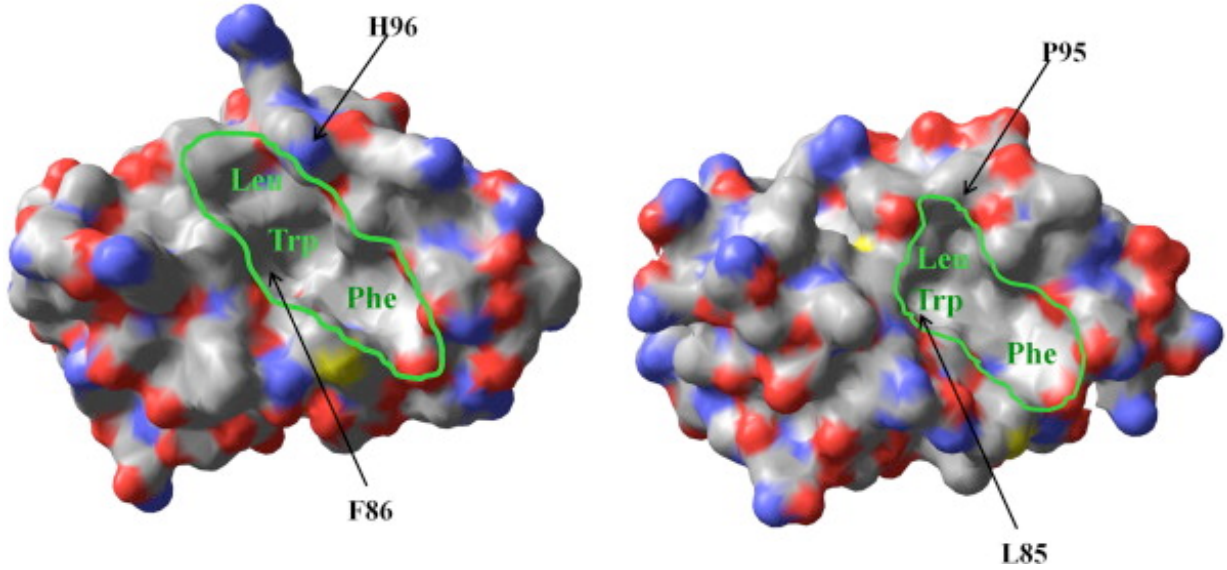
The HLR group led by Lyubomir Vassilez, as well as other researchers to follow, have illustrated how the *para*-chloroarenes stemming from the imidazoline core of Nutlin-3 mimic the α-helix of p53 (transactivation domain) responsible for binding MDM2. A three-dimensional computer rending of the p53 transactivation domain interacting with HDM2 (and its homologue HDMX) is shown in Figure 4 (p53 helix removed for clarity).

NMR and computer docking studies in recent years have shown how the p53 α-helical residues occupy the hydrophobic HDM2/MDM2 binding pocket[21] consisting of Phe^{19}, Trp^{23}, and Leu^{26}. HDM2 has an elongated and relatively deep hydrophobic pocket compared to HDMX, and for that reason, HDM2 has been traditionally viewed as the more "druggable" protein with

[20] Chene, P. *Nat. Rev. Cancer* **2003**, *3*, 102.
[21] Laurie, N. A.; Donovan, S. L.; Shih, C. S.; Zhang, J. K.; Mills, N.; Fuller, C.; Teunisse, A.; Lam, S.; Ramos, Y.; Mohan, A.; Johnson, D.; Wilson, M.; Rodriguez-Galindo, C.; Quarto, M.; Francoz, S.; Mendrysa, S. M.; Guy, R. K.; Marine, J. C.; Jochemsen, A. G.; Dyer, M. A. *Nature* **2006**, *444*, 61. Kussie, P. H.; Gorina, S.; Marechal, V.; Elenbaas, B.; Moreau, J.; Levine, A. J.; Pavletich, N. P. *Science* **1996**, *274*, 948.

conventional organic small molecules.[22] Nutlin-3 is one of many suitable small molecules due to the fact that the two *para*-chloroarenes of Nutlin-3 reside agreeably in the hydrophobic HDM2 binding pocket,[14] occupying Trp[23], and Leu[26]. This high affinity protein-ligand interaction disrupts p53-HDM2 PPI, culminating in stabilization and accumulation of apoptotic WT p53 through blockage of its extracellular exportation and degradation pathway.

Figure 4. Surface representations of HDM2 (left) and HDMX (right) in bound states with p53 ligand (p53 residues 15–29) not shown for clarity. Each protein is colored according to its elemental make-up (C, gray; O, red; N, blue; S, yellow). The p53-binding pockets with labeled Leu, Trp and Phe subsites (green) are outlined to highlight the topological differences in the binding pockets. The solvent exposed residues responsible for variations in binding pocket structure are H96 and F86 (HDM2) and is replaced with P95 and L85 in HDMX.[22]



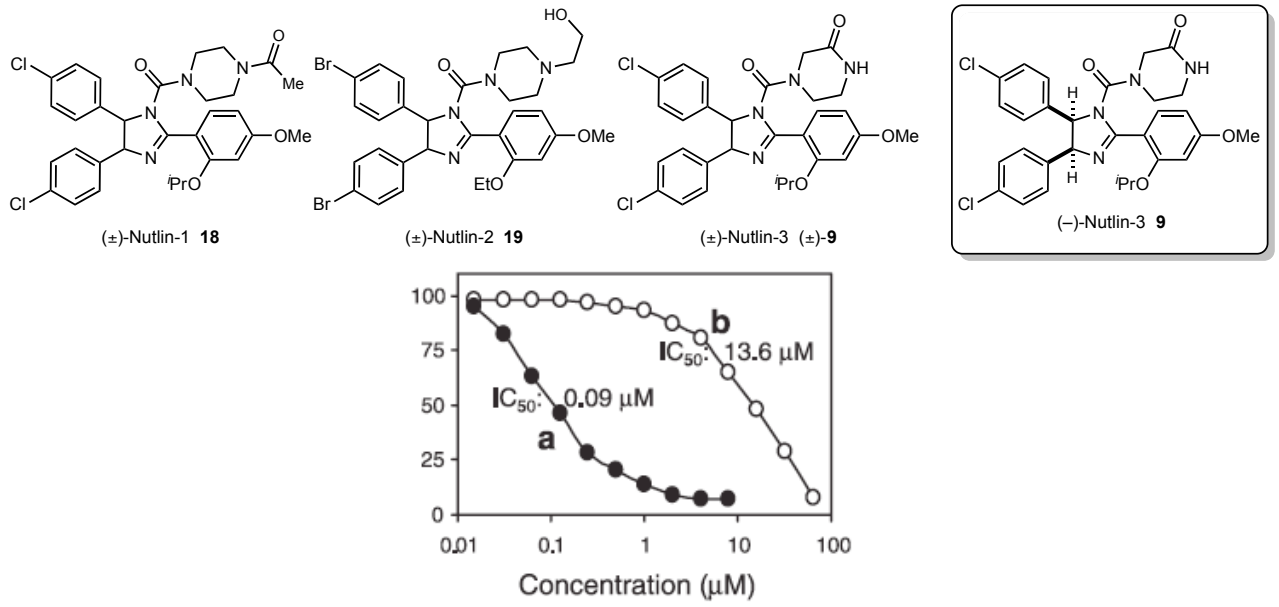
Since the identification of the Nutlin class from HLR was a result of extensive high throughput-screening (HTS) efforts, Nutlins 1-3 were originally isolated as racemates (Figure 5). Following medicinal chemistry optimization, separation of the enantiomers via chiral chromatography, and ensuing binding affinity assays for each enantiomer, (4*S*,5*R*)- or (–)-Nutlin-

[22] Datta, S.; Bucks, M. E.; Koley, D.; Lim, P. X.; Savinov, S. N. *Bioorgan. Med. Chem.* **2010**, *18*, 6099.
Figure 4 image reprinted from "Functional profiling of p53-binding sites in Hdm2 and Hdmx using a genetic selection system" Datta, S.; Bucks, M. E.; Koley, D.; Lim, P. X.; Savinov, S. N. *Bioorgan. Med. Chem.* **2010**, *18*, 6099. with permission from Elsevier

3 (**a**, Figure 5) was shown to have superior potency in wild-type p53 cell assays over its enantiomer, with an IC_{50} of 0.09 μM versus 13.6 μM, respectively. When (–)-Nutlin-3 was tested against cell lines with mutant p53, potency was diminished (IC_{50} value of 13 to 21 μM), suggesting that p53 activation is only viable in wild type p53.[14]

The protein-protein inhibitory capacity of this class of small molecules exemplifies real potential in this area of p53-mediated tumor suppression and cancer research. More recent studies of cell-cycle arrest pathways have revealed that the MDM2 homologue, MDMX or MDM4 (HDMX in humans), is also a critical negative regulator of p53[23] and important for controlling nuclear p53 levels.[24] Although MDMX does not exhibit distinct E3-ubiquitin ligase activity as in MDM2, MDMX does augment MDM2-mediated p53 degradation upon binding the transactivation domain of p53 through a slightly different mechanism of action. As previously

Figure 5. Structures of the Nutlin family. Enantiomers of Nutlin-3 were separated (**a** and **b**) and enantiomer-**a** ((–)-Nutlin-3, **9**) was 150 times more potent inhibiting p53-MDM2 than its enantiomer. (Adopted from Vassilev *et al.* **2004**)



[23] Gu, J. J.; Kawai, H.; Nie, L. G.; Kitao, H.; Wiederschain, D.; Jochemsen, A. G.; Parant, J.; Lozano, G.; Yuan, Z. M. *J. Biol. Chem.* **2002**, *277*, 19251.
[24] Linares, L. K.; Hengstermann, A.; Ciechanover, A.; Muller, S.; Scheffner, M. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 12009.

mentioned, MDM2 and MDMX are structural homologues and therefore bind p53 in a competitive manner (dissociation constant, K_d = 0.5 μM for both MDM2 and MDMX).

As can be seen in Figure 4, the binding pocket of HDMX is smaller and shallower compared to HDM2 due to the variation in a pair of solvent-exposed residues - H96 and F86 in HDM2 is replaced with P95 and L85 in HDMX. These tertiary structural changes in the two proteins are made more apparent when bound to a ligand such as racemic Nutlin-3. (±)-Nutlin-3 ((±)-**9**) binds MDM2 with an inhibition constant (K_i) of 0.7 μM and MDMX much weaker with a K_i of 28 μM.[21]

The overexpression and amplification in MDM2 and MDMX is prevalent in a host of human malignancies, thus providing evidence that p53 suppression is promoted in early stage tumor growth and metathesis.[13] More specifically MDMX is overexpressed in about 20% of breast, lung, and colon cancers, 50% of head and neck squamous carcinomas, and 65% of retinoblastomas.[25] A more recent report found MDMX to be overexpressed in approximately 65% of aggressive human melanomas.[26]

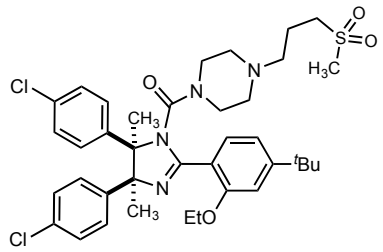
These new realizations regarding MDM2/MDMX-p53 regulation have drawn significant attention to the field in recent years. Fortunately for cancer researchers, the small molecule (–)-Nutlin-3 also inhibits p53-MDMX but is roughly 40 times less potent than (–)-Nutlin-3 p53-MDM2 inhibition. Still, Nutlin is considered an important small molecule tool in probing these protein-protein-binding events between both MDM2/MDMX-p53. The increasing number of reports have justified significant efforts to uncover more selective MDMX-p53 inhibitors or *dual*

[25] Ma, H. Q.; Weng, D. S.; Chen, Y. B.; Huang, W.; Pan, K.; Wang, H.; Sun, J. C.; Wang, Q. J.; Zhou, Z. W.; Wang, H. Y.; Xia, J. C. *Mol. Cancer* **2010**, *9*.
[26] Gembarska, A.; Luciani, F.; Fedele, C.; Russell, E. A.; Dewaele, M.; Villar, S.; Zwolinska, A.; Haupt, S.; de Lange, J.; Yip, D.; Goydos, J.; Haigh, J. J.; Haupt, Y.; Larue, L.; Jochemsen, A.; Shi, H. B.; Moriceau, G.; Lo, R. S.; Ghanem, G.; Shackleton, M.; Bernal, F.; Marine, J. C. *Nature Med.* **2012**, *18*, 1239.

MDM2/MDMX-p53 inhibitors in hopes of disovering more robust anti-cancer treatments.[27] Researchers at Hoffmann-La Roche recently suggested that upregulation of MDMX has negative effects on MDM2-p53 small molecule inhibitors (i.e. Nutlin-3) in cancer cell-based assays, since MDMX occupies the same transactivation domain of p53 and is a competitive receptor.[28]

Notably, the same group at Hoffman-La Roche has a 4,5-dimethyl *cis*-imidazoline derivative, RG7112, in late-stage clinical trials for patients with advanced solid tumors (Figure 6).[29] Although structurally different, the *para*-chloro stilbene *cis*-diamine structure are still present and essential to MDM2 activity. Though MDMX has since been validated as a worthy target for PPI drug discovery efforts, a potent and selective small molecule inhibitor of MDMX-p53 remains to be discovered.[30] As alluded to before, (–)-Nultin-3 exhibits strong inhibition of MDM2-p53 resulting in accumulation of WT p53 in the nucleus, however (–)-Nutlin-3 is inadequate at inducing accumulation of p53 or apoptosis in cells where MDMX is significantly amplified. Discussed hereafter are collaborative efforts detailing novel chemistry and technique to probe MDMX-p53 protein-protein interactions.

Figure 6. An MDM2-p53 inhibitor in late stage clinical trials for solid tumors.



RG7112
(Hoffmann-La Roche)

[27] Graves, B.; Thompson, T.; Xia, M. X.; Janson, C.; Lukacs, C.; Deo, D.; Di Lello, P.; Fry, D.; Garvie, C.; Huang, K. S.; Gao, L.; Tovar, C.; Lovey, A.; Wanner, J.; Vassilev, L. T. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 11788.
[28] Hu, B. L.; Gilkes, D. M.; Farooqi, B.; Sebti, S. M.; Chen, J. D. *J. Biol. Chem.* **2006**, *281*, 33030.
[29] For clinical trial updates see Roche-trials.com ; Tovar, C.; Graves, B.; Bradford, G.; Packman, K. *et* al. *Cancer Research.* **2013**. DOI:10.1158/0008-5472.
[30] It should be noted a relatively potent stapled-peptide has been reported to inhibit HDMX-mediated p53 degradation by mimicking the alpha-helix of p53. Bernal, F.; Wade, M.; Godes, M.; Davis, T. N.; Whitehead, D. G.; Kung, A. L.; Wahl, G. M.; Walensky, L. D. *Cancer Cell.* **2010**, *18*, 411.

1.4 The Enantioselective Synthesis of Unsymmetrical Masked cis-Stilbene Diamines and Synthesis of Exotic Nutlin Derivatives

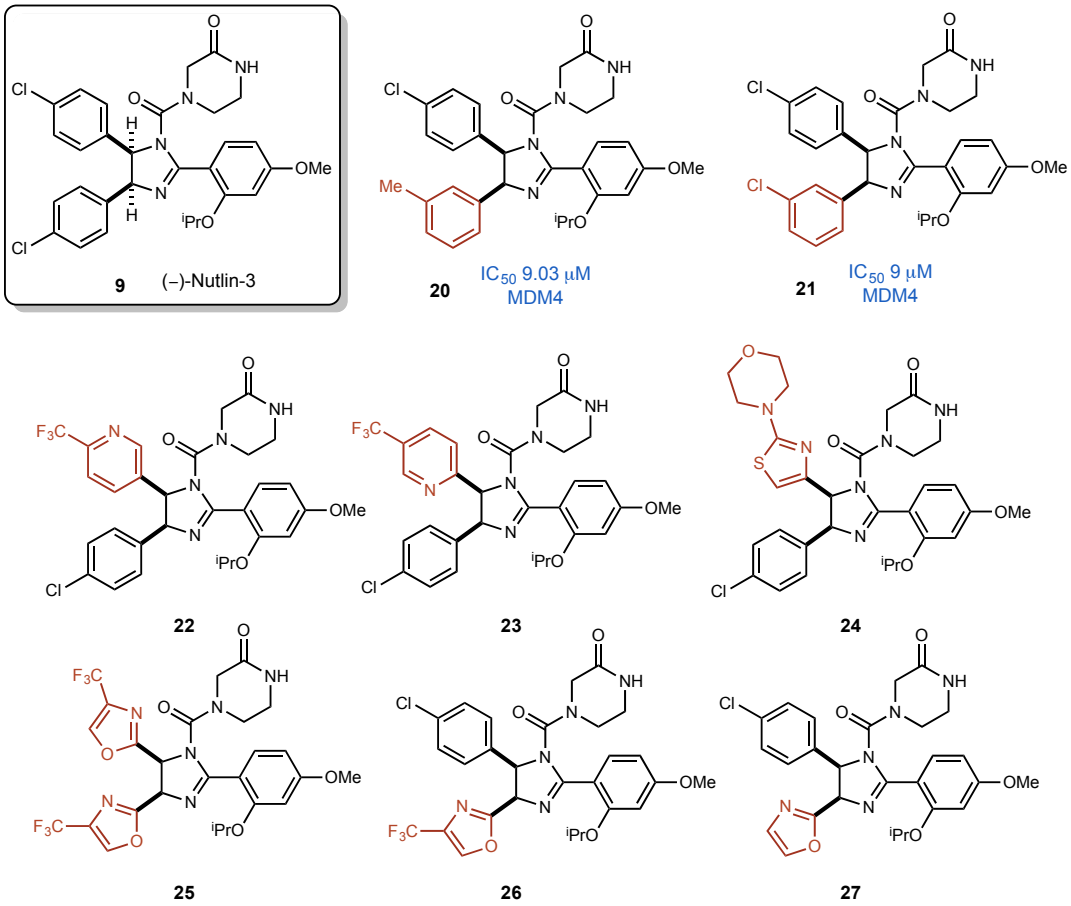
Building off of the first efficient enantioselective synthesis of (–)-Nutlin-3 (**9**) by our group reported in early 2011,[9] we sought to develop unique, unsymmetrical (4*S*,5*R*)-Nutlin-3 derivatives that may help researchers understand how p53 binds MDMX, and further probe these derivatives for anti-cancer activity in suitable assays. Molecular modeling and NMR studies, carried out by our collaborator Kip Guy and his group at St. Jude Children's Hospital (SJCH) in Memphis, resulted in a defined set of derivatives, which were arbitrarily prioritized for synthesis.

In total, the group initially devised six unique (4*S*,5*R*)-Nutlin-3 derivatives that could be prepared from the BAM-catalyzed enantioselective aza-Henry chemistry to furnish the masked *cis*-stilbene diamine core of the Nutlins. As outlined in Figure 7, the targets contained decorated heterocycles that may have favorable drug-like properties, including trifluoromethylated heterocycles, thiazole, and oxazole pharmacophores. It's worth mentioning that non-heteroaromatic derivatives **20** and **21** were previously prepared by chemists in the Guy group and tested in cell-based assays. As in the HLR Nutlin-3 synthesis, these compounds from SJCH were prepared as their racemates and the enantiomers were separated by preparatory chiral chromatography, again resulting in 50% loss of material (at a minimum). Fortunately, compounds **2** and **3** had IC_{50} of 9.03 and 9.00 μM, respectively, in MDMX-p53 cell based assays incentivizing further investigation and synthetic studies.

Previous attempts in the group to generate trifluoromethyl oxazoles or nitromethyl oxazole (as the proposed precursors to derivatives **25**-**27**, respectively, Figure 7) proved to be very challenging early on and further efforts were suspended. Fortunately, the reagent 2-chloro-5-trifluoromethyl pyridine was commercially available from vendors and the corresponding

imine was prepared in small quantities. Issues preparing and isolating the desired trifluoromethyl aldehyde or nitroalkane, however, proved quite difficult and time consuming. The work presented hereafter outlines the steps taken towards the completion of three "exotic" (4*S*,5*R*)-Nutlin derivatives (derivatives **22**, **23**, and **24**, Figure 7).

Figure 7. List of (–)-Nutlin derivatives proposed by the Guy at St. Jude. **20** and **21** were previously prepared by the group and showed activity towards MDMX(MDM4)-p53 inhibition. The remaining six compounds were requested for enantioselective synthesis chemistry. Major structural changes from **9** are highlighted in maroon.



The targeted (4*S*,5*R*)-Nutlin-3 derivative **23** was desirable for several reasons, both chemically and structurally. As previously mentioned, 2-chloro-5-trifluoromethyl pyridine is commercially available and inexpensive compared to other trifluoromethylated pharmacophores. The halogen handle at the 2-position of the pyridine ring allows for optimization to access

intermediates desired (Scheme 7). The trifluoromethyl pyridine ring may illuminate valuable stereoelectronic interactions such as increased hydrogen bonding of active site residues with fluorine and nitrogen on the ligand, hopefully increasing overall binding affinity.

Scheme 7. Proposed route to generate the aryl Boc-imine derivative **31** and subsequent aza-Henry transformation.

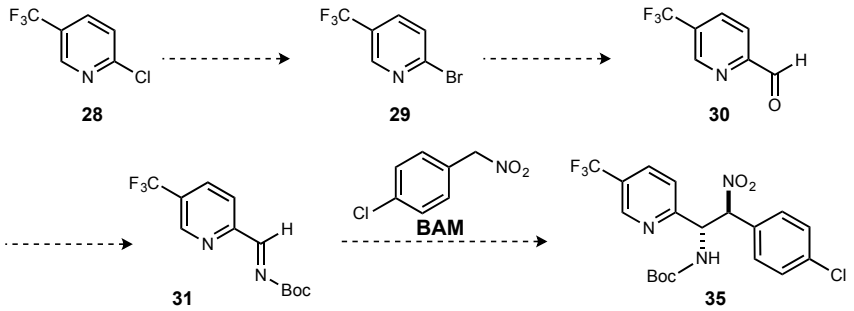
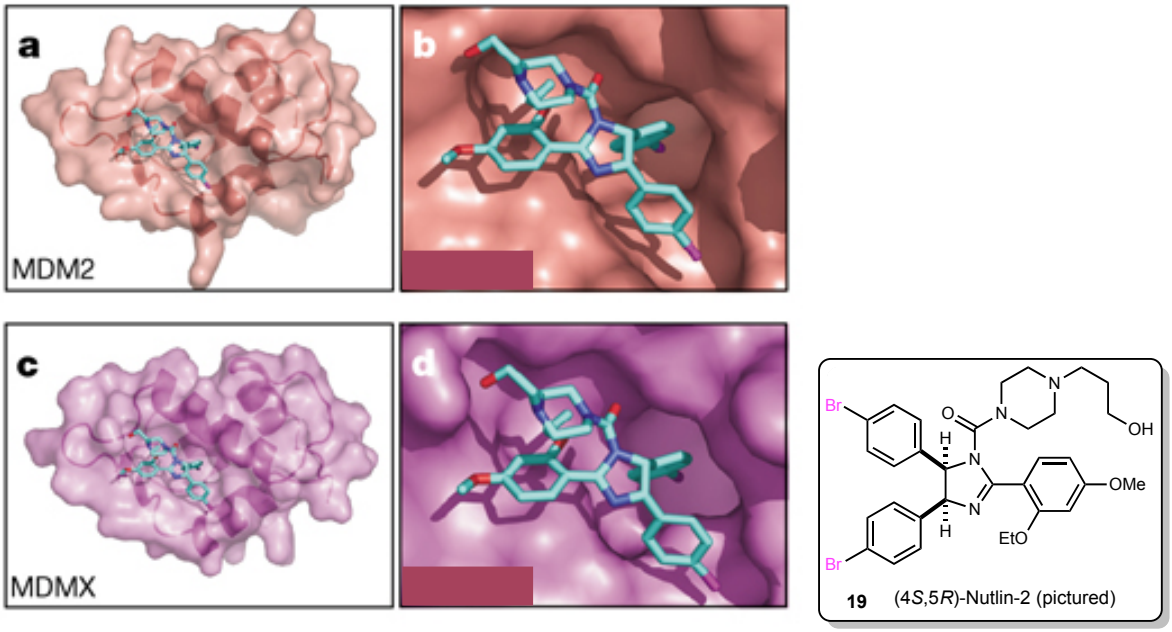


Figure 8. Computational docking studies of Nutlin-2 bound to MDM2 (**b**) and bound to MDMX (**d**). (–)-Nutlin-2 is pictured. (Image modified from its original context[21])



As is evident in the informative modeling of (4*S*,5*R*)-Nutlin-2 ((4*S*,5*R*)-**19**) bound to both MDM2 and MDMX (Figure 8)[21] the deepest cavity within the binding pocket (occupied by Trp^{23}) appears slightly larger in MDMX. This may allow for increased flexibility when designing new MDMX-p53 inhibitors in comparison to MDM2. Preliminary model studies carried out by the Guy group also suggest that the increased hydrophobicity of the trifluoromethyl moiety may prove similar or even more efficacious than (4*S*,5*R*)-Nutlin-3 since CF_3-groups are known bioisosteres of chlorine.[31]

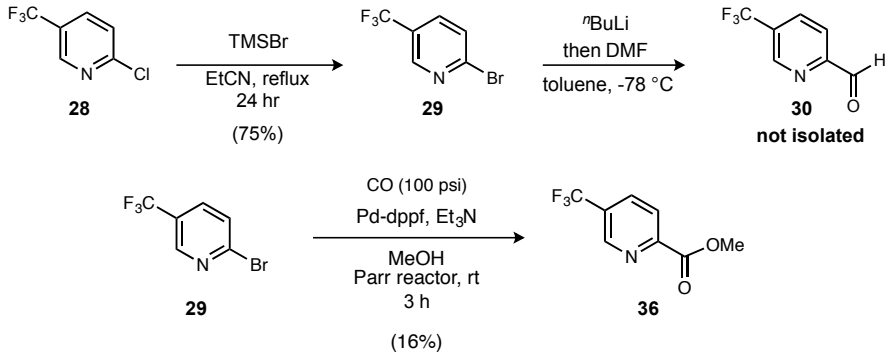
These aspects of chemical variation may bring about enhanced and/or novel bioactivity and insight into new chemotherapeutics of the Nutlin type, and at the very least, provide new NMR and molecular modeling data to improve upon structure-activity relationships. Additionally from a synthetic standpoint, the preparation of heteroaromatic aza-Henry precursors and their use in enantioselective reactions is a long-standing challenge in the field and one that had only been attempted intermittently in our lab. Aware of the challenges that lay ahead, the synthesis of unsymmetric trifluoromethyl pyridine (4*S*,5*R*)-*cis*-imidazoline **5** was first pursued.

Early on, the most straightforward route to access the Boc-imine precursor **31** was through pyridyl aldehyde **30** (Scheme 7). Although a successful halogen exchange reaction replaced the chlorine in pyridine **28** with a bromine (**29**), initial attempts to isolate aldehyde **30** was met with failure (Scheme 8). This was attempted by a lithium-halogen exchange with *n*-butyllithium (*n*-BuLi) and quenching the lithiate species with DMF at -78 ºC. This resulted in modest conversion to the desired aldehyde **30** (^{1}H NMR analysis of crude reaction mixture upon further examination) but the compound could not be chromatographed or isolated (Scheme 8).

[31] Kennewell, E.; Willett, P.; Luttmann, C. *Journal of Computer-Aided Molecular Design,* **2006**, 20, 6, 385-394.

It was reasonable to assume that aldehyde **30** was volatile and/or unstable. We sought to generate the methyl ester **18** and carry this intermediate forward under milder reducing conditions to aldehyde **30**. Unfortunately, the carbonylation of the pyridine ring was minimally successful and the desired methyl ester was isolated in a dismal 16% yield – presumably also

Scheme 8. Attempts to generate the aryl aldehyde **30**.

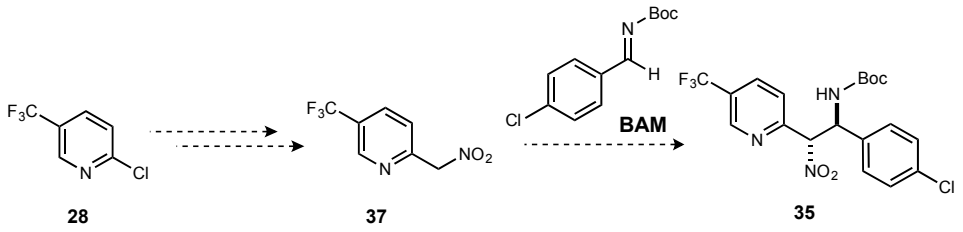


volatile. After several attempts to isolate aldehyde **30** or methyl ester **36** in manageable yields, it was apparent that a trifluoromethyl pyridine carbonyl intermediate was highly unstable or volatile in either state, and a change of direction was needed to move forward.

Past work has shown within the group and externally, the synthesis of various aryl nitromethane derivatives is not trivial. Although their use as pronucleophiles is slowly gaining momentum in various addition-type reactions, efficient syntheses of these compounds from commercially available halogenated arenes remains very difficult,[32] although progress has been made.[33] In hopes of adding diversity to the groups' nitroalkane library, we examined the formation of 5-trifluoromethyl-2-nitromethyl pyridine (**37**, Scheme 9). Scheme 9 outlines this newly proposed route to the pyridyl nitromethane **37**. Bearing these challenges in mind, we identified precedence for the addition of cyanomethanes to haloarenes and even halopyridines.[34]

[32] Ono, N. *The Nitro Group in Organic Synthesis.* Wiley-VCH. New York, New York. 2001.
[33] Kozlowski, M. C.; Metz, A; *Org. Lett.* **2012**, *14*, 760.
[34] Skerlj, R. T.; Bogucki, D.; Bridger, G. J. *Synlett* **2000**, 1488.

Scheme 9. Envisioned route to access arylnitromethane **19** based off of known addition reactions with cyanomethane. The desired Mannich addition adduct **20** is pictured.



Bearing the similarities of cyanomethane and nitromethane, we reasoned the nucleophilicity of the resulting nitronate following deprotonation should be comparable to known methods.

Beginning with more direct methods to make the pyridyl nitromethane derivative **37**, we attempted to carry out a nucleophilic aromatic substitution reaction (S_NAr) of 2-chloro- and 2-bromo-5-trifluoromethyl pyridine (**29**) with nitromethane and base.[35] In hindsight, the smaller and more polarizable fluorine atom installed at the 2-position would have been a better chance for an S_NAr reaction, but this substrate was more cost-restrictive. Initial trials with 2-chloro and 2-bromo pyridines afforded no addition of the desired nucleophile and only resulted in unreacted starting material. In some instances when using KOH as base, trace amounts of side product were observed by NMR.

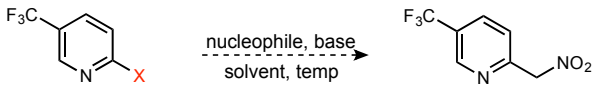
An extended summary of reactions attempted to install a suitable handle to furnish the nitroalkane is outlined in Table 2. A range of nucleophiles, solvents, and reaction temperatures were explored. Nearly all attempts resulted in unreacted starting material. From this data, it was evident that tedious synthetic efforts would be additionally needed if the desired trifluoromethyl nitroalkane or aldehyde were to be generated.

Ultimately, our approach returned to generating the 2-pyridyl aldehyde **15** and Boc-imine as previously mentioned. Although met with low conversion and isolation previously, there was hope the desired compound(s) could be generated *in situ* and carried on to the Mannich addition

[35] WO2004/096772

crude without purification. Similar literature transformations (patents using similar heterocycles)

Table 2. Attempts to generate nitroalkane **37** from a 2-halopyridine **28** or **29**.



28 or **29** **37**

entry	X	nuc.	base	temp. (˚C)	solvent	result
1	Cl	$MeNO_2$	KOH	17	DMSO	SM
2	Cl	$MeNO_2$	K^{t}OBu	25	toluene	SM
3	Cl	$MeNO_2$	NaH	60	THF	SM
4	Br	$MeNO_2$	NaH	60	THF	SM
5	Cl	$MeNO_2$	NaH	60	toluene	SM
6	Br	$MeNO_2$	NaH	80	neat	SM
7	Cl	$MeNO_2$	K^{t}OBu	80	neat	SM
8	Cl	$MeNO_2Ac$	^{n}BuLi	-78	toluene	SM
9	Cl	$MeNO_2Ac$	KOH	70	NMP	SM
10	Cl	$BrCH_2NO_2$	^{n}BuLi	-78	toluene	SM
11	Br	$BrCH_2NO_2$	^{n}BuLi (2 eq)	-78	toluene	SM

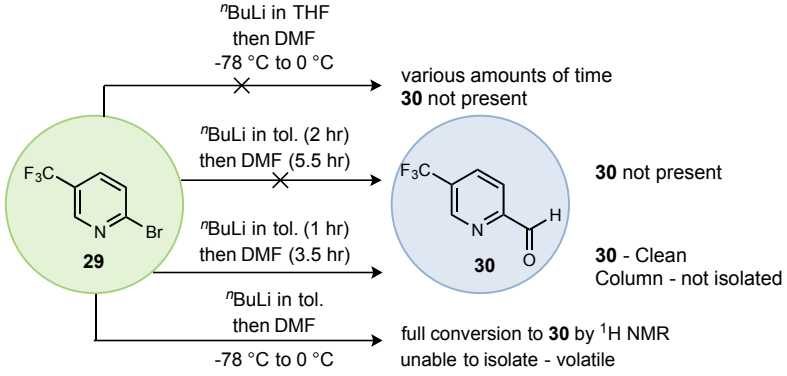
All reactions were run in the corresponding solvent at 0.2M concentration. SM = starting material

show that 2-halopyridines readily undergo metallation and react with suitable electrophiles.

An article from early 2000, beautifully discussed the phenomenon we witnessed during the problematic lithium-halogen exchange.[36] Somewhat surprisingly, solvent choice was essential to regioselective metallation at various mono- and dibromo pyridines. Using 2,5-dibromopyridine, *n*-BuLi in dry THF, lithiation only occurred at the 5-position of the pyridine, which is otherwise the less reactive site. When replacing THF with toluene, lithiation shifted 100% to the 2-position, which was desired to geneate the desired carbonylated pyridine in this work moving forward.

[36] Reider, P. *Tetrahedron Lett.* **2000**. *41*, 4335.

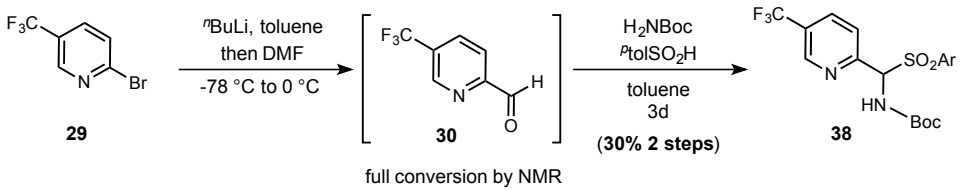
Figure 9. Optimization of the formylation reaction from **29** to generate pyridyl aldehyde **30**.



After exploring these conditions with our trifluoromethyl substrate **29**, we were pleased to see very similar regioselective lithiation results (Figure 9). Reacting **29** with *n*-BuLi in THF at -78 °C, no reaction was observed and only resulted in recovered starting material – evidence that metallation never occurred. Manipulating the reaction time of lithium-halogen exchange from 2 hours to 1 hour in toluene, followed by the addition of dimethyl formamide (DMF), gave near quantitative conversion by NMR to the desired aldehyde **30**. However, ensuing column chromatography yielded none of the desired product. After scaling up this reaction to 0.5 mmol, it was shocking to observe pure solidified **30** evaporate under a steady stream of air. Although unable to isolate, the problem with this substrate was now quite clear and we quickly attempted to solve this issue of volatility.

Understanding the volatility of **30**, it was evident isolation wasn't possible to generate the aryl α-amido sulfone, the necessary precursor to the desired imine. After quenching and drying metallation-addition reaction containing aldehyde **30**, Boc-carbamate and sulfinic acid (the sodium salt was not a viable option in toluene) were added to the stirring solution at room temperature, and the desired sulfone **38** was isolated in a 30% yield (2 steps) after 3 days (Scheme 10). As is typical with other aryl sulfone derivatives in the past, we were fortunate this

Scheme 10. Synthesis of the aldehyde **30** was carried through *in situ* to generate sulfone **38**.



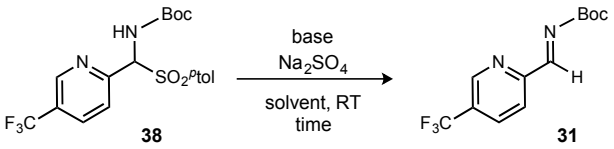
substrate was insoluble in toluene at low concentrations, making isolation of pure sulfone straightforward via vacuum filtration (see Experimental).

After scaling up this reaction to 5 mmol of **29**, sulfone **38** was carried on to Boc-imine **31** following optimization of elimination conditions. Unlike more traditional and cooperative aryl Boc-imines used in the past, this heterocyclic pyridyl adduct posed challenges. Under standard basic elimination conditions (K_2CO_3, Na_2SO_4 in THF at reflux),[37] this substrate decomposed readily and another milder elimination protocol was needed in order to be successful. A series of basic screens were carried out – altering the inorganic base, solvent, and reaction time. Temperatures remained ambient throughout, as to not disrupt stability of the sensitive substrate.

These experiments were qualitative in nature, and ^{1}H NMR data was gathered from the crude reaction product in order to determine percent conversion to imine **31** from unreacted α-amido sulfone **38** (Table 3). Some reaction conditions were adapted from literature procedures.[38] After examining a variety of conditions, Cs_2CO_3 in toluene after 3 hours (Entry 8, Table 3) generated the imine in near full conversion from the aryl sulfone **38** (by ^{1}H NMR) with minimal byproducts. Mindful of substrate sensitivity, imine **31** was carried through *in situ* to the enantioselective aza-Henry reaction.

[37] Davis, T. A. *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.* Ph. D. Thesis, Vanderbilt University. **2011**.
[38] Deng, L. *Org. Lett.* **2007**, *9*, 603.

Table 3. Qualitative evaluation of eliminating conditions to generate imine **31** in clean conversion.[a]



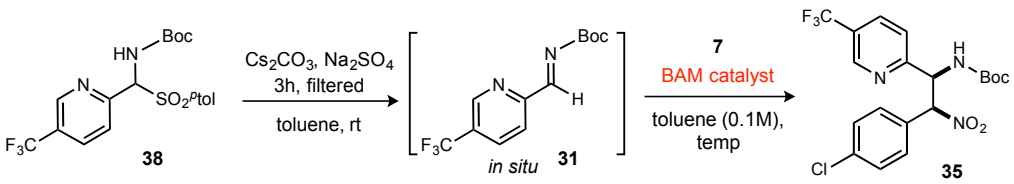
entry	base (equiv.)	time (h)	solvent	imine present
1	Na_2CO_3 (8)	3	DCM	no
2	Cs_2CO_3 (8)	3	DCM	yes
3	Cs_2CO_3 (8)	3	THF	yes, cleaner
4	Cs_2CO_3 (8)	2	THF	yes
5	0.1M Na_2CO_3 (2)	3	DCM	no
6	sat. Na_2CO_3 (~8)	5	DCM	no
7	Cs_2CO_3 (1)	3	THF/tol.	yes
8	Cs_2CO_3 (8)	3	Toluene	yes, cleanest

[a]Reactions ran at 0.1M in the corresponding solvents for the allotted time at room temperature. Reactions were cooled, filtered and conversion was assessed by ^{1}H NMR

In the original asymmetric synthesis of (–)-Nutlin-3, various PBAM catalysts were explored and optimized until the desired aza-Henry adduct was isolated in a 13:1 diastereomeric ratio (dr) and 91% enantiomeric excess (ee) using [6,7](MeO)$_2$PBAM (**2b**, Chart 1). In hopes of obtaining analogous results with trifluoromethyl pyridyl Boc-imine **31** and *para*-chloroaryl nitromethane **7**, a general screen of various PBAM catalysts was examined. One difference in this transformation worth addressing is the presence of an aryl nitrogen on the Boc-imine. From the outset, it wasn't apparent how this nitrogen (although not significantly Brønsted basic due to the electron-withdrawing nature of the trifluoromethyl group) may affect reactivity and enantioselection in the reaction.

The enantioselective aza-Henry reaction under modified conditions to access imine **31** was carried out as depicted in Table 4. α-Amido sulfone **38** was treated with the optimal elimination conditions to generate imine **31** *in situ*, followed by filtration through celite. The designated catalyst was added (5 mol% BAM catalyst) to the toluene mixture at room temperature and chilled to -78 °C. Nitroalkane **7** was added and the reaction stirred for an allotted time at -78 °C (or transferred to -20 °C after 24 hours to promote full conversion to product). The results from these experiments are outlined in Table 4. The catalysts evaluated showed a wide range of stereocontrol. Interestingly, [6,8](MeO)$_2$PBAM (**2e**, Entries 6 and 7) gave -42% ee favoring the opposite enantiomer as confirmed by chiral HPLC. This experiment was run in duplicate, as were many others not listed in Table 4. PBAM **2a** (Entry 8) proved to be the optimal catalyst for this substrate at 5 mol% catalyst loading, giving 15:1 dr and 63% ee and was sufficiently scaled to give 376 mg of the aza-Henry adduct **35**.

Table 4. Elimination to imine **31** and conversion to aza-Henry product **35** under various conditions. Summary of enantioselective, catalytic conditions to give **35**.

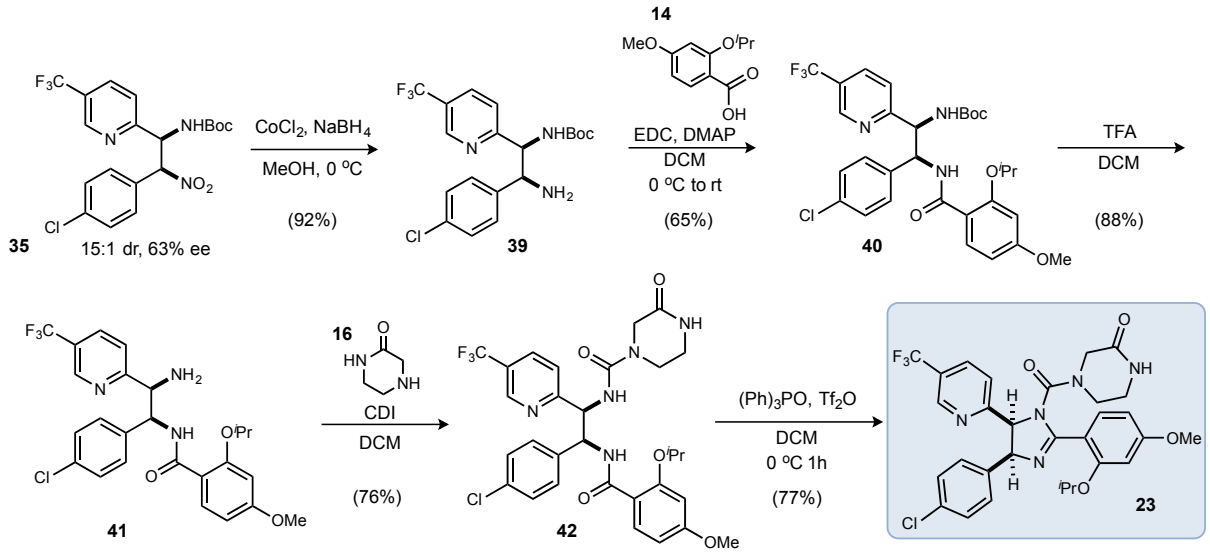


entry	catalyst (mol %)	temp (˚C)[§]	time (hr)	dr/%ee[*]	yield (2 steps)
1	**2e** (5)	-78	36	7:1/45	6%
2	**2a**•HOTf (5)	-78	36	7.5:1/51	6%
3	**2a** (5)	-78 to -20	36	16:1/59	34%
4	**2a** (5)	-78 to -20	42	29:1/55	33%
5	**2b** (5)	-78 to -20	36	23:1/65	22%
6	**2e** (5)	-78 to -20	36	27:1/-42	12%
7	**2e** (5)	-78 to -20	36	8:1/-42	53%
8	**2a** (5)	-78 to -20	55	15:1/63	61%

[§]Reactions with temperatures at -20 ˚C were transferred from -78 ˚C after the denoted time and stirred for an additional 2 hours. [*]%ee of major diastereomer reported

Once this β-amino nitroalkane **35** was in hand in modest ee and good dr the next five synthetic steps were carried out in analogous procedural fashion to (–)-Nutlin-3 (Scheme 11).[9] Cobalt chloride-mediated hydride reduction of the nitro group on **35** afforded the protected *cis*-stilbene diamine **39** in 92% yield. Now liberated, the free amine underwent an EDC mediated amidation reaction with the benzoic acid derivative **14** generating benzamide **40** in 65% yield. This Boc-carbamate (**40**) was deprotected with trifluoroacetic acid (TFA) yielding amine **41** in 88% yield. This free amine was treated with carbonyl diimidazole (CDI) to form the isocyanate *in situ*, where upon trapping with oxapiperazine **16**, afforded the penultimate urea **42** in 77% yield. During purification of urea **42**, diastereomers could be separated and the desired stereoisomer was isolated in >20:1 dr (by ^{1}H NMR). A dehydrative cyclization promoted with triphenyl phosphineoxide (Ph_3PO) and triflic anhydride (Tf_2O) generated a phosphonium anhydride *in situ* (Hendrickson's Reagent), which furnished the *cis*-imidazoline core of Nutlin **23** in 77% yield. This was the first *nonsymmetric* Nutlin-3 derivative ever prepared (compound **23**)

Scheme 11. Final steps to access the first heteroaromatic, unsymmetrical Nutin-3 derivative **23** using asymmetric catalysis.

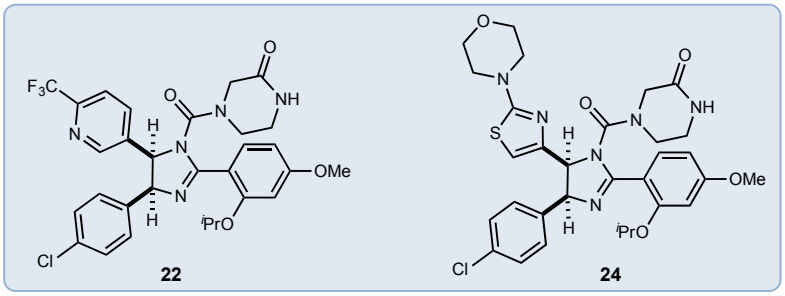


in enantioselective fashion.

In sum, 55 mg of the nonsymmetric (4*S*,5*R*)-Nutlin-3 analogue **23** was prepared (63% ee, as a single diastereomer) and submitted to the Guy group at SJRH to be assayed. The next two (4*S*,5*R*)-*cis*-imidazoline derivatives pursued were compounds **22** and **24** (Figure 10). These targets also contain a trifluoromethyl pyridine moiety (constitutionally isomeric to **23**) and a drastically different morpholo-thiazole ring system (**24**). These targets made for very interesting cases, both chemically and biologically, but especially when examining the aza-Henry reaction to generate the nonsymmetric masked *cis*-stilbene diamine. Outlined hereafter will be the syntheses of these compounds, although abbreviated since the steps taken are analogous to the synthesis of (4*S*,5*R*)-Nutlin derivative **23** previously discussed.

The next two heteroaromatic ("exotic") Nutlin analogues described hereafter (**22** and **24**) were prepared in a similar fashion to the aforementioned trifluoromethyl pyridine analogue **23**. The synthetic challenges encountered when preparing these unique aza-Henry precursors, notably the heteroaromatic *N*-Boc-imines, are traditionally difficult to prepare and few literature examples (if any) exist detailing the assembly of these sensitive yet useful building blocks. The preparation of the following exotic Nutlins focus more on the enantioselective aza-Henry

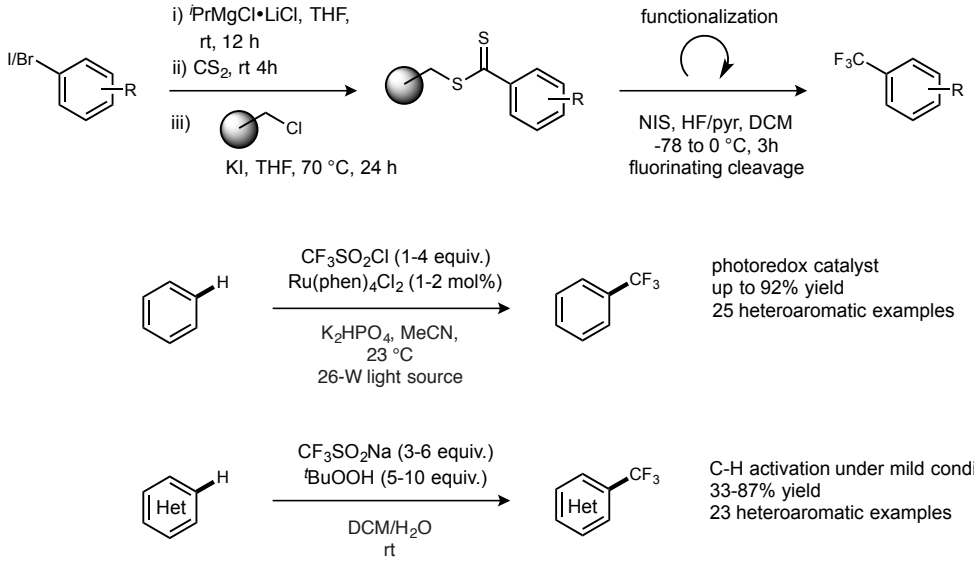
Figure 10. Two novel heteroaromatic *cis*-imidazoline analogues targeted for synthesis: trifluoromethyl pyridine **22** and morpholine-thiazole derivative **24**.



reaction and the role of the *bis*(amidine) catalysts.

We were fortunate the previous intermediate to access Nutlin analogue **23**, 2-chloro-5-trifluoromethyl pyridine (**28**), was commercially available at reasonable prices. Aryl trifluoromethylation reactions are notoriously challenging and have received the lion's share of attention in recent years as a result.[39] A few of the challenges were evident in this synthesis.

Figure 11. Trifluoromethylation reactions. Method **A** involves solid-support functionalization with late stage fluorination. **B** involves elegant C-H activation using photoredox catalysis pioneered by MacMillan *et al*. Method **C** employs more mild C-H activation using a more practical CF_3-salt, although a large excess of reagent is needed.



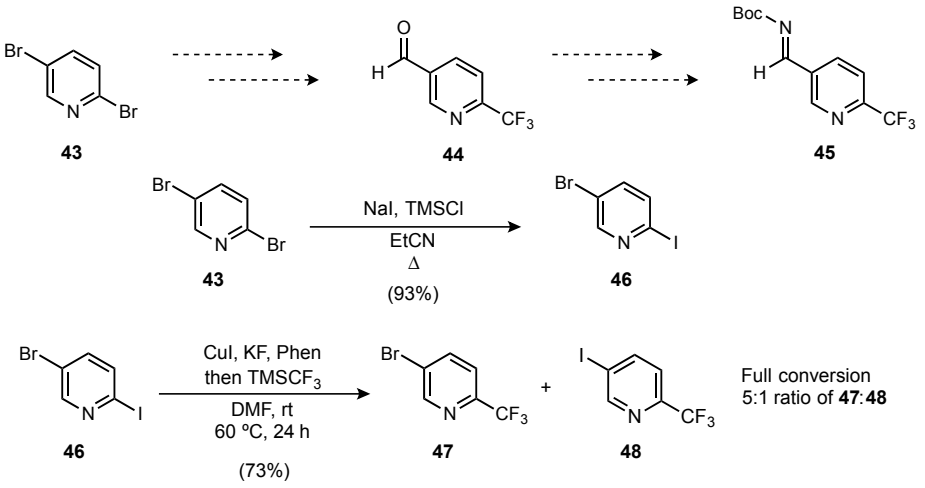
Pronucleophilic trifluoromethyl reagents such as Ruppert's Reagent ($TMSCF_3$) and trifluoromethyl iodide are most commonly utilized in S_NAr chemistry so we decided to first investigate approaches using these compounds. Conventionally, trifluoromethyl anions are carefully generated *in situ* and these basic species can be stabilized through various "chaperone" species, usually metal ligands. But common side reactions and byproducts are a major concern and usually result from radical degradation, hydrogen atom abstraction, and other irreversible

[39] Ji, Y. N.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14411. Schlosser, M. *Eur. Org. Chem.* **2003**, 1559. Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

transformations due to fluorine's high electronegativity.[40] A few recent examples of aryl trifluoromethylation reactions are shown in Figure 11.[41]

We employed Ruppert's Reagent as a source of trifluoromethyl anion to displace bromine from readily available 2,5-dibromopyridine **43**, a known procedure. With the resulting halo-trifluoromethyl pyridine in hand, we anticipated the generation of the aldehyde **44** and pyridyl Boc-imine **45** (Figure 12) seamlessly in subsequent steps. Following optimization, the trifluoromethylation generating 5-bromo-2-trifluoromethyl pyridine **47** was finally accomplished under copper(I)-mediated, freeze-pump-thaw conditions from the iodo pyridine **46**.[42] Although the reaction went to completion by NMR, a cross-halogenation (or "halogen dance"[43]) side product (**48**) was also observed. Luckily, together with NMR and LCMS analysis, it was apparent this was the 5-iodo pyridine adduct **48** and therefore should not interfere in subsequent

Figure 12. Proposed synthesis to generate trifluoromethylated Boc-imine **45** and the synthetic steps taken.



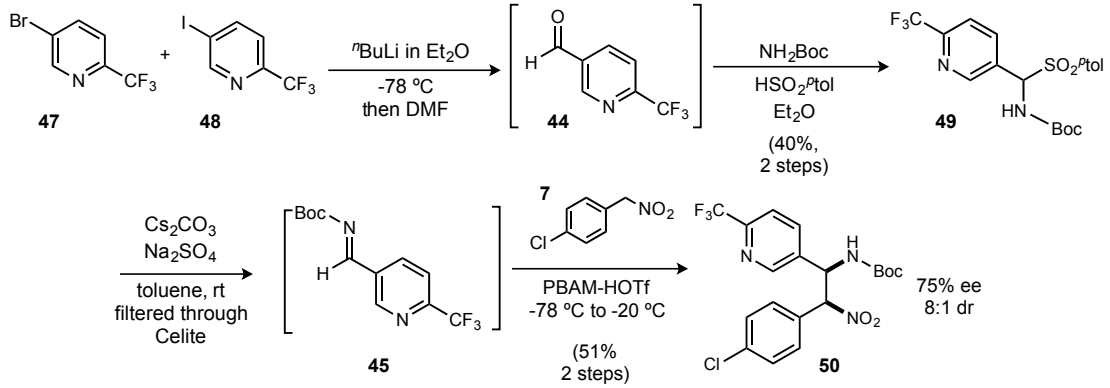
[40] Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.
[41] Ji, Y. N.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14411. Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. Dobele, M.; Wiehn, M. S.; Brase, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11533.
[42] Amii, H. *Chem. Comm.* **2009**, 1909.
[43] Stambuli, J.P. *Synthesis*. **2011**, *19*, 3083.

steps. With this intermediate in hand, a lithiation/formylation at the 5-position of **47**/**48** was next pursued.

Past experience highlighted effective ways to lithiate mono- and dihalogenated pyridines in a controlled manner.[44] When reacting **47**/**48** with *n*-BuLi at -78 °C in an ethereal solvent (preferably diethyl ether) and quenching with DMF, near quantitative conversion to the desired aldehyde **44** was observed. Volatility issues were encountered once again and aldehyde **44** was carried through *in situ* to generate the stable aryl sulfone **49**. The sulfone was isolated as a pure white solid in 40% yield over the two steps.

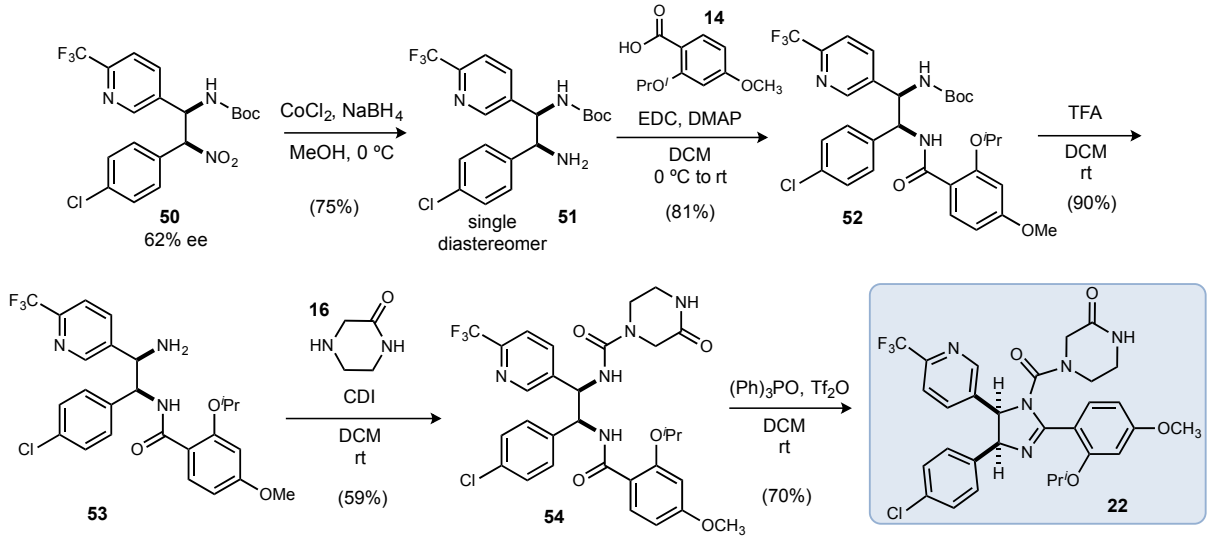
After a brief investigation of elimination conditions to afford Boc-imine **45**, Cs_2CO_3 in toluene once again proved to be optimal, and the imine was carried on crude for the aza-Henry transformation. Evaluation of a host of PBAM catalysts led to more interesting results and higher ee was generally observed in comparison to the previous trifluromethyl pyridyl imine **31**. In general, the 1:1 Brønsted acid/PBAM derivatives afforded the aza-Henry adducts in higher yields and selectivity compared to those of the free base form. We propose the acidic nature of the catalyst may protonate the pyridine nitrogen when hydrogen bonded to the imine. Adding a

Scheme 12. Synthesis of imine **45** and its efficacy in the aza-Henry reaction.



[44] Reider, P. *Tetrahedron Lett.* **2000**, *41*, 4335.

Scheme 13. Final synthetic steps taken afforded the desired Nutlin-3 derivative **22**.

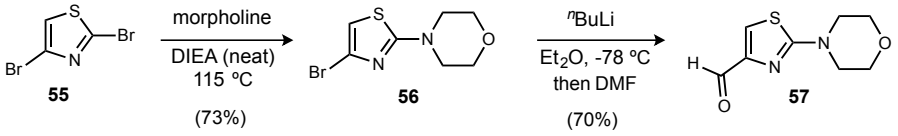


full equivalent of acid to the reaction was explored, but this control experiment was inconclusive. **2a**•HOTf (Scheme 12) proved optimal and gave the desired compound **50** in 8:1 dr, 75% ee and 51% yield over the two steps. Attempting to replicate these results on a larger 1 mmol scale, however, proved suboptimal and gave only 250 mg of the desired adduct (51% yield, 2 steps) with 4:1 dr and 62% ee. Not completely satisfied with the degree of selectivity, this material was nonetheless carried through to the final (4*S*,5*R*)-*cis*-imidazoline derivative.

Scheme 13 details the last half of the completed synthesis for this target (4*S*,5*R*)-Nutlin compound **22**. Fortunately, diastereomers could be separated following the reduction of the nitro group to the free amine **51** and the desired compound was isolated and carried through as the single desired diastereomer. This free amine was coupled with acid **14** to generate the benzamide intermediate **52** in 81% yield. The Boc-carbamate was then deprotected using TFA to deliver the free amine **53** in 90% yield.

CDI-mediated coupling of oxapiperizine **16** with the revealed amine **53** generated urea **54** in 59% yield. The yield for this step was somewhat lower than previous trials due to residual

Scheme 14. Optimized conditions to generate aldehyde **57**.



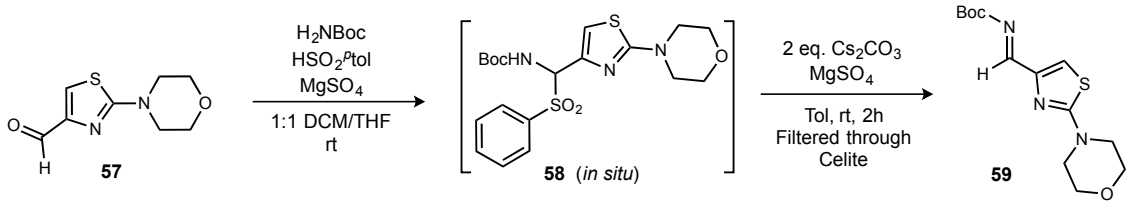
benzoic acid that was present, since compound **52** was washed and carried through only semi-pure. The triphenylphosphine oxide and Tf_2O-mediated dehydration/cyclization furnished the desired imidazoline core of the (4*S*,5*R*)-*cis*-imidazoline **22** in 70% yield. 30 mg of material was characterized and shipped to collaborators at St. Jude for testing. With two heterocyclic derivatives completed, it was encouraging that the synthesis to access these small molecule therapeutics was quite robust and tolerant to various substitutions (although higher ee was desired).

Although seemingly structurally more complex, (4*S*,5*R*)-*cis*-imidazoline **24** was relatively straightforward to prepare. A patent outlined a chemoselective construction of the morpholine-thiazole ring system and allowed for a bromine handle at the 2-poistion of the thiazole.[45] Scheme 14 details the synthesis of this scaffold as a precursor to Nutlin derivative **6**.

Beginning from commercially available 2,4-dibromo thiazole (**55**), this material was refluxed with morpholine and smoothly afforded the coupled product **56** in 73% yield following chromatography. Regioselectivity was further confirmed by ^{13}C NMR and HMBC NMR studies. With previous experience utilizing lithium-halogen exchange reactions on aromatic rings, similar reaction conditions were implemented on **56**. Initially, this reaction was carried out in toluene under dilute conditions, with *n*-BuLi and DMF, and resulted in 50% conversion (by ^1H NMR) to the desired aldehyde **57**. When using dry diethyl ether under more concentrated conditions, aldehyde **57** was generated in an improved 70% yield (Scheme 14).

[45] Kan, J.; Coate, H.; Chen, X. U.S. *Patent 2009197862*, **2009**.

Scheme 15. Generation of sulfone **58** which was carried through *in situ* to generate imine **59**.



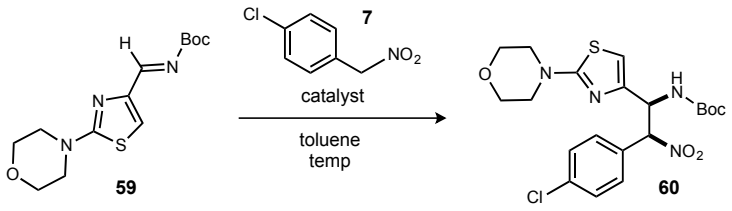
Aldehyde **57** was subjected to sulfone-forming conditions (*para*-toluene sulfinic acid and Boc-carbamate in diethyl ether) to generate the desired aryl sulfone **47** in near 90% conversion from the aldehyde. After four attempts to optimize sulfone formation, a small amount of dichloromethane (~5% of the total solution) was found to promote the rate of sulfone formation and conversion (92% from **57**).[46]

Traditionally, aryl sulfones are easily isolated as white solids upon filtration. Heterocyclic sulfone **58**, however, was an oil at room temperature, and was easier to work with when carried through *in situ* to form imine **59** (Scheme 14). To the stirring sulfone mixture, was added additional base and magnesium sulfate (to reduce imine hydrolysis) to afford the desired aryl imine **59**. This mixture however, contained Boc-carbamate and trace amounts of aldehyde and could not be purified via column chromatography due to the imines propensity to hydrolyze on silica gel. Therefore, **59** was used without purification in the aza-Henry reaction and may be a reason leading to lower enantioselectivity.

Differing from past imine substrates, higher catalyst loading was found to be beneficial with this substrate, although yields were typically lower (Table 5). PBAM•HOTf (**2a**•HOTf, Table 5, entry 4) gave aza-Henry adduct **60** in 20:1 dr and 70% ee but in a more dismal 16% yield over two steps from the sulfone **58**. 15 mol % catalyst loading of PBAM-HOTf at -78 °C was found to be optimal (Table 5, entry 8) and was sufficiently scaled up to give 54 mg of **59**.

[46] Zhu, J.; George, N. *Eur. J. Org. Chem.* **2011**, 3695.

Table 5. Evaluation of conditions to afford the asymmetric nitro-Mannich adduct **60**.



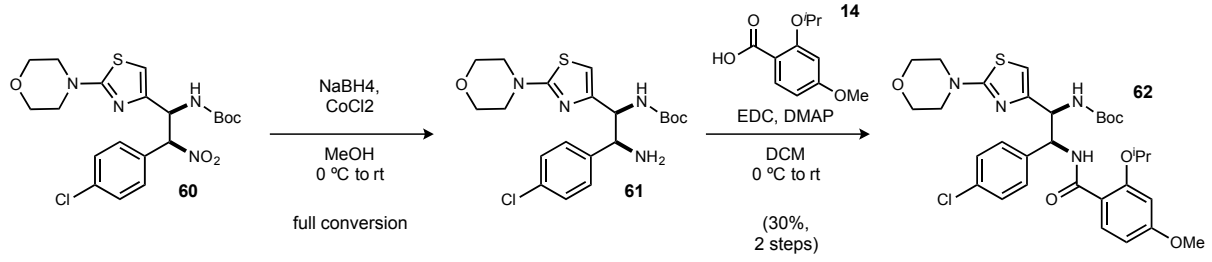
entry	catalyst (mol %)	temp (ºC)[a]	time (h)	d.r./%e.e.[b]	yield (%, 2 steps)
1	**2a** (9)	-78 to -20	36	7:1/59	39%
2	**2a**•HOTf (10)	-78 to -20	50[c]	7:1/68	50%
3	**2b**•HOTf (10)	-78 to -20	50[c]	6:1/62	31%
4	**2a**•HOTf (20)	-78 to -20	36	20:1/70	16%
5	**2d** (10)	-78 to -20	36	11:1/53	27%
6	**2a**•HOTf (10)	-78	36	7:1/58	34%
7	**2a**•HOTf (20)	-78 to -20	36	6:1/63	24%
8	**2a**•HOTf (15)	-78	40	14:1/67	41%

[a]Reactions with temperatures at -20 ˚C were transferred from -78 ˚C after the denoted time and stirred for an additional 2 hours. [b]% e.e. of major diastereomer reported. [c]24 hours at -20 ˚C

Low levels of stereocontrol in these reactions may be attributed to a few factors: 1) the impure nature of the imine, 2) the increased conformational flexibility of the morpholine ring system, and 3) the presence of a Brønsted basic tertiary amine. These characteristics may decrease substrate rigidity and compatibility within the catalyst binding pocket resulting in lower stereocontrol.

The remaining synthetic steps to access the derivative can be seen in Scheme 16. The cobalt chloride mediated reduction of the β-amino nitroalkane **60** with $NaBH_4$ showed a mixture

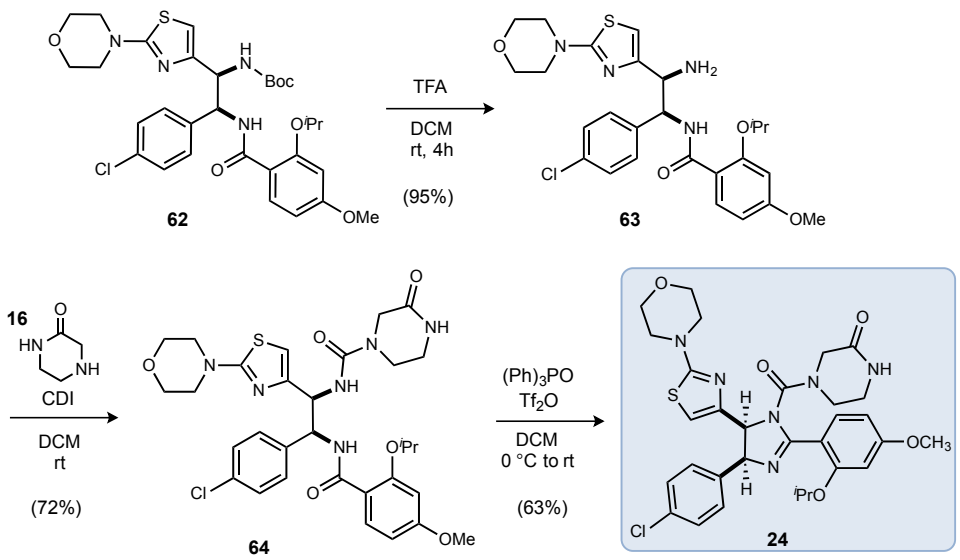
Scheme 16. Transformations from the enantioenriched aza-Henry adduct **60** to benzamide **62**.



of products, yet all the critical peaks seemed to be present and starting material was no longer visible – this material was carried through without purification. The subsequent step was the ethyl diazodicarbonyl mediated coupling of the protected *cis*-amine **61** with the benzoic acid **14**. Following column chromatography, the desired amide **62** was isolated in a 30% yield over these two steps.

A possible explanation is that the amine starting material was a mixture of products and wasn't nearly as pure as the crude ^{1}H NMR suggested. These reactions were later attempted with more material solidifying the notion that the $CoCl_2$ reduction step was leading to poor conversion. Following column chromatography, *cis*-diamine **61** was isolated in a 30% yield from 125 mg of the aza-Henry adduct **60** (Scheme 16). Nonetheless, diastereomers could be separated using flash chromatography at this stage. The EDC coupling of **61** with acid **14** proceeded in 60% yield. Overall, in comparison to the trial reaction previously discussed (Scheme 16) that resulted in a 30% yield to amide **62** over two steps, the more recent reaction ran and purified by flash chromatography resulted in a more dismal 17% yield over those same two steps.

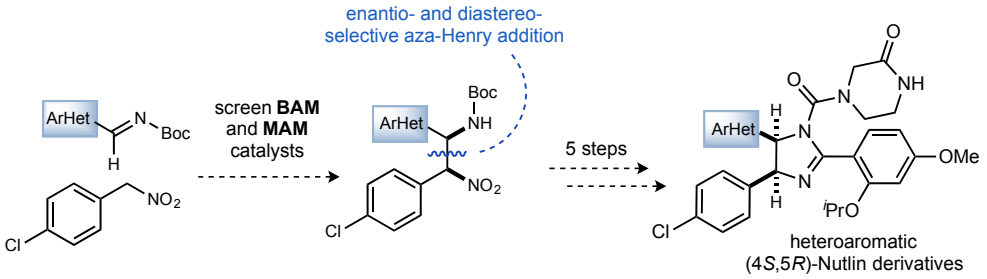
Scheme 17. Final synthetic steps to generate the morpholine-thiazole (–)-Nutlin derivative **24**.



Following isolation of the coupled benzamide product **62**, remaining reactions went as expected, and compounds were isolated in good yields. Boc-carbamate deprotection with TFA went as expected and generated the free amine **63** in 95% yield. The urea functionality was installed with oxapiperazine **16** and CDI, and the desired penultimate compound **64** was isolated in 72% yield. The dehydrative cyclization furnished the desired *cis*-imidazoline **24** in 63% isolated yield – 12 mg of this final (4*S*,5*R*)-Nutlin derivative **24** was prepared, and a portion was sent for testing.

Although enantioselectivity was not optimal in the catalyzed aza-Henry reaction, (up to 75% ee seen for aza-Henry adduct **60** (Scheme 12)) the targeted derivatives were assembled in an expedient and consistent manner. This chemistry exemplifies the ability to generate nonsymmetric, heterocyclic *cis*-stilbene diamines in an enantioselective fashion and transform these intermediates into useful small molecules (Figure 13).

Figure 13. General strategy to access unsymmetric, heterocyclic *cis*-stilbene diamines. These masked diamines can be easily transformed to powerful small molecules, such as Nutlin derivatives.

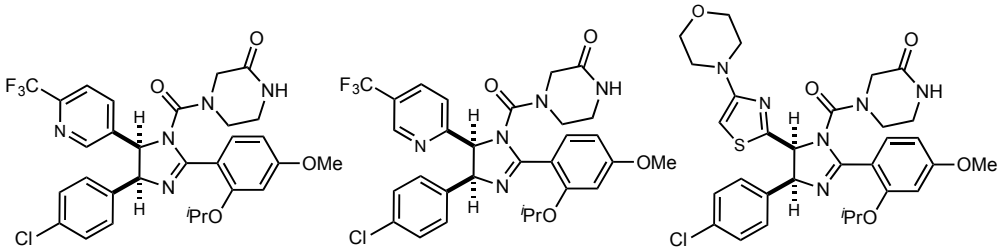


It should be noted that recrystallizations at several points during the syntheses of these heteroaromatic compounds were attempted to enhance ee. Unfortunately, the racemate tended to recrystallize before the desired enantiomer in many cases, and further attempts proved fruitless.

From a small-molecule discovery standpoint, enantioenriched or enantiopure compound is the highest valued material to all groups involved. Delivering the desired (4*S*,5*R*)-*cis*-

imidazoline adducts in >60% ee, although not ideal, and in an expedient fashion was an encouraging start and proof of concept. In order to test the activity of these novel Nutlin derivatives against MDMX-p53 inhibition, Kip Guy and his group have developed a robust fluorescence polarization (FP) binding assay with high-throughput screening (HTS) capabilities. This assay is based on the retention of emission during fluorescence spectroscopy of the WT (or mutant) p53 peptide labeled with a fluorophore such as fluorescein isothiocyanate (FITC). Experimentally, the affinity/inhibition of a small molecule can be quantified based on the degree of fluorophore-MDMX conjugation and detection using a fluorescence spectrophotometer.[47]

Figure 14. Nutlin analogues prepared in moderate levels of stereocontrol. The fluorescence polarization (FP) MDMX-p53 binding affinity data for each compound is listed. FP data courtesy of Kip Guy & St. Jude.



22

62% ee (75% ee)
single diastereomer

MDMX-p53
FP assay: >40 μM

23

63% ee
single diastereomer

MDMX-p53
FP assay: >40 μM

24

67% ee
20:1 dr

MDMX-p53
FP assay: >40 μM

As Figure 14 indicates, the heteroaromatic *cis*-imidazoline analogues were unfortunately weak inhibitors of MDMX-p53 in FP assays. It was reported that each analogue tested exhibited IC_{50} values greater than 40 μM, whereas (4*S*,5*R*)-Nutlin-3 has an IC_{50} value of around 20 μM for MDMX-p53. These data suggest that altering stereoelectronics with heteroatoms or larger substitutions (i.e. morpholine) of an aryl ring is not tolerable when targeting MDMX-p53 PPI. For this reason the priority for preparing remaining heteroaromatic Nutlin derivatives **22**, **23**, and

[47] Reed, D.; Shen, Y.; Shelat, A. A.; Arnold, L. A.; Ferreira, A. M.; Zhu, F. Y.; Mills, N.; Smithson, D. C.; Regni, C. A.; Bashford, D.; Cicero, S. A.; Schulman, B. A.; Jochemsen, A. G.; Guy, R. K.; Dyer, M. A. *J. Biol. Chem.* **2010**, *285*, 10786.

24 as proposed in Figure 7 were attenuated. Although these FP assay results were not encouraging, new chemistry was being developed in our group that would assist in the synthesis of other Nutlin analogues in much higher levels of stereocontrol and scope.

1.5 Application of a New Class of Mono(Amidine)-Amide Catalysts to the aza-Henry Reaction and the Synthesis of a Library of Nutlin Derivatives

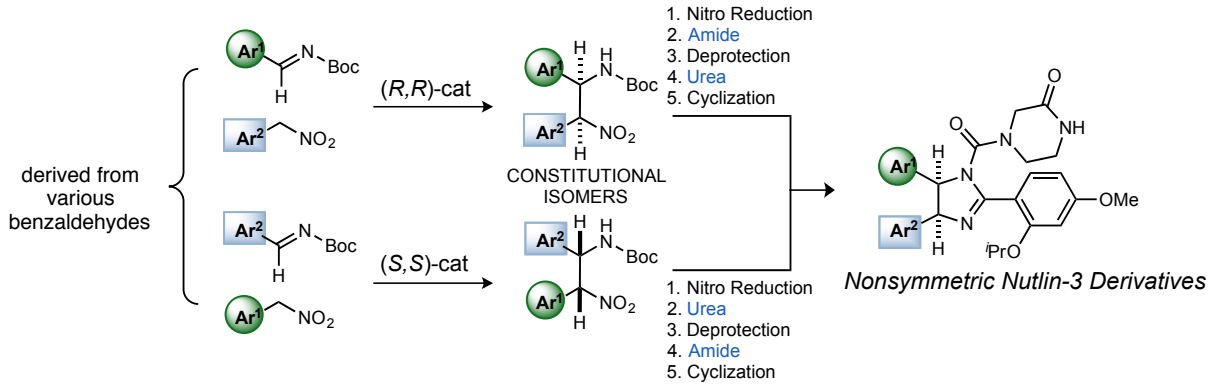
The synthesis of masked *cis*-stilbene diamines via an asymmetric aza-Henry reaction, as outlined in the 2011 *Chemical Science* article, proved vital in the first diastereoselective and enantioselective preparation of the small molecule (–)-Nultin-3. Following the synthesis of the aza-Henry adduct, five short and scalable steps remain to arrive at the target *cis*-imidazoline compound. Since it was then clear that the last five synthetic steps were tolerable to a range of heteroaromatic substrates, we turned our attention to improving the overarching practicality, stereoselection, and scope of the asymmetric aza-Henry reaction.

Experimentally, our published protocol for assembling the aza-Henry adducts was imperfect and improvements were desired. The reactions required cryogenic temperatures (usually -78 °C) for at least 24 hours to obtain >90% ee, and a decrease in ee and dr was observed with substituted aryl nitromethanes (*para*-nitrophenyl nitromethane gave just 76% ee and 2:1 dr with the optimal catalyst employed). Additionally, these substituted aryl nitromethanes are challenging to prepare and purify from benzyl bromide precursors using known Kormblum methods. From a synthetic standpoint, we set out to alleviate these challenges by improving upon the efficiency of the key aza-Henry addition reaction and the scope of aryl

nitromethanes (and imines) beginning from cheap and readily available substituted benzaldehydes. Improvements in enantioselectivity, diastereoselectivity, and the scope of aza-Henry substrates will significantly increase synthetic utility and accessibility of (4*S*,5*R*)-Nutlin analogues.

Two pairs of extra hands at various stages of the project – John Tellis and Vanessa Arrendondo – helped move our goals forward. John was a visiting summer REU student who was pivotal is establishing a new flexible synthetic framework for accessing Nutlin analogues. With his help we came to the realization that since the masked *cis*-stilbene diamines aza-Henry adducts could be assembled in high ee and dr, the relative assignment of the aryl groups in the final Nutlin product could be *inverted* from this common intermediate. The possibility of accessing the identical (4*S*,5*R*)-Nutlin scaffold from two constitutionally isomeric nitro-Mannich intermediates seemed very feasible (Figure 15). We posited that employing the enantiomer of the catalyst in conjunction with a reversal in the order of ensuing synthetic steps, the same final

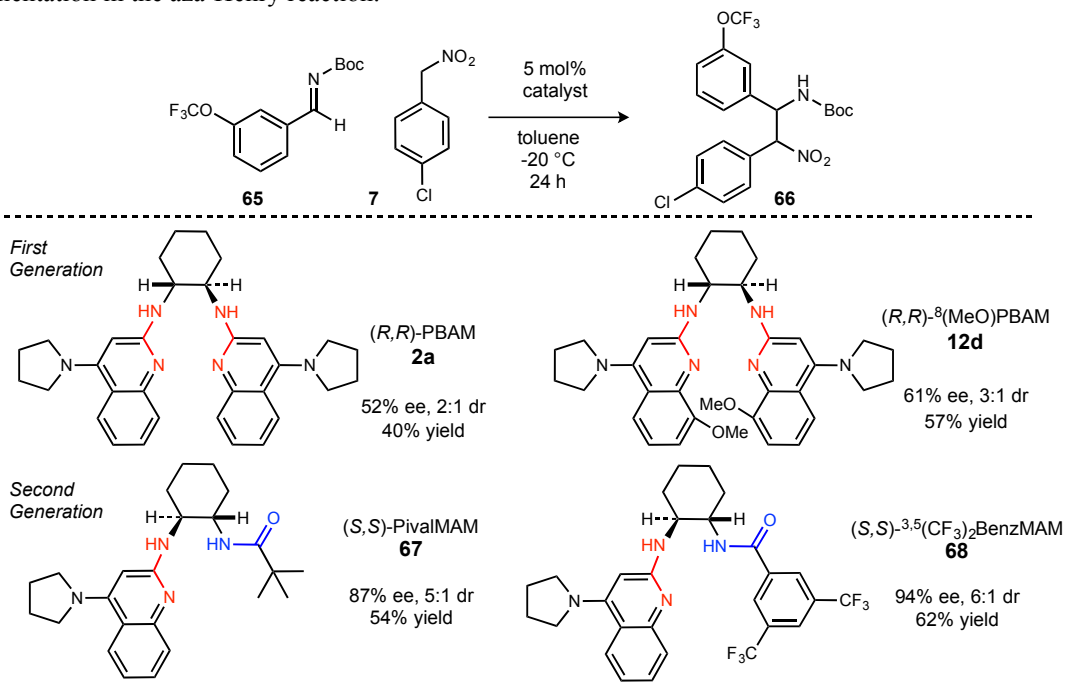
Figure 15. Envisioned synthetic flexibility allows for the formation of the same Nutlin derivative from constitutional isomers and a variety of available benzaldehydes.



compound could be accessed. Considering a single catalyst is rarely optimal for every substrate combination, interchangeability might significantly broaden our ability to arrive at highly enantioenriched Nutlin derivatives.

Conscious of this proposed synthesis, our principle goal was to address the overall efficiency of the key enantioselective nitro-Mannich reaction under more robust and practical conditions (24 h at -20 °C). Employing a new aryl *N*-Boc imine **65** as a more complex model substrate, a brief evaluation of our most reactive and selective catalyst was conducted with *para*-chloro arylnitromethane **7** as the standard pronucleophile of choice (Figure 16). Fortunately, this 3-trifluoromethoxy aryl Boc-imine **65** could be prepared following standard procedure and in good yield from the commercially available aldehyde.[48] Examining a previously optimal first generation, C_2-symmetric *bis*(amidine) catalysts PBAM **2a** and ^{8}(MeO)PBAM **2d** afforded the aza-Henry adduct **66** in 52% ee and 61% ee, respectively. Although the reactivity and diastereoselectivity was comparable to past PBAM catalysts, enantioselectivity was diminished.

Figure 16. Evolution of first generation BAM catalysts to second generation MAM catalysts and their implementation in the aza-Henry reaction.[a]



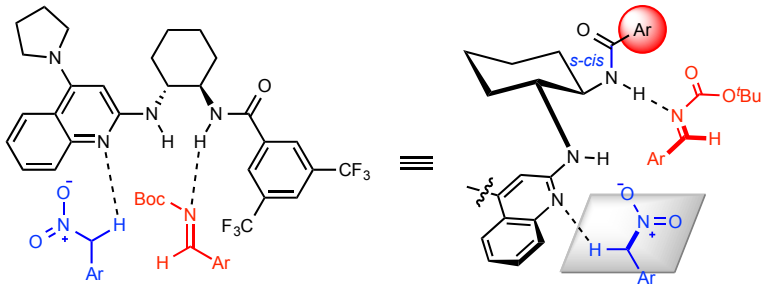
[a]1.1 equiv of nitroalkane was employed in toluene (0.1 M) with a 24 h reaction time. Diastereomeric ratio (dr) and enantiomeric excess (ee) were determined by chiral HPLC.

[48] Petrini, M. *Chem. Rev.* **2005**, *105*, 3949. Petrini, M.; Torregiani, E. *Tetrahedron Lett.* **2006**, *47*, 3501. Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem. Eur. J.* **2007**, *13*, 8338. Yin, B.; Zhang, Y.; Xu, L.-W. *Synthesis* **2010**, 3583.

This may be due to the elevated temperature of the reaction (-20 °C compared to -78 °C of past reactions) and/or deletarious steric interaction with the catalyst. Elsewhere in the group, non-C_2-symmetric pyrollidine **M**ono(**AM**idine)-amide (MAM) catalysts were being prepared for use in new transformations.[49] While exploring the function and behavior of these newly developed asymmetric catalysts within the group, we evaluated a subset of these catalysts in the asymmetric aza-Henry transformation.

To our delight, a set of these second-generation amidine-amide catalysts (Figure 16, **67** and **68**) proved most efficacious. Under these reactions conditions, (*S*,*S*)-PivalMAM **67** afforded the addition adduct in 87% ee and 5:1 dr, while (*S*,*S*)-$^{3,5}(CF_3)_2$BenzMAM **68** afforded the adduct in an impressive 94% ee and 6:1 dr (62% yield). For a serendipitous discovery, these new non-symmetric catalysts were a quite impressive improvement over the C_2-symmetric *bis*(amidines) previously published.

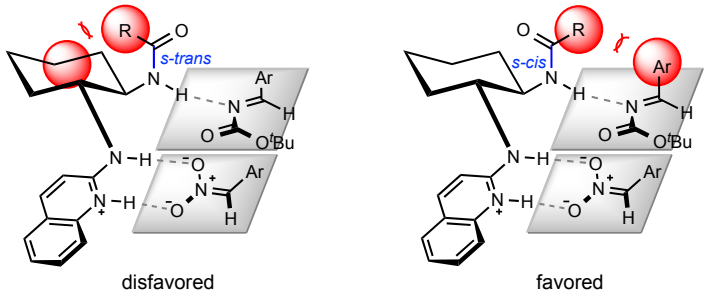
To date, formal mechanistic studies have not been carried out with these new catalysts in the aza-Henry transformation, but notable trends have been observed that help establish general stereochemical models. In agreement with past bifunctional Brønsted basic organocatalyst studies, a general diagram of catalyst-substrate activation is described in Model A. To help arrive at a reasonable stereochemical model, a library of non-C_2-symmetric amidine-amide catalysts



Model **A**

[49] Danneman, Johnston. *Unpublished Results.*

were prepared that altered the stereoelectronics around the amide nitrogen.[49] Hypothetically, amidine-mediated deprotonation of the pronucleophile leads to the formation of an aryl nitronate while the *N*-Boc-imine is simultaneously activated in a Brønsted acidic (chiral proton) environment. From these experiments, the acidity of the amide N-H amide moiety seems essential to activating the imine while keeping an organized hydrogen bond network leading to high levels of stereoselectivity.



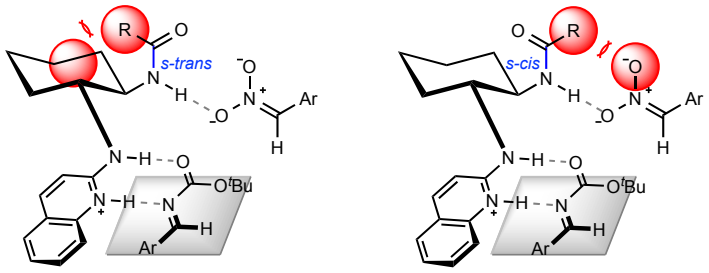
Model **B**

This notion is further supported by the absence of a strong Brønsted acid counter ion employed in past PBAM-mediated addition reactions.[50,] Model B suggests another plausible binding mode for both the imine and nitronate in the chiral environment. Following formation of the nitronate, the oxyanions of the nitronate can bind the two hydrogens of the amidinium (similar to urea-based catalyst models proposed by Jacobsen[51]) while the amide arranges in an *s-trans* or *s-cis* orientation. In order to minimize deleterious steric interactions the amide should arrange in an *s-cis* fashion (Model B, favored) while hydrogen bonding to the imine.

[50] For examples of BAM catalyzed aza-Henry addition reactions with strong Brønsted acid counterions: Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027. Shackleford, J. P.; Shen, B.; Johnston, J. N. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 44. Davis, T. A.; Danneman, M. W.; Johnston, J. N. *Chem. Commun.* **2012**, *48*, 5578. Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. Hess, A. S.; Yoder, R. A.; Johnston, J. N. *Synlett* **2006**, 147. Wilt, J. C.; Pink, M.; Johnston, J. N. *Chem. Commun.* **2008**, 4177.

[51] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, 1919.

Conversely, Model C is another possible stereochemical model where the Boc-imine is bound to the amidinium and the nitronate is hydrogen bonded (although presumably more weakly) to the amide NH. This arrangement is possible based on past data from *bis*(amidine) catalyzed reactions where only the amidine is present, suggesting consistent levels of stereochemical control with Boc-imines in particular. As additional experiments to be discussed will explain, Model C is plausible based on more consistent stereoselectivity from a wide range of diverse aryl Boc-imines.



Model **C**

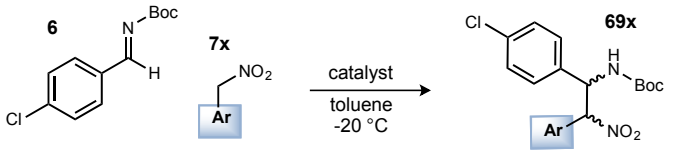
Although other models for stereochemical induction are possible, these examples represent a logical, organized arrangement of the substrates through hydrogen-bonding interactions that lead to high levels of stereochemical induction. Michael Danneman carried out more detailed studies on these new catalysts.[49]

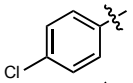
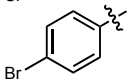
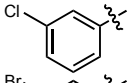
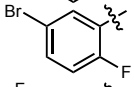
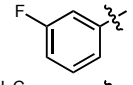
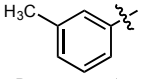
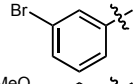
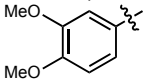
Since we were encouraged to see uniformly higher diastereoselectivity and enantioselectivity with second generation amidine-amide catalysts **67** and **68** and a flexible synthetic plan in mind to target a wide variety of Nutlin analogues, the scope of the aza-Henry reaction was examined. We first examined the utility of substituted aryl nitromethanes with 4-chloroaryl Boc-aldimine **6**, keeping the parent (–)-Nutlin-3 compound in mind (Table 6).

A host of electron-rich and electron-deficient aryl nitromethanes were prepared from commercially available aldehydes in modest yields and many are new to the literature. Procedurally, various benzaldehydes were condensed with hydroxylamine and base to form the

aldoxime, which were then treated with *m*-chloroperoxy benzoic acid (MCPBA) to afford the desired aryl nitroalkane after tedious (usually) purification. Gratifyingly, the prepared aryl nitromethanes were well tolerated under these developed catalytic conditions (Table 6). We first examined MAM catalyst efficacy with *p*-chloro aryl nitroalkane **7** and *p*-chloro aryl Boc-imine **6** (Table 6, entry 1), which would render the *cis*-stilbene diamine backbone to access (–)-Nutlin-3.

Table 6. The enantioselective, MAM-catalyzed reaction and exploration of various aryl nitromethanes with **6**.



Entry	Ar	Catalyst[b]	product	ee (%)[c]	dr[c]	Yield[c]
1		**68**	**8**	96	53:1	72%
2		**68**	**69a**	94	>200:1	75%
3		**67**	**69b**	93	>200:1	81%
4		**2f**	**69c**	92	3:1	65%
5		**68**	**69d**	92	35:1	54%
6		**67**	**69e**	93	21:1	65%
7		**67**	**69f**	91	24:1	57%
8		**68**	**69g**	76	18:1	76%

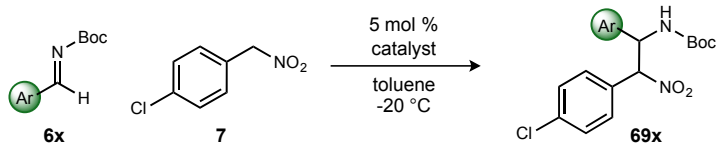
[a]All reactions were employed 1.1 equiv of nitroalkane in toluene (0.1 M) at -20 °C with 24–36 h reaction time. [b](*R*,*R*)-mono(amidine) amide catalyst unless otherwise noted. [c]Diastereomeric ratio (dr) and enantiomeric excess (ee) were determined by chiral HPLC following Buchner vacuum filtration or silica column chromatogaphy (see Experimental). [c]Isolated yields

$^{3,5}(CF_3)_2$BenzMAM (**56**) provided the adduct in 96% ee and 53:1 dr at -20 °C – a welcomed improvement from the previously reported first generation *bis*(amidine) ^{8}(MeO)PBAM catalyst **2d** at -78 °C (91% ee and 13:1 dr).[52] After screening this small set of catalysts, a range of electron-deficient (Table 6, Entry 2-5) and electron-neutral (Table 6, entry 6) aryl nitromethanes (**7**) were well tolerated and provided the aza-Henry adducts with excellent asymmetric induction (92-94% ee). 2-Fluoro-5-bromo nitromethane (Table 6, entry 4) provided an interesting case however, as the *bis*(amidine) free

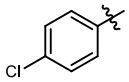
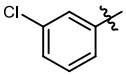
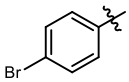
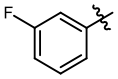
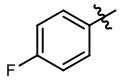
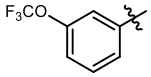
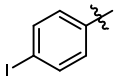
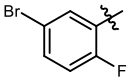
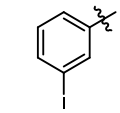
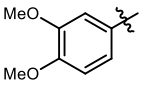
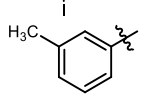
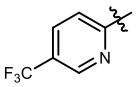
[52] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.

base of [8](MeO)PBAM **2d** provided the aza-Henry adduct in the highest ee compared to **67** and **68**. Experiments to be discussed later may help formulate a hypothesis to this phenomenon. Highly electron-rich 3,4-dimethoxy nitromethane (entry 8) saw decreased enantioselectivity and reaction rate due to diminished α-carbon acidity. Interestingly, **67** enhanced the enantioselectivity for *meta*-substituted arenes (entries 3, 6-7) possibly due to a larger chiral environment. For example, the 3-chloro aryl nitroalkane (Table 6, entry 3) gave 81% ee with [3,5]$(CF_3)_2$BenzMAM (**68**), and saw a significant improvement to 93% ee when PivalMAM (**67**) was employed.

Table 7. The catalyzed nitro-Mannich addition of *p*-chloro nitromethane **7** to various aryl Boc-imines **6**.[a]



6x **7** **69x**

entry	Ar	catalyst[b]	product	ee (%)[c]	dr[c]	yield (%)[d]	entry	Ar	catalyst[b]	product	ee (%)[c]	dr[c]	yield (%)[d]
1		**68**	**8**	96	53:1	72	7		**68**	**69l**	97	9:1	71
2		**68**	**69g**	93	>200:1	88	8		**68**	**69m**	88	60:1	98
3		**68**	**69h**	94	18:1	82	9		*ent*-**68**	**68**	94	6:1	62
4		*ent*-**68**	**69i**	99	>200:1	77	10		**68**	**69n**	84	35:1	53
5		*ent*-**67**	**69j**	99	>200:1	80	11		**68**	**69o**	92	25:1	54
6		**67**	**69k**	88	50:1	98	12		**68**[b]	**35**	85	3.5:1	40[e]

[a]All reactions were employed 1.1 equiv of nitroalkane in toluene (0.1 M) and 24–36 h reaction time unless otherwise noted. [b](*R,R*)-BAM catalyst used unless otherwise noted. [c]Diastereomeric ratio (dr) and enantiomeric excess (ee) were determined by chiral HPLC following Buchner vacuum filtration or silica column chromatography [d]Isolated yield [e]Isolated yield over two steps and ran at -78 C

Content with the range of aryl nitromethanes employed as pronucleophiles in the aza-Henry reaction, we next investigated the substrate scope of aryl Boc-imine electrophiles with these catalysts (Table 7). The synthesis of aryl Boc-aldimes from α-amido sulfones is well established and a wider array of aryl substrates can be prepared compared to aryl nitromethanes using known methods.[53]

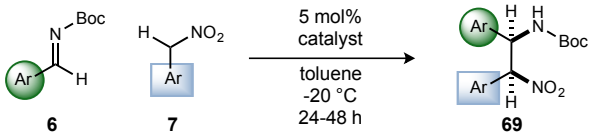
An extensive scope of aryl Boc-imines (**6**) is provided and β-amino nitroalkane adducts (**69**) were isolated in very high enantio- and diastereoselectivity (up to 99% ee and >200:1 dr; Table 7, entries 4-5). Electron-deficient imines (Table 7, entries 7-10), electron-neutral, and gratifyingly electron-rich imines (Table 7, entries 11-12) perform well. We were encouraged that heteroaromatic imine, 5-trifluoromethyl pyridyl imine from previous experiments to afford adduct **35**, was more compatible with the new reaction conditions and amidine-amide catalyst. Considering the presence of a basic aromatic nitrogen and increased electrophilicity at the aldimine carbon, this was a welcomed improvement (Table 7, entry 12). An important point to note is that stereoelectronic changes to aryl imines seem to have less of an effect on asymmetric induction relative to analogous aryl nitromethane substrates discussed in Table 6. We set out to further affirm this notion by directly comparing aryl equivalents as their imine and nitroalkane counterparts in the aza-Henry reaction.

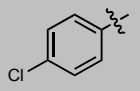
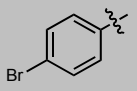
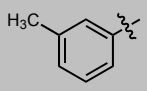
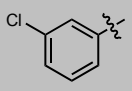
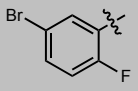
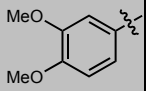
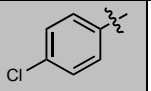
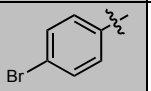
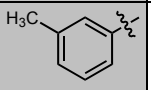
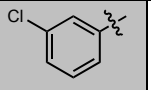
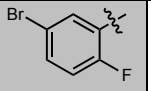
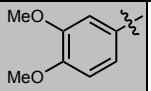
A comprehensive cross examination of imine and nitroalkane substrates with C_2-symmetric amidine-amide catalysts is outlined in Table 8. This study was informative for several reasons. First, we hoped to gain catalytic/substrate binding information on a compare and contrast basis, and establish which substrates are more consistent with the proposed catalytic model. Second, if one wants to target a nonsymmetric *cis*-imidazoline derivative, the cross-

[53] Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem. Eur. J.* **2007**, *13*, 8338.

examination of substrates delivers insight and guidance when choosing a desired aryl substitution as either the aryl Boc-imine or the aryl nitroalkane. Additionally, with the proposed flexible synthesis to afford identical (4*S*,5*R*)-Nutlin derivatives from constitutionally isomeric nitro-Mannich adducts, we hoped to identify the most efficacious (ee and dr) pairings of aryl Boc-imines and aryl nitromethanes.

Table 8. Comprehensive cross-examination of arylnitromethanes (**7**) and aryl Boc-imines (**6**) to determine optimal pairing with amidine-amide (MAM) catalysts.



Aryl nitro-methane / Aryl Boc-aldimine	 **a**	 **b**	 **c**	 **d**	 **e**	 **f**
 **1**	**68** **96% ee** 53:1 dr 72% yield	**68** **94% ee** >200:1 dr 75% yield	**67** **93% ee** 21:1 dr 65% yield	**67** **93% ee** >200:1 dr 81% yield	**12d** **92% ee** 3:1 dr 65% yield	**68** **76% ee** 37:1 dr 76% yield
 **2**	**68** **93% ee** >200:1 dr 88% yield	**68** **84% ee** 9:1 dr 75% yield	**68** **87% ee** 7:1 dr 92% yield	**68** **95% ee** 5:1 dr 80% yield	**68** **93% ee** 3:1 dr 80% yield	**8** **73% ee** 31:1 dr 51% yield
 **3**	**68** **88% ee** 50:1 dr 98% yield	**68** **85% ee** 68:1 dr 88% yield	**68** **86% ee** 50:1 dr 95% yield	**68** **99% ee** >20:1 dr 97% yield	**67** **68% ee** 5:1 dr 91% yield	**68** **78% ee** 20:1 dr (NMR) 70% yield
 **4**	**68** **97% ee** 9:1 dr 71% yield	**68** **90% ee** 70:1 dr 78% yield	**68** **85% ee** 8:1 dr 74% yield	**67** **93% ee** 30:1 dr 90% yield	**68** **76% ee** 1:1 dr 66% yield	**68** **70% ee** 23:1 dr 68% yield
 **5**	**68** **84% ee** 25:1 dr 53% yield	**68** **86% ee** 60:1 dr 87% yield	**68** **82% ee** 40:1 dr 42% yield	**67** **88% ee** 8:1 dr 90% yield	**68** **78% ee** 2:1 dr 56% yield	**68** **56% ee** 4:1 dr 70% yield
 **6**	**68** **92% ee** 25:1 dr 54% yield[b]	**68** **85% ee** 9:1 dr 60% yield	**68** **70% ee** 10:1 dr 70% yield[b]	**68** **93% ee** 56:1 dr 64% yield	**67** **42% ee** 3:1 dr 67% yield[b]	**68** **50% ee** 5:1 dr 72% yield

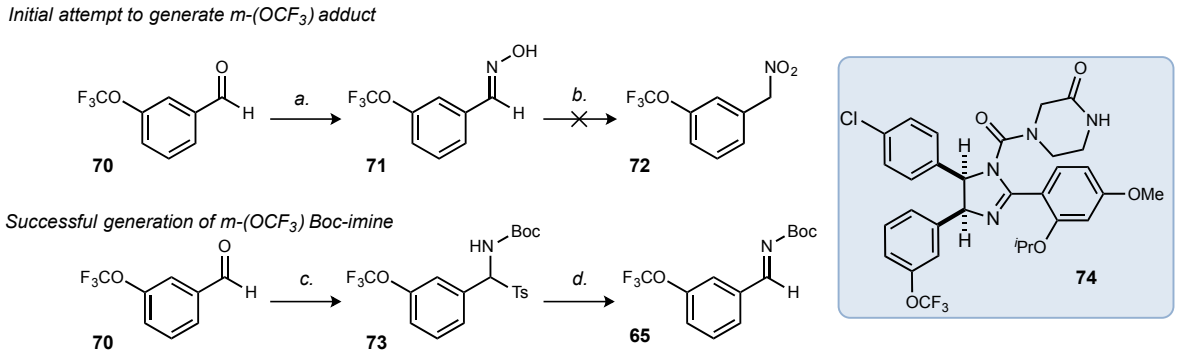
To our delight, higher asymmetric induction can be obtained by making this simple adjustment, illustrated by Table 8. Aryl Boc-imines (Table 8, entries 1-6) and aryl nitromethanes

(Table 8, entries a-f) were compared and cross-examined under optimized nitro-Mannich conditions. As was expected, the ee and dr observed for neutral and moderately electron deficient aryl nitromethanes are uniformly high at -20 °C (Table 8, entries 1-4, a-d); in general seeing no significant drop using one substrate over the other. Comparing entries 4c with 3d is an exception, however. Under identical reaction conditions with $^{3,5}(CF_3)_2$BenzMAM (**68**), 3-chloro aryl nitromethane (Table 8, entry d) behaves remarkably better than its imine counterpart (entry 4) when reacted with the 3-methyl arene partner (99% ee, >20:1 dr by ^{1}H NMR and 85% ee, 8:1 dr, respectively).

A few generalizations can be made from the data generated. aza-Henry adducts where the electron-poor 2-fluoro-5-bromo arene is employed as the nitroalkane (Table 8, entries 1e-6e) consistently resulted in low dr – presumably from the increased acidity at the α-hydrogen (up to 5:1 dr, entry 3e). Fortunately, switching to the 2-fluoro-5-bromo arylimine (entry 5) provides the adducts with improved diastereoselectivity and enantioselectivity in specific cases (Table 8, entry 5c, 82% ee/40:1 dr compared to entry 3e, 68% ee/5:1 dr). In the particular case of the 3,4-dimethoxyarene substrate, employing this electron-rich arene as the nitroalkane (Table 8, entries 1f-6f) proved unsatisfactory (up to 78% ee/20:1 dr, entry 3f) in almost every case.

Gratifyingly, a dramatic enhancement in ee and dr was seen when this arene was employed as the aryl Boc-imine (up to 93% ee/56:1 dr, Table 8, entries 6a-6f). To exemplify this point it's worth directly comparing entries 4f and 6d. These two experiments demonstrate elegant flexibility when targeting unsymmetrical aza-Henry adducts when high stereoselectivity is paramount. As exemplified in Table 8, a wide variety of aryl substrates are tolerable to reaction conditions at -20 °C and are quite general for the newly developed non-C_2-symmetric amidine-amide catalysts.

Figure 17. Unsuccessful attempts to isolate the aryl nitromethane **72** which led us to synthesize the aryl Boc-imine **85** in order to access the desired *cis*-imidazoline analogue **74**.

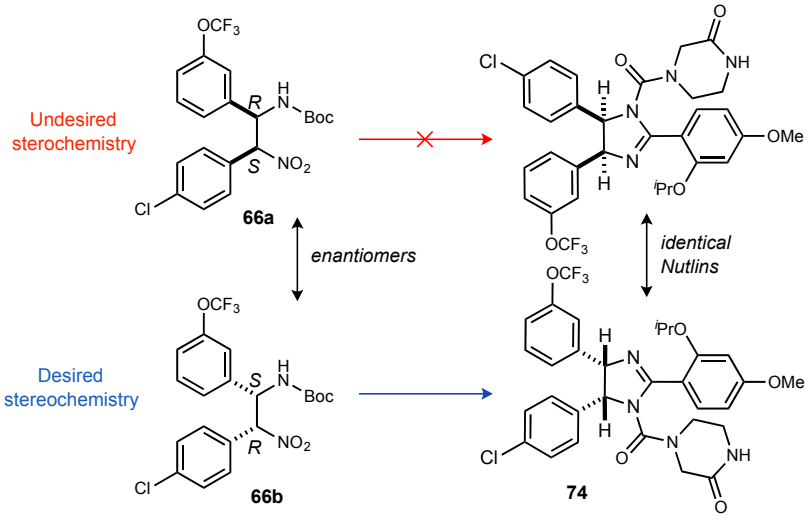


a) H_2NOH•HCl, pyr, EtOH, rt, 53%; **b)** MCPBA, DCM; **c)** $HSO_2{}^{p}$tol, $BocNH_2$, Et_2O, rt, 27%; **d)** Cs_2CO_3, Na_2SO_4, THF, rt, 98%.

The inclusion of various aryl groups in the aza-Henry reaction can be used in a forward planning direction to best choose the appropriate nitroalkane or aldimines when outlining a synthesis. This is illustrated by a synthesis that arrives at identical Nutlin derivatives beginning from constitutionally isomeric aza-Henry adducts. This was examined with the 3-trifluoromethoxy aza-Henry adduct (**65**, Figure 17) to generate the desired (4*S*,5*R*)-Nutlin analogue (**75**, Figure 17). After several unsuccessful attempts to generate 3-trifluoromethoxy arylnitromethane **72** under the standard protocol, we knew the 3-trifluoromethoxy Boc-aldimine **65** could be prepared in good yield (Figure 17).

This inherent limitation when synthesizing challenging aryl nitromethane derivatives provides further justification that an alternative route to target Nutlin derivatives is highly desirable. Since we were limited to employing the 3-trifluoromethoxyarene as the Boc-imine **65** and as the arylnitromethane, it was realized the (*S*,*S*)-enantiomer of the catalyst was needed to afford the desired (1*S*,2*R*)-β-amino nitroalkane (**66b**, Figure 18). A stereochemical diagram of this scenario is discussed in Figure 18. The desired (4*S*,5*R*)-Nutlin analogue **63** should then be

Figure 18. Strategy to access the desired (4*S*,5*R*)-Nutlin derivative **74** calls for the synthesis of the (1*S*,2*R*)-aza-Henry adduct **66b**.

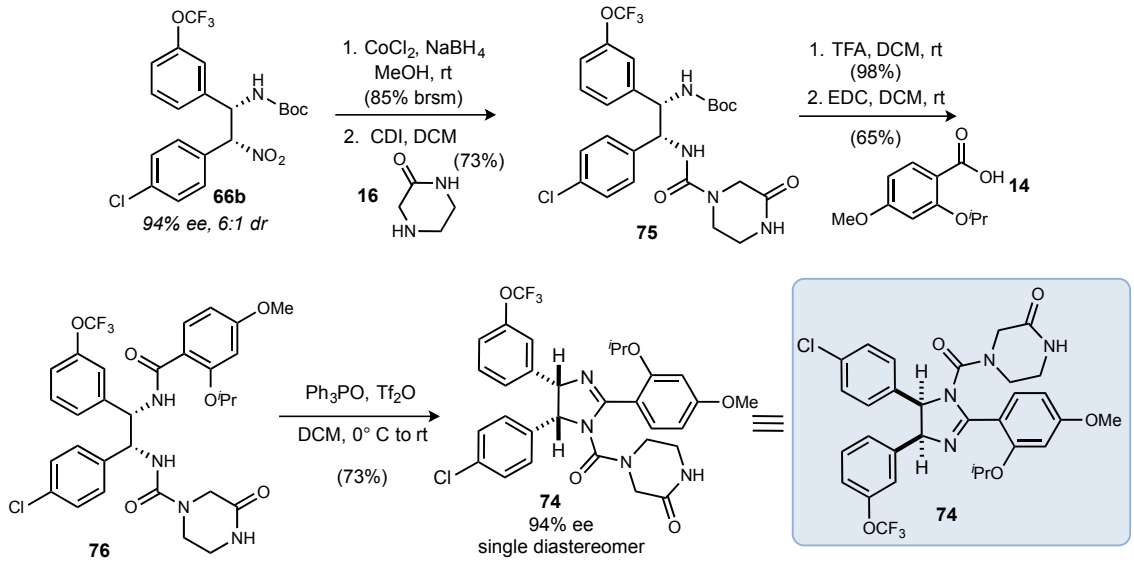


accessible from enantiomer **55b** followed by a reversal of the order of the remaining synthetic steps.

By employing (*S*,*S*)-^{3,5}(CF$_3$)$_2$BenzMAM ((*S*,*S*)-**68**), the proper β-amino nitroalkane enantiomer **66b** was generated in 94% ee and 6:1 dr.[54] This masked *cis*-stilbene diamine could now be converted to the targeted (4*S*,5*R*)-Nutlin derivative following proposed synthetic methods (Scheme 18). Nitro group reduction with $CoCl_2$ and $NaBH_4$ rendered the free amine followed by a putative isocyanation with carbonyl diimidazole (CDI) and the subsequent trapping of this intermediate with oxopiperazine **16**. Facile Boc-deprotection with TFA afforded the free amine, which underwent an acylation with acid **14** and EDC to generate the benzamide urea **76**. Triphenylphosphine oxide and triflic acid generated a phosphonium anhydride *in situ* (Hendrickson's Reagent) promoting the regioselective dehydrative cyclization to render the imidazoline core of the envisioned trifluromethoxy (4*S*,5*R*)-*cis*-imidazoline analogue **74** as a single diastereomer with 94% ee.

[54] Configuration assigned by analogy to an adduct whose absolute and relative configuration was assigned by X-ray. crystallography. Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.

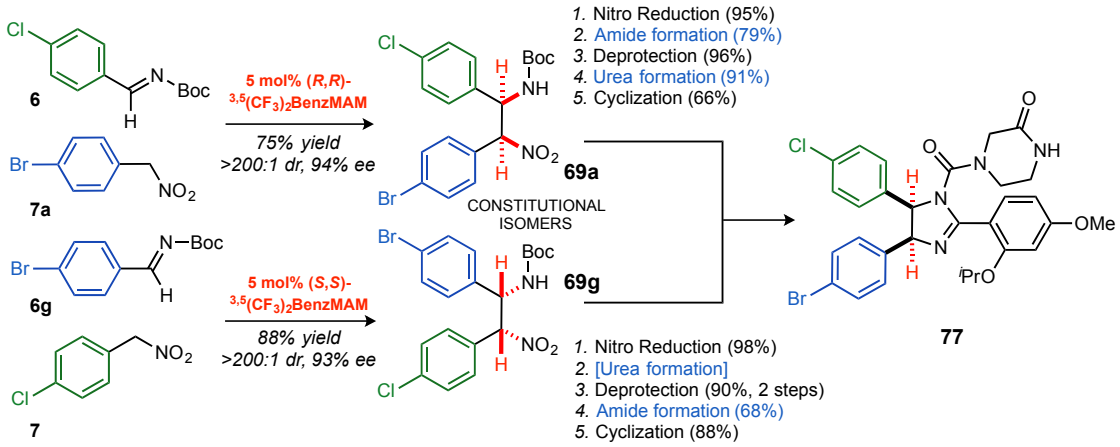
Scheme 18. Synthesis of (4*S*,5*R*)-Nutlin derivative **74** in a regioselective fashion from the (1*S*,2*R*)-aza-Henry adduct **66b**.



Encouraged by the ease of synthetic flexibly to access a desired Nutlin analogue from isomeric, enantioenriched adducts, we set out to directly compare both synthetic strategies by targeting the *p*-bromo (4*S*,5*R*)-Nutlin analogue **77** (Scheme 19). As was expected from previous substrate pairing experiments (refer to Table 8) the desired (1*R*,2*S*)- and (1*S*,2*R*)-aza-Henry adducts were generated in high levels of stereocontrol (94% ee for **69a** and 93% ee for **69g**, respectively, as single diastereomers) by using both enantiomers of catalyst **68**. The remaining steps were successfully implemented to arrive at the identical (4*S*,5*R*)-Nutlin derivative in good yield (optical rotation and spectroscopic data confirmed match, see Experimental).

Gratifyingly, varying the order of these synthetic modifications had no major detrimental effects on isolation, yield, or solubility of any intermediate at any point along the way. The key synthetic modifications stem from 1) the use of the correct enantiomer of the catalyst (highlighted in red), and 2) order of the urea and benzamide formation (highlighted in blue above the arrows (Scheme 19). These modifications allow for an overall comparable synthesis of the same unsymmetrical *p*-bromo (4*S*,5*R*)-Nutlin derivative **77** in good yields.

Scheme 19. Adaptable synthesis arriving at the same (4*S*,5*R*)-*cis*-imidazoline derivative **77** originating from constitutional isomeric aza-Henry adducts.



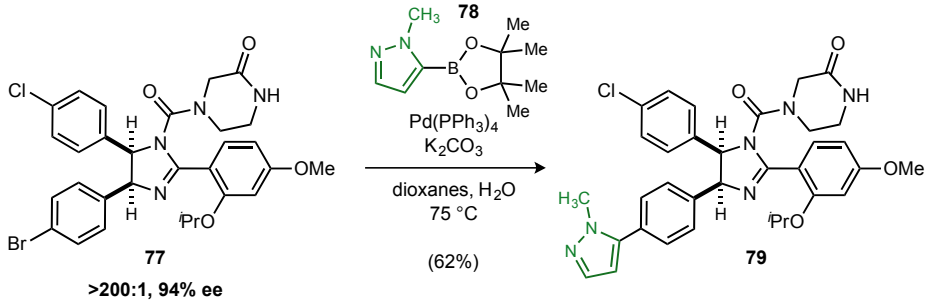
The ability to generate nonsymmetric *cis*-imidazoline derivatives from a host of halogenated arenes and constitutionally isomeric nitro-Mannich adducts has allowed for efficient derivatization of the (4*S*,5*R*)-Nutlin-3 scaffold. We thought we could utilize the induced asymmetry in the final Nutlin molecule to further advance synthetic functionalization and derivatization. We postulated the *p*-bromo Nutlin derivative **77** in Scheme 19 could be functionalized selectively at the 4-bromo position – metallation and/or oxidative addition should be accelerated compared to the neighboring *p*-chloro arene.

To our knowledge, no late-stage or metal-mediated coupling reactions or modifications have been demonstrated on Nutlin small molecules. Traditional palladium cross-couplings under various conditions to generate new sp^2-sp^2 C–C bonds or sp^2 carbon-heteroatom bonds are plausible given this induced asymmetry. An unlikely but potential problem we could foresee is oxidation from the imidazoline to imidazole at high reaction temperatures.[55]

[55] This phenomenon is not unprecedented. While conducting FP assays or after long periods of compound storage in DMSO (for example) oxidized Nutlin has been found and characterized. Researchers at Hoffmann-La Roche have submitted a submitted manuscript detailing metabolic oxidation of the same nature: Tovar, C.; Graves, Bradford, G.; Packman, K. *et* al. *Cancer Research.* **2013**, *73*, 2587.

We first employed traditional Suzuki cross coupling conditions with $Pd(PPh_3)_3$ and pyrazole boronic ester **78** to test this hypothesis (Scheme 20)[56]. After stirring for 24 hours at 75 °C the desired pyrazole adduct **79** was isolated following column chromatography in 62% yield (unoptimized). The presence of the aryl chloride was confirmed by HRMS and evidence for decomposition or oxidation was not observed. These results are very encouraging from a synthetic and medicinal chemistry standpoint, as it allows for late-stage derivatization of unsymmetrical Nutlin analogues in a site-selective fashion.

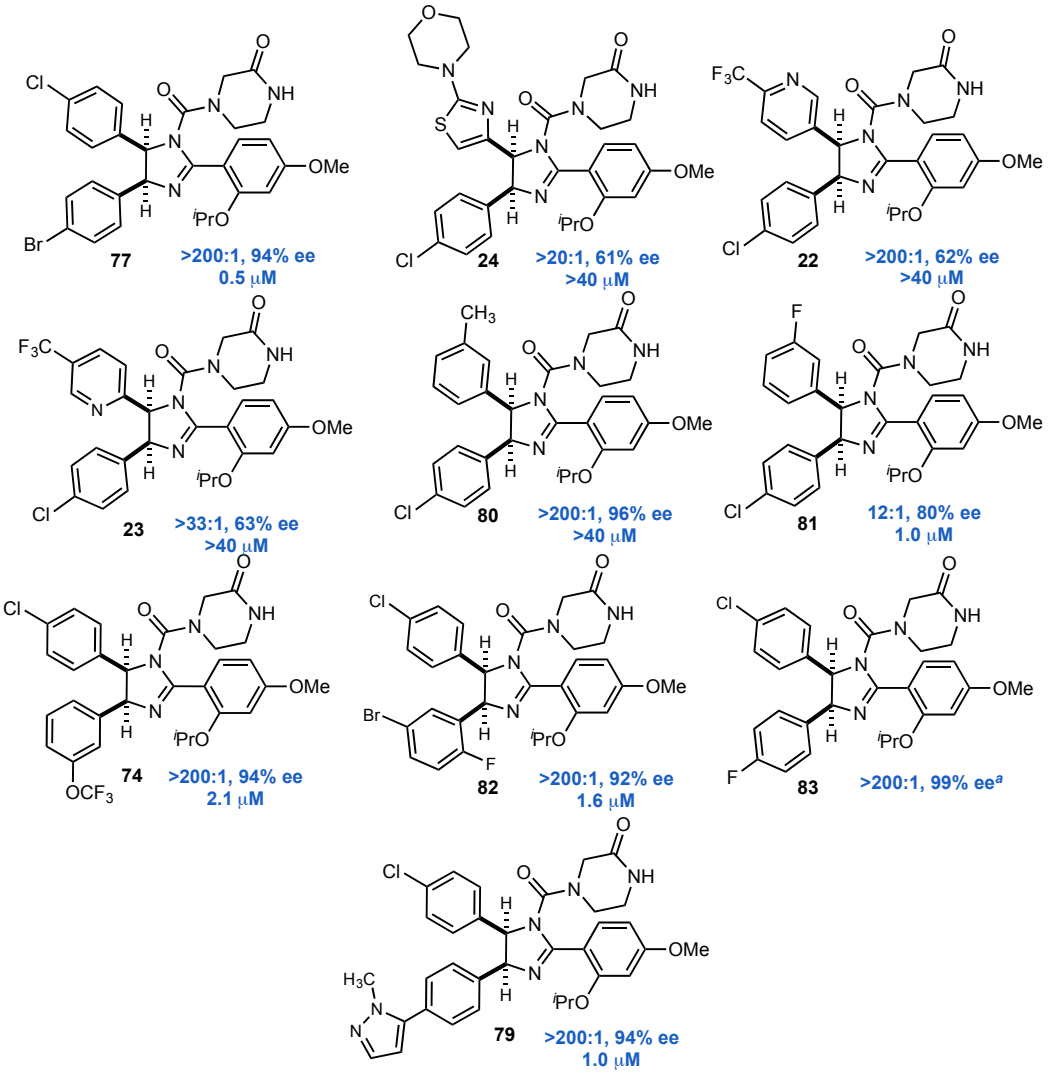
Scheme 20. Susuki cross-coupling reaction of unsymmetric halogenated Nutlin analogue **77** allows for regioselective modifications.



In summary, using the novel asymmetric chemistry developed in the group and with the discovery of *mono*(amidine)-amide (MAM) catalyst, we were able to synthesize a variety of nonsymmetric *cis*-imidazoline (Nutlin) derivatives in highly enantioselective fashion in hopes of probing MDMX-p53 protein-protein interactions and unveil a potent inhibitor. In total ten novel (4*S*,5*R*)-Nutlin derivatives (Chart 2) were prepared, most designed by Kip Guy and projected to be effective MDMX-p53 inhibitors.

[56] WO2008/98104. **2008**, 173.

Chart 2. A list of (4*S*,5*R*)-*cis*-imidazoline derivatives synthesized in the Johnston Group using highly stereoselective nitro-Mannich addition reactions. Each compound was isolated in good dr and ee and were subjected to MDM2-p53 assays (IC_{50} values shown).[a]



[a]The MDM2-p53 IC_{50} values were acquired through florescence polarization assays developed by Guy and coworkers [b]The corresponding aza-Henry product was enriched from 88% ee to 99% ee and >200:1 dr following a single recrystallization.

The derivatives shown were first screened against MDM2-p53 FP assays, and their corresponding MDM2 IC_{50} data are listed in Chart 2. Interestingly, the bulky pyrazole derivative **79** was comparable to the parent (–)-Nutlin-3 compound (MDM2-p53 FP IC_{50} = 1.0 μM). In addition, a handful of compounds were screened against HDMX/MDMX-p53 assays and compared to (–)-Nutlin-3 – fortunately a few derivatives showed comparable potency to (–)-Nutlin-3. Derivatives **81**, **74**, **82**, and **83** all showed improved potency against MDMX-p53 in

comparison to *rac*-Nutlin-3 (K_i < 28 μM, values not pictured). The fluorine and bromine-containing (4*S*,5*R*)-Nutlin-3 derivative **82** expressed IC_{50} values against HDMX-p53 and HDM2-p53 of 3.9 and 1.6 μM, respectively, in FP cell-based assays.[57] To date, however, much of the MDMX-p53 inhibition data has not released to us, as researchers at St. Jude are currently attempting to secure intellectual property (IP) rights over this class of potential therapeutics.[58]

In sum, over 15 *cis*-imidazoline derivatives were prepared through collaborative efforts by chemists at Vanderbilt and St. Jude. Chemists at St. Jude also included structural variations along the dialkoxy arene portion of the Nutlins using this developed chemistry to explore these solvent-exposed regions (not shown[59]), although MDM2 inhibition was only marginally affected by these adjustments.

1.6 Conclusion and Future Directions

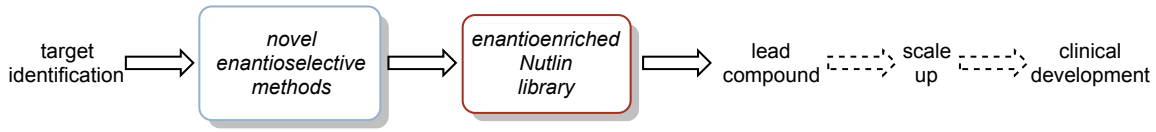
This more efficacious addition reaction of aryl nitromethanes to aryl Boc-imines using MAM catalysts has been optimized and applied to the work presented herein, ultimately achieving high enantioselection in the assembly of various masked *cis*-stilbene diamines. Superior levels of stereocontrol (up to 99% ee and 200:1 dr) were shown with a host of stereoelectronically-diverse aryl nitromethanes and aryl Boc-imines, thanks to increased tolerance from two novel MAM catalysts. Additionally, this chemistry has allowed for the synthesis of identical, nonsymmetric (4*S*,5*R*)-*cis*-imidazoline analogues from constitutionally

[57] *Unpublished data* courtesy of Kip Guy, Jaeki Min, and Kristin Finch; St. Jude Children's Research Hospital.
[58] Tentative patent titling: "MDMX-p53 cis-imidazoline Inhibitors" Mayasundari, A.; Min, J.K.; Vara, B.A.; Johnston, J.N.; Guy, R.K. *et al. Provisional U.S. Patent Filed* 2014
[59] For the full report on these compounds prepared by ourselves and collaborators at St. Jude see: Vara, B. A.; Mayasundari, A.; Tellis, J. C.; Danneman, M. W.; Arredondo, V.; Davis, T. A.; Min, J.; Finch, K.; Guy, R. K.; Johnston, J. N. *J. Org. Chem.* **2014**, *79*, 6913.

isomeric aza-Henry adducts – a phenomenon inherent to masked *cis*-stilbene diamines. As was exemplified, this chemistry has proven to be robust, scalable, and flexible as applied to the synthesis of more than ten novel, unsymmetric (4*S*,5*R*)-Nutlin-3 derivatives. Of these Nutlin derivatives in Chart 2, four proved more efficacious towards the inhibition of MDMX-p53 protein-protein interactions

Many new opportunities in MDM2/MDMX-p53 PPI have been unlocked as a result of our collaboration with Kip Guy and St. Jude collaboration. As is now evident, the chemistry to generate nonsymmetric *cis*-imidazoline (Nutlin) derivatives via the aza-Henry reaction is truly valuable and additional analogues can be easily examined in the future. At the time this

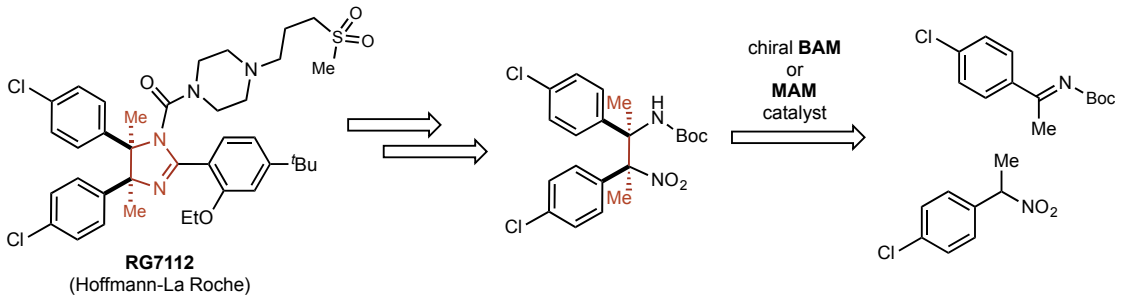
Scheme 21. New enantioselective methods have driven the development of novel Nutlin derivatives.



document was compiled, St. Jude had taken over the medicinal chemistry focus of the project. The synthesis of a vast library of enantioenriched Nutlin analogues has been prepared using the asymmetric methods developed herein. To our knowledge, a number of lead compounds inhibiting MDMX-p53 have undergone thorough preclinical testing (efficacy, DMPK, animal models, etc.) and may soon be ready for more expansive *in vivo* testing. For these late stage preclinical trials, potentially tens of grams (or more) of compound may be needed. We hope to have a patent issued on these molecules soon and data to be released in the coming years.

An attractive area to next explore with this chemistry is the synthesis of other, stereochemically-rich MDM2-p53 inhibitors. Upon inspection of Roche's clinical trial candidate, RG7112, the basic chiral *cis*-imidazoline scaffold (highlighted in maroon, Scheme 22) is

Scheme 22. Retrosynthetic breakdown of RG7112 using the BAM/MAM-catalyzed asymmetric nitro-Mannich reaction.

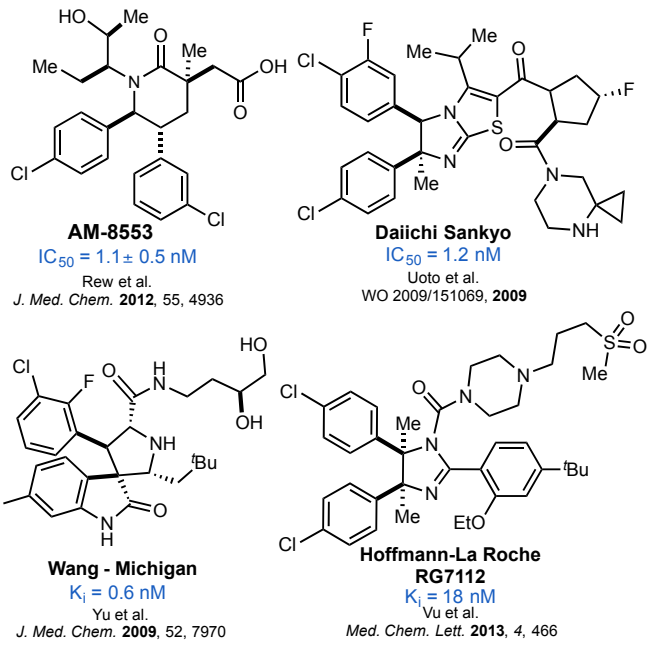


analogous to Nutlin-3 and our aza-Henry chemistry may be useful. The reaction needed to be developed would be between two very hindered components, a 2º aryl nitromethanes and an aryl Boc-ketimine. This system has been briefly explored in the group but yielded little promising results, and may require the development of new catalysts to increase reactivity and modulate stereoselectivity in the future. The overarching challenge here of course is setting two adjacent quaternary centers in a highly stereoselective manner.

A small sampling of current, potent MDM2-p53 inhibitors are depicted in Figure 19. As pictured many of the more potent MDM2-p53 inhibitors can be broken down to arrive at a chiral amine intermediate, potentially accessible from aza-Henry -type reactions. True to the class, all molecules contain halogenated arenes strategically positioned to fit the same hydrophobic binding pocket that the Nutlin *p*-chloro arenes target. This is a truncated list of compounds[60] but many small molecules in the field display similar structural design.

[60] For a recent review and extensive list of MDM2-p53 inhibitors see the following: Popowicz, G. M.; Domling, A.; Holak, T. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2680. Millard, M.; Pathania, D.; Grande, F.; Xu, S. L.; Neamati, N. *Curr. Pharm. Design* **2011**, *17*, 536. Rew, Y.; Sun, D. Q.; De Turiso, F. G. L.; Bartberger, M. D.; Beck, H. P.; Canon, J.; Chen, A.; Chow, D.; Deignan, J.; Fox, B. M.; Gustin, D.; Huang, X.; Jiang, M.; Jiao, X. Y.; Jin, L. X.; Kayser, F.; Kopecky, D. J.; Li, Y. H.; Lo, M. C.; Long, A. M.; Michelsen, K.; Oliner, J. D.; Osgood, T.; Ragains, M.; Saiki, A. Y.; Schneider, S.; Toteva, M.; Yakowec, P.; Yan, X. L.; Ye, Q. P.; Yu, D. Y.; Zhao, X. N.; Zhou, J.; Medina, J. C.; Olson, S. H. *J. Med. Chem.* **2012**, *55*, 4936. Lucas, B. S.; Fisher, B.; McGee, L. R.; Olson, S. H.; Medina, J. C.; Cheung, E. *J. Am. Chem. Soc.* **2012**, *134*, 12855.

Figure 19. Recent potent and selective MDM2-p53 small molecule inhibitors to hit the clinic. All contain halogenated arenes and at least 2 stereocentrers. RG7112 is the most advanced molecule in clinical trials.



In the immediate future we plan on opening up new and finishing current collaborations using these novel small molecules. With improved catalysts in hand, we may also examine scaling up the synthesis of (–)-Nutlin-3 or a new derivative for use in *in vivo* studies. Dual MDM2-p53 and MDMX-p53 inhibition may be a promising therapeutic strategy in the near future, and this developed chemistry may prove very impactful.

Chapter II

II. Enantioselective Synthesis of β-Amino-α-Fluoronitroalkanes via the Aza-Henry Reaction

2.1 Introduction to the Fluorine Atom and Fluorine-Containing Compounds

The unique properties of the fluorine atom make it significant in pharmaceutical, agrochemical and material sciences.[61] Industry sources estimate that as many as 30−40% of agrochemicals and 20% of pharmaceuticals on the market contain fluorine[62] – numbers only expected to increase in the coming years given the plethora of favorable data. Fluorine finds use as a biochemical tracer element or tag for the study of various biological processes, as the NMR activity of the ^{19}F nuclei enables *in vivo* magnetic resonance imaging.[63] In addition, ^{18}F-positron-emitting tomography (PET imaging[64]) is used daily in hospital settings for diagnosing, tracing, and detecting the recurrence or progression of various diseases including cancer.[65]

Fluorine arguably retains some of the most unique physiochemical properties of non-metal or halogen-based elements employed in synthetic organic chemistry. The small covalent

[61] Hiyama, T. In *Organofluorine Compounds; Chemistry and Applications*; Yamamoto, H., Ed.; Springer: New York, **2000** and references therein
[62] Thayer, A. M. Enzymes at Work. *Chem. Eng. News* **2006**, 84, 15-25. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
[63] Porcari, P.; Capuani, S.; Campanella, R.; La Bella, A.; Migneco, L. M.; Maraviglia, B. *Phys. Med. Biol.* **2006**, *51*, 3141.
[64] Tredwell, M.; Gouverneur, V. *J Labelled Compd Rad* **2011**, *54*, 389.
[65] Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501.

radius of fluorine (C–F, F radii 1.47 Å) coupled with the highest electronegativity of all elements contribute to the atom's unique characteristics – handling, stability, and incorporation of this element into small molecules is thus challenging using traditional synthetic techniques and methods[66]. Adding to the mystique of the element, naturally occurring fluorinated compounds are nearly nonexistent in nature, and yet a significant number drugs in the pharmaceutical pipeline contain at least one fluorine atom.[67] The small handful of fluorinated natural products that are known are produced in subequatorial plants, one being fluoroacetic acid;[68] these compounds, however, have no known biological relevance in humans. Nonetheless, synthetic organofluorine compounds have attracted much attention across a number of chemical disciplines[69] in the assembly of materials,[70] polymers, surfactants, and organic compounds for a variety of reasons.

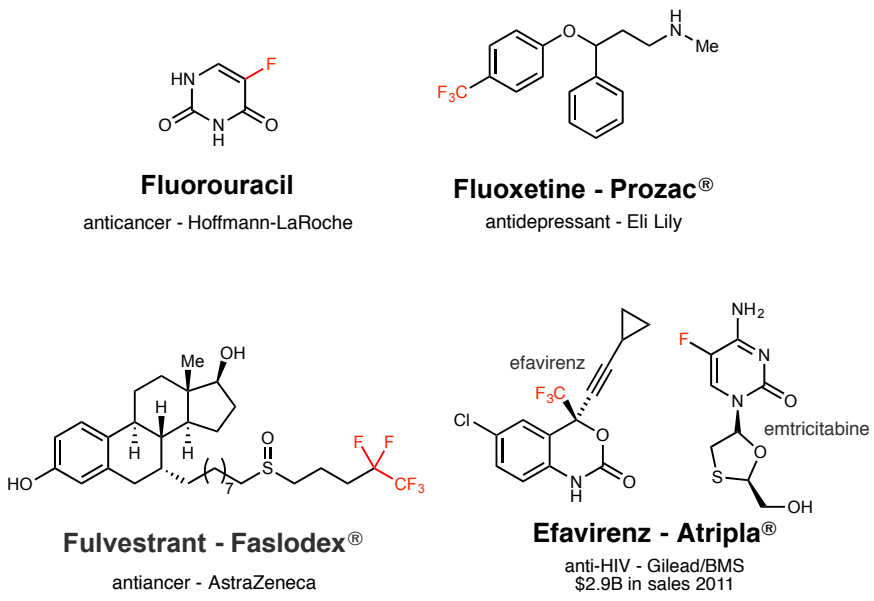
The C–F covalent bond inherent to organofluorine compounds and materials is one of the strongest known with a bond dissociation energy of ~116 kcal/mol, enhancing the molecule's overall thermal and chemical stability. The high electronegativity of fluorine has a number of obvious consequences, one being increased bond polarization, imparting less covalent and more electrostatic character ($C^{\delta+}$–$F^{\delta-}$) to the C–F bond. This leads to a relatively large dipole which can interact with other dipoles in close proximity and thus the preferred conformations or geometry of organofluorine compounds can often be rationalized by considering these electrostatic interactions.[66] Collectively, fluorine substituents can potentiate a number of chemical properties, such as the acidity or basicity of neighboring groups, dipole moment, and

[66] A wonderful tutorial review by O'Hagan details the chemical effects of fluorine O'Hagan, D. *Chem. Soc. Rev*. **2008**, *37*, 308.
[67] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
[68] Vartiainen, T.; Kauranen, P. *Anal. Chim. Acta* **1984**, *157*, 91.
[69] Monofluorination of Organic Compounds: 10 Years of Innovation. Champagne, P. A.; Desroches, J.; Hamel, J. D.; Vandamme, M.; Paquin, J. F. *Chem. Rev.* **2015**, *115*, 9073.
[70] Leblanc, M.; Maisonneuve, V.; Tressaud, A. *Chem. Rev.* **2015**, *115*, 1191.

pharmaceutically-relevant properties such as lipophilicity, metabolic stability, and bioavailability.

Discovered in 1957, the antineoplastic agent 5-fluorouracil was the earliest reported fluorinated pharmaceutical.[71] It shows high anticancer activity by inhibiting the enzyme thymidylate synthase, thereby preventing the cellular synthesis of thymidine. This simple addition to the pyrimidine nucleobase uracil greatly enhanced its desirable biological properties, and has since sparked the broad interest seen in modern fluorine medicinal chemistry. Fluoxetine (Prozac®, antidepressant), Faslodex® (anticancer), and Efavirenz (antiviral) are three drugs that illustrate the wide range of disease areas benefiting from fluorine chemistry and, from a

Figure 20. Structurally diverse fluorinated pharmaceutical across many disease areas.



molecular point of view, the structural diversity of the fluorinated component (Figure 20).

Prozac is one of the more well-known drugs of all-time, hauling in close to $1B annually in sales at its peak. In 1994 was repurposed to treat bulimia and obsessive-compulsive disorders.

[71] Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J.; Pleven, E.; Scheiner, J. *Nature* **1957**, *179*, 663.

The inclusion of a trifluoromethyl group in the *para*-position of the phenolic ring increases the potency for inhibiting 5-hydroxytryptamine (5-HT, serotonin) *uptake by 6-fold*, compared to the non-fluorinated parent compound.[72]

Efavirenz, marketed as three-drug antiretroviral cocktail from Gilead and BMS in the U.S. (and by Merck & Co. in developing countries), include two structurally diverse fluorinated components (tenofovir is the third component in the cocktail, a carbonate prodrug, Figure 35, Chapter 3). Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 and emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI, Figure 20). Structure-activity relationship studies showed the presence of the trifluoromethyl group in efavirenz improved drug potency by lowering the pKa of the cyclic carbamate, which makes a key hydrogen bond contact with the protein.[73] Furthermore, the trifluoromethyl group attached to the stereogenic center acts to improve binding to the reverse transcriptase enzyme, remote from the active site, altering the enzyme's conformation and inhibiting its activity.

Aryl trifluoromethyl groups are arguably the most common installment of fluorine in medicinal and agrochemical compounds – their relative ease of synthesis and strong electron withdrawing capabilities make this an attractive substructure. Although not discussed here in great detail, the installation of perfluorinated groups (i.e. trifluoromethyl, thiotrifluoromethyl, etc.) has gained attention for their ability to also improve the same favorable drug-like and material properties discussed previously.[74] In contrast to monofluorination methodologies, completely different chemical approaches have been developed (yet are still needed) to integrate

[72] Wong, D. T.; Bymaster, F. P.; Engleman, E. A. *Life Sci.* **1995**, *57*, 411.
[73] Rabel, S. R.; Sun, S.; Maurin, M. B.; Patel, M. *Aaps Pharmsci* **2001**, *3*.
[74] Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. Wang, J. *et al. Chem. Rev.* **2014***, 114*, 2432.

these useful perfluorinated moieties into compounds. Teflon® (polytetrafluoroethylene) is a famous example displaying the remarkable properties of perfluorinated materials.

2.2 Enantioselective Monofluorination Reactions in Chemical Synthesis and Drug Discovery Chemistry

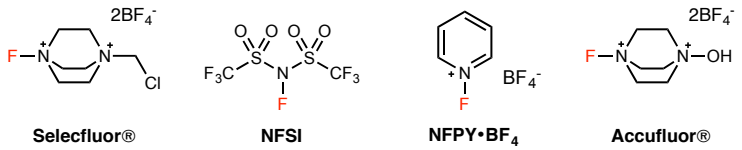
The recent advent of various, bench stable fluorinating reagents has in large part fuelled the expanse of fluorine chemistry into every-day organic synthesis. New fluorinating reagents and fluorination processes have increased the range of synthetic fluorinated building blocks amenable to broader functional group manipulation. The strategic use of fluorine substitution in drug design has culminated with the production of some of the key drugs available on the market. While new fluorinating reagents have come online, asymmetric catalysis centered around fluorine has grown closely in stride,[75] yet arguably has not kept up with the large number of non-asymmetric reactions in the literature. This is, in part, due to the need to fully understand the reactivity of these fluorinating reagents before pursuing asymmetric catalysis – new catalysts, activation modes, and parameters to control the reactivity of fluorine are understandably slower to be developed. Insightful words from the editor of a *Chemical Reviews* article in 1996 proclaims the general feelings towards fluorine chemistry at the time, but a comment that still resonates today:

[75] Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119.

"…although fluorine chemistry is much less abstruse now than when I entered the field a generation ago [1986]*, it remains a specialized topic and most chemists are unfamiliar, or at least uncomfortable, with the synthesis and behavior of organofluorine compounds."*[76]

This 1996 special review on fluorine chemistry reported no asymmetric fluorination examples. Since this report, the organic chemistry community has undergone dramatic changes regarding the subject. Some of that chemistry is introduced in this section.

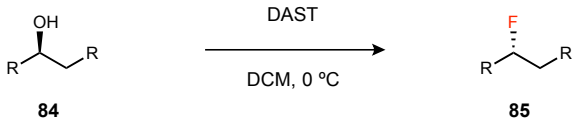
Figure 21. Common, bench-stable electrophilic fluorine sources.



Many of the common electrophilic fluorinating reagents used in organic synthesis are outlined in Figure 21. Over the past 10 years, electrophilic fluorine sources (F^+) have been the most commonly employed reagent in asymmetric synthesis – many are bench stable, reactive salts that can be readily paired with phase transfer organocatalysis, Lewis acid catalysis, and metal-based catalysis.[77] It has been the development of these more "tamed" electrophilic fluorine species that have allowed for robust enantioselective methods to be developed.

One of the most popular routes to stereoselectively introduce fluorine attached to a chiral

Scheme 23. Common stereoselective preparation of chiral fluorides in industry.



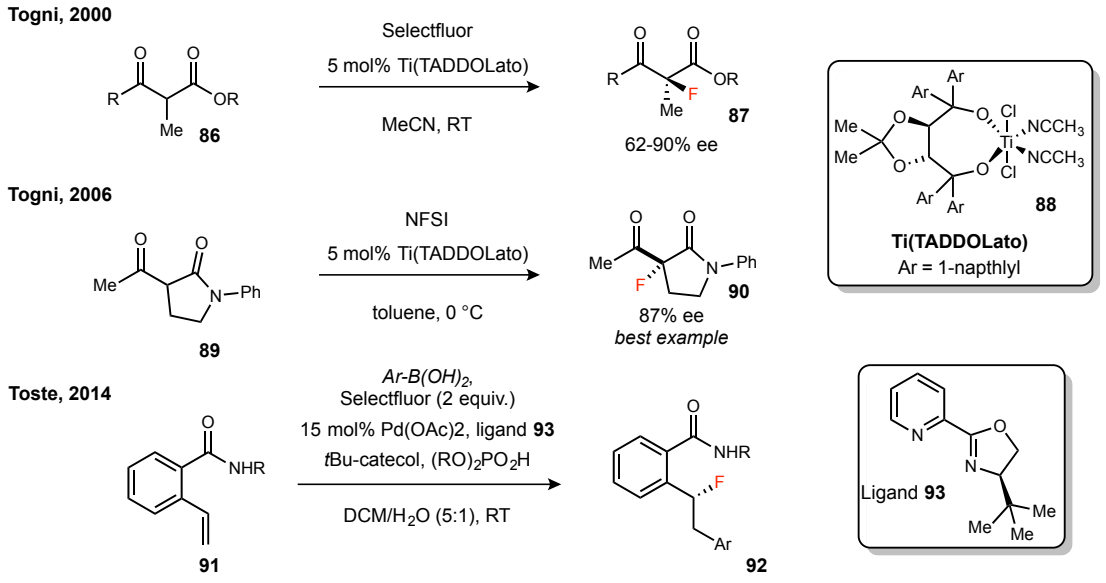
[76] Smart, B. E. *Chem. Rev.* **1996**, *96*, 1555.
[77] Yang, X. Y.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826.

center in the pharmaceutical industry is using the fluorinating reagent diethyl(aminosulfur) trifluoride (DAST) with a chiral alcohol **84**. In predictable S_N2 fashion, fluoride is delivered with inversion of stereochemistry (Scheme 23). However, alcohol elimination is a common competing pathway with DAST and other similar reagents (i.e. deoxyfluor).

The earliest examples of enantioselective monofluorination reactions came to fruition using activated metal enolates as the nucleophilic components. In 2000, Togni and coworkers pioneered this concept using a Ti/TADDOL complex and Selectfluor, which allowed for a rigid metal-enolate complex to form imparting high enantioselection (up to 90% ee, Scheme 24)[78]. This work arguably set the stage for future developments in this area.

Later in 2006 the group applied the Ti(TADDOLato) catalyst (**88**) to the asymmetric

Scheme 24. Pioneering methods in catalytic, asymmetric monofluorination chemistry using nucleophilic enolates and styrenes.



fluorination of lactam enolates using NFSI instead of Selectfluor (Scheme 24).[79] Since these efforts, a wide range of asymmetric monofluorination reactions using Ti, Pd[80], Ni[81], and Cu[82]

[78] Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4359.
[79] Perseghini, M.; Massaccesi, M.; Liu, Y. Y.; Togni, A. *Tetrahedron* **2006**, *62*, 7180.

(CuBOX) metal catalysts, among others, have been advanced using enolate-derived chemistry. These methods of course are not without limitations. One of the more prevalent is the inherent preparation of nearly *exclusively* enantioenriched α-fluorocarbonyl compounds, many of which are specially tailored to fit the given reaction. Enantioselection can often vary dramatically from substrate to substrate.[83]

An elegant, non-enolate, metal-catalyzed fluorination reaction was reported by Toste recently in 2014 in the preparation of chiral benzyl fluorides (**92**) using palladium (Scheme 24). This reaction is a three-component coupling between Selectfluor, styrene derivative **91**, and an aryl boric acid resulting in fluorinated compounds with no adjacent (activated) heteroatom in up to 96% ee.[84] These all-carbon fluorinated motifs are still very challenging to access using a broad scope of asymmetric methods.

Stoichiometric *N*-fluoroamine organocatalysts were pursued in the early days of asymmetric monofluorination chemistry, yet a transformational shift took place in 2000 when Shibata reported the use of a chiral cinchona alkaloid and Selectfluor to furnish chiral α-fluorocarbonyls.[85] Under phase transfer conditions (chiral *N*-fluoroammonium salts and Selectfluor), fluorination of the generated enolates from acyl enol ethers proceeded in good ee, which was later extended to a catalytic version in 2006 (Scheme 25).[86]

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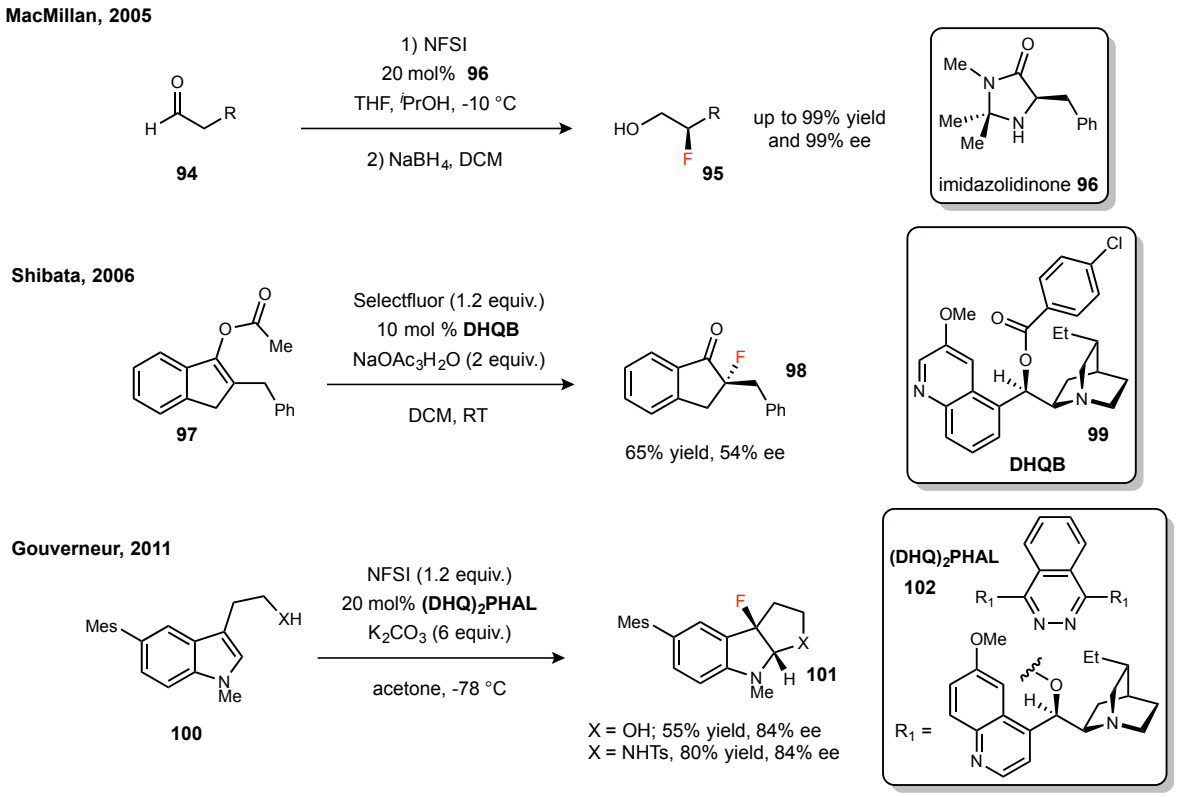
[80] Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.; Goto, T.; Sodeoka, M. *Tetrahedron* **2006**, *62*, 7168. Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309.
[81] Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 5435.
[82] Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703. Balaraman, K.; Vasanthan, R.; Kesavan, V. *Tetrahedron-Asymmetry* **2013**, *24*, 919.
[83] Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309.
[84] Talbot, E. P. A.; Fernandes, T. D.; McKenna, J. M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 4101.
[85] Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc*. **2000**, *122*, 10728.
[86] Fukuzumi, T.; Shibata, N.; Sugiura, M.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2006**, *127*, 548.

Ever-popular proline-based organocatalysis also saw success in this chemistry using readily available aldehydes to generate α-fluoroaldehydes (Jørgensen[87]) and β-fluoro alcohols (**95**) (MacMillan, Scheme 25), to name just a pair. MacMillan employed linear aliphatic aldehydes and an organocatalyst (imidazolidinone **96**) to generate the nucleophilic enamine which then is primed to abstract fluorine from NFSI.[88] Interestingly the addition of 10% *i*-PrOH greatly improved ee, and α- and β-branched aldehydes to generate more substituted α-fluoro alcohols were not explored using this robust chemistry. MacMillan later reported a highly enantioselective fluorination of cyclic ketones in 2011,[89] marking the first example of its kind

Scheme 25. Asymmetric, organocatalyzed monofluorination reactions through enolates or enolate-equivalents.



[87] Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 6039.
[88] Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.
[89] Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2011**, *133*, 1738.

using enamine catalysis (a cinchona alkaloid-derived amine, not shown).

In 2011, Gouverneur and coworkers reported the asymmetric monofluorination of prochiral indolinones (**100**) using NFSI and $(DHQ)_2PHAL$ (**102**).[90] In this tandem fluorination-cyclization protocol, the authors generate chiral fluorinated analogues of the hexahydropyrrolo[2,3-*b*]indole or the tetrahydro-2H-furo-[2,3-*b*]indole class of natural products, although ee only exceeded 80% ee in a few cases (Scheme 25).

As a final noteworthy example, Toste and coworkers have led the charge to develop

Scheme 26. The asymmetric monofluorination of activated olefins using innovative phase-transfer conditions.

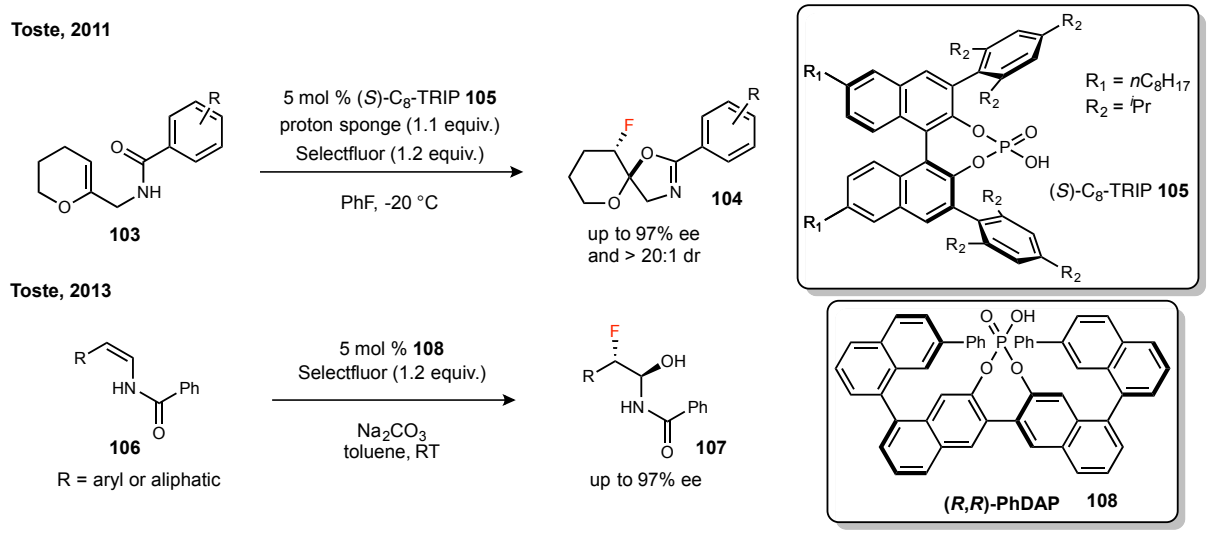
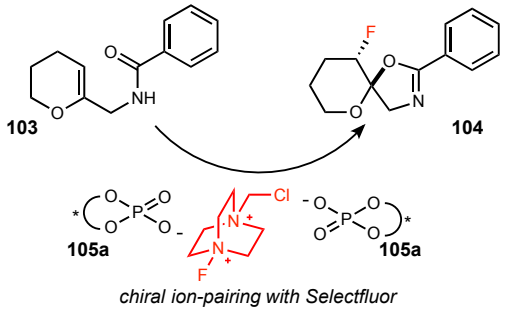


Figure 22. Representation of ion-pairing responsible for enantioselective induction from Toste *et al.* under the catalytic phase transfer conditions.



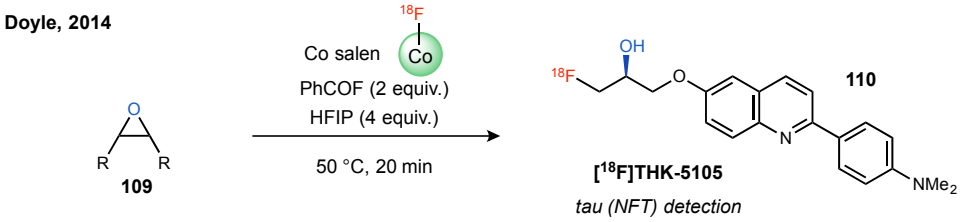
[90] Lozano, O.; Blessley, G.; del Campo, T. M.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 8105.

highly efficacious anionic phase-transfer systems using phosphoric acid organocatalysts and available electrophilic sources of fluorine (Scheme 26). In 2011, the group reported an elegant fluorocyclization reaction where chiral ion pairs (between Selectfluor and the phosphoric acid catalyst, (*S*)-C_8-TRIP **105/105a**) formed in non-polar media, creating a significant driving force and a strong stereochemical dependence (Figure 22).[91] Upon ion pair complexation with the highly electron-rich enol ether substrates, chiral fluoro oxazolines (**104**) were isolated in high ee (Scheme 26). The products of this reaction are nothing special (perhaps a bit awkward), yet the mechanistic discoveries were transformational. This was later extended to an intermolecular, asymmetric oxyfluorination reaction generating arguably more useful enantioenriched β-fluoro-α-oxy amides (**107**) in high ee using a new hindered phosphoric acid catalyst **108** (Scheme 26).[92] These reactions are additionally noteworthy from the perspective that *two vicinal stereocenters* are created in high levels of control, the first example of which contains an elusive quaternary spirocyclic center.

In sum, the lion's share of examples to date in the literature use enolate chemistry (or enoalte equivalents) as the nucleophile surrogate to furnish enantioenriched α-fluorocarbonyls and their immediate derivatives. The reactions discussed here are only select instances of what has been accomplished in the field of asymmetric monofluorination chemistry and advancements in this arena are constantly unveiled. The implementation of robust, bench-stable electrophilic fluorinating reagents has played an enormous role in the advancement of the field, yet new technologies, catalysts, and reagents are needed if chemists want to explore functionalities other than α-fluorocarbonyls and their derivatives.

[91] Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.
[92] Shunatona, H. P.; Fruh, N.; Wang, Y. M.; Rauniyar, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 7724.

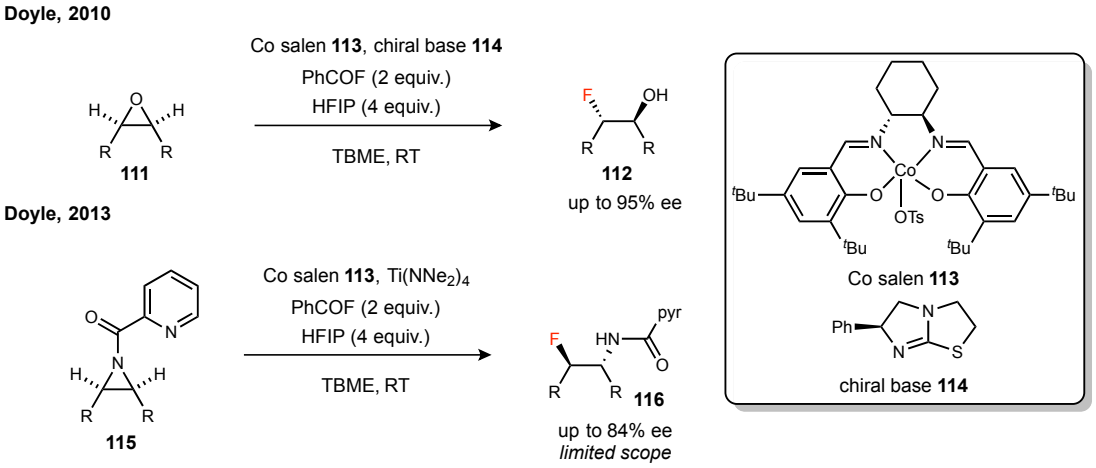
Scheme 27. Example of a recent ^{18}F-monofluorination reaction and its application to the synthesis of PET tracers.



Nucleophilic fluorination chemistry has only been harnessed in the context of asymmetric catalysis more recently when compared to their electrophilic counterparts – the primary reason for this is the high basicity of the fluoride anion in conjunction with its low nucleophilicity. However, in the world of biological imaging technologies critical to the detection and diagnosis of diseases, *nucleophilic fluoride* is currently the only practical and generally available source of ^{18}F (half life 110 min) needed to prepare PET tracers (**110**) with high specific activity (Scheme 27).[93]

Most advancements in nucleophilic fluorination chemistry has targeted the synthesis of

Scheme 28. Modern asymmetric fluorination methods using nucleophilic sources of fluorine.



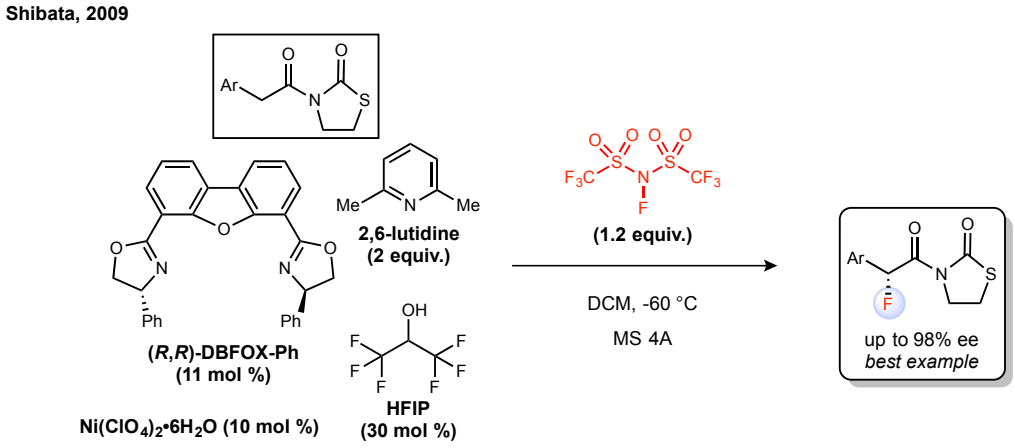
[93] Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed*. **2013**, *52*, 8214. Graham, T. J. A.; Lambert, R. F.; Ploessl, K.; Kung, H. F.; Doyle, A. G. *J. Am. Chem. Soc.* **2014**, *136*, 5291.

aryl fluorides, yet much less is reported to make alkyl fluorides, especially in asymmetric fashion. Metal salen catalysts pioneered by Jacobsen have been the most successful in this realm, specifically in the fluoride ring openings of epoxides (**111**)[94] and aziridines (**115**).[95] The kinetic resolutions of racemic and *meso*-epoxides yielding enantioenriched β-fluoro alcohols (**112**) have garnered more attention lately using fluoride sources such as silver fluoride (AgF), HF (generated *in situ* from benzoyl fluoride), or Et_3N•HF (or equivalents). Doyle and coworkers in particular have found success using benzoyl fluoride and the cobalt(III) salen catalyst **113** in the kinetic resolutions of various *rac*-epoxides and protected *meso*-aziridines (Scheme 28).

2.3 Synthesis and Application of Fluoronitroalkanes

Asymmetric monofluorination chemistry, while highly useful and rapidly advancing, brings with it a number of operationally challenging obstacles. As discussed, controlling the

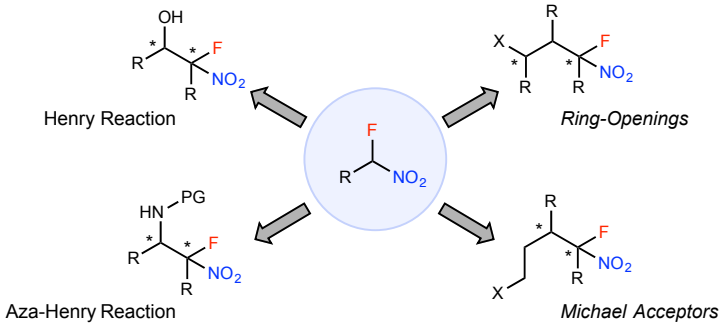
Scheme 29. An illustrative example of the poor atom economy and general requirements facing enantioselective monofluorination reactions – large MW ligands, catalysts, and tailored substrates are often required.



[94] Bruns, S.; Haufe, G. *J. Fluorine Chem*. **2000**, *104*, 247. Haufe, G.; Bruns, S. *Adv. Synth. Catal*. **2002**, *344*, 165.
[95] Kalow, J. A.; Doyle, A. G. *Tetrahedron* **2013**, *69*, 5702.

reactivity of such a small, reactive, and capricious atom is far form facile. A number of new catalysts, activation methods, and general understanding of its behaviors is at the very least required. In regard to atom economy[96] and the green nature of these reactions, current standards for delivering a fluorine atom in asymmetric fashion fall short. State-of-the-art enantioselective fluorinations require a large molecular weight reagents and catalysts – the latter of which are complex, non C_2-symmetric, metal-based complexes that require many steps to prepare. Additionally, the fluorinating reagents employed, while useful, are also high molecular weight species, all to deliver a single fluorine atom (i.e., Selectfluor MW: 354.26) – this observation is depicted in Scheme 29. Various additives, organic/inorganic bases, Lewis acids, and detailed solvent combinations are often needed to obtain desired reactivity or stereoselection. In union with these constraints, the complexity of the final fluorinated product – is often just that – fluorinated. Presently and in contrast to the swaths of asymmetric carbon-carbon bond forming reactions, little if any *additional* stereocenters are created in current asymmetric monofluorination reactions. Furthermore, new hetero- or carbon atoms are often not introduced, which would add desirability and more complexity to these methods while creating a more diverse class of chemicals.

Scheme 30. Applications of fluoronitroalkanes in asymmetric catalysis. The products may contain stereocenters.



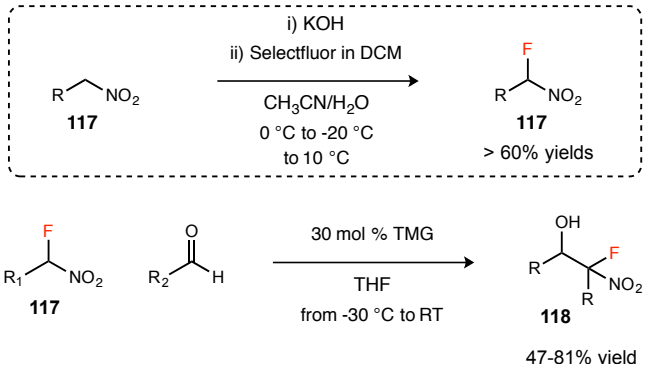
[96] Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259.

As discussed in Chapter 1, nitroalkanes are tremendously useful pronucleophiles used in a myriad of asymmetric transformations and subsequent derivatizations. The synthesis of fluoronitroalkanes, whilst not new, has reentered mainstream organic synthesis in the past few years. A report from Kornblum in 1956 prepared the first fluoronitroalkane using harsh conditions (F_2, high temps) but recent advances in fluorination chemistry have allowed for using more mild conditions.

The implementation of these dynamic pronucleophiles have a number of attractive characteristics: they are 1) readily isolable and stable solids or oils, 2) their relative low acidity is amenable to numerous and mild Brønsted basic catalysts (chiral and achiral), 3) they can conceivable be used with any electrophile (carbonyls, imines, activated olefins, etc.), 4) high atom economy (all atoms from substrate are contained in the product), and 5) they may introduce diverse functionalities centered around the fluorine atom, the products of which bear chiral centers (Scheme 30). It's for these reasons that this class of pronucleophiles offers exciting and intriguing reagent alternatives to fluoronium (F^+) or fluoride (F^-) sources, while retaining the potential to capitalize on stereochemical induction.

Treating a variety of nitroalkanes (aryl nitromethanes and aliphatic nitroalkanes) with

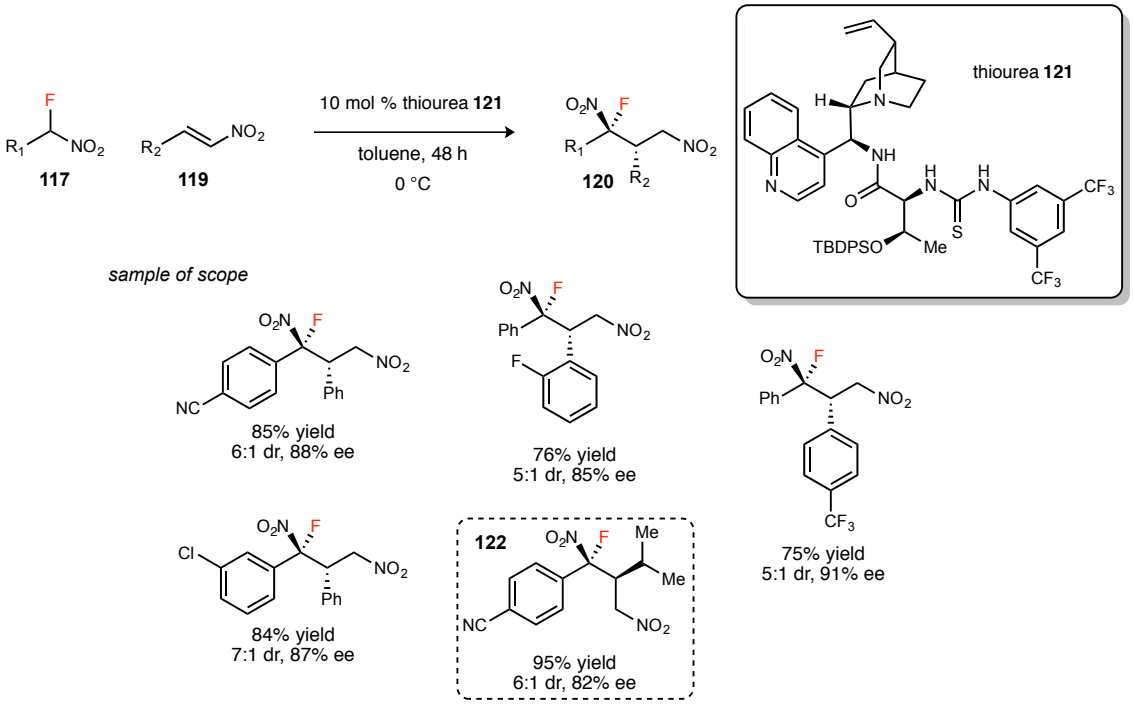
Scheme 31. State-of-the-art synthesis of fluoronitroalkanes. A recent example detailing the synthesis of racemic Henry products.



KOH and quenching the nitronate with Selectfluor generates fluoronitroalkanes **117** (>95% monofluorination) in good yields (Scheme 31).[97] α-Fluoronitroesters were the earliest fluoronitroalkane pronucleophiles to be employed in addition chemistry (to a Michael acceptor),[98] but the Henry reaction using TMG as the base to generate racemic α-oxy fluoronitroalkanes (**118**) was reported soon after.[97] Koizumi in the early 1980's was the first to generally explore fluoronitroalkanes and fluoronitroesters and their utility, yet since then, substantial progress has not been made.

Asymmetric, organocatalyzed reactions using these fluorinated pronucleophiles have more recently been reported. The Lu group from the University of Singapore published a pair of asymmetric reactions using fluoronitroalkanes and fluoronitroesters – nitro olefins were

Scheme 32. Seminal report from Lu describing the asymmetric, organocatalyzed addition of aryl fluoronitromethanes to nitro olefins and subsequent sample of reaction scope.



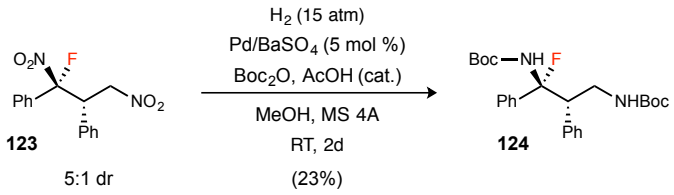
[97] Hu, H. W.; Huang, Y. G.; Guo, Y. *J. Fluorine Chem* **2012**, *133*, 108.
[98] Cui, H. P.; Li, P.; Wang, X. W.; Chai, Z.; Yang, Y. Q.; Cai, Y. P.; Zhu, S. Z.; Zhao, G. *Tetrahedron* **2011**, *67*, 312.

employed as the electrophiles in both cases (Scheme 32).

Their first report described the enantioselective addition of aryl nitromethanes **117** to nitro olefins **119** in good levels of ee using quinidine- and quinine-derived organocatalysts.[99] The optimal catalyst in this work, quinine-derived catalyst **121**, interestingly included an appended enantioenriched amino acid, generating the threonine-OTBDPS thiourea. Use of 10 mol % catalyst loading in toluene at 0 °C afforded the product in 5:1 dr, 90% ee, and 82 % yield.

The substrate scope here was reasonably broad, including electronically-diverse aryl nitro olefins, a heteroaromatic example, and a couple of alkyl nitro olefins, although the adducts of the latter electrophiles were isolated in lower ee (**122**, 82% ee, Scheme 32). Diastereoselection was not generally high, up to 8:1 dr in the best cases. Notably and quite perplexing, *aliphatic* fluoronitroalkanes were not tolerated under this quinine-thiourea catalytic system – the authors do not speculate why this is the case.

Scheme 33. Reductive hydrogenation of α-fluoronitroalkanes using Lindlar's catalyst.



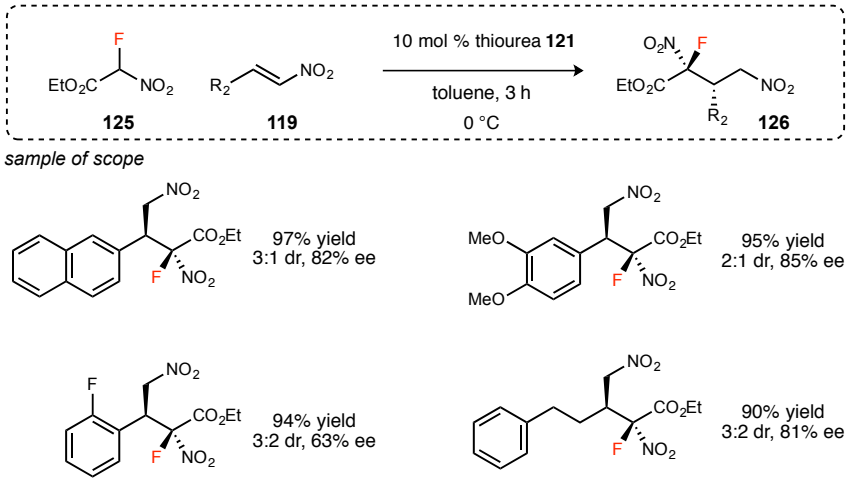
After "much experimentation" the authors were able to selectively reduce the nitro group of **123** to the Boc-protected amine **124** using Lindlar's catalyst ($Pa/BaSO_4$) and 15 atm H_2, although only in 23% isolated yield (Scheme 33). The great challenge is the elimination of fluoride (F^-) once a lone-pair is freed on the α-heteroatom – Koizumi and others theorized the α-

[99] Kwiatkowski, J.; Lu, Y. X. *Chem. Commun.* **2014**, *50*, 9313.

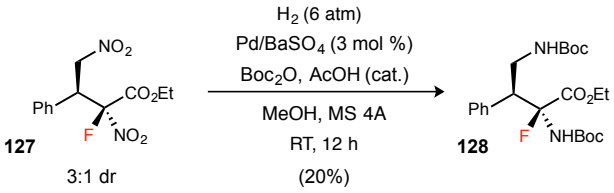
fluoroamine motif (broadly) is highly unstable in nature and may not exist for any extended period of time.[100]

The next report from Lu used α-fluoro-α-nitro acetates **125** in an extension of this asymmetric, organocatalyzed addition to nitro olefins **119**.[101] The same quinine-based thiourea catalyst **121** was used in this work as well, generating the α-fluoro-α,δ-dinitro esters in moderate to good ee but generally very low dr (up to 3:1 dr; Scheme 34). The electronics of the *aryl* nitro olefin coupling partner had more of a dramatic effect on ee in this work, potentially due to the more reactive (or Brønsted acidic) nucleophile being employed.

Scheme 34. Lu's report employing α-fluoronitro acetates **125** in the enantioselective addition into nitro olefins and a sample of the reaction scope.



Scheme 35. Reductive hydrogenation of the nitro group to the Boc-amine **128** using Lindlar's catalysts again results in low yields.



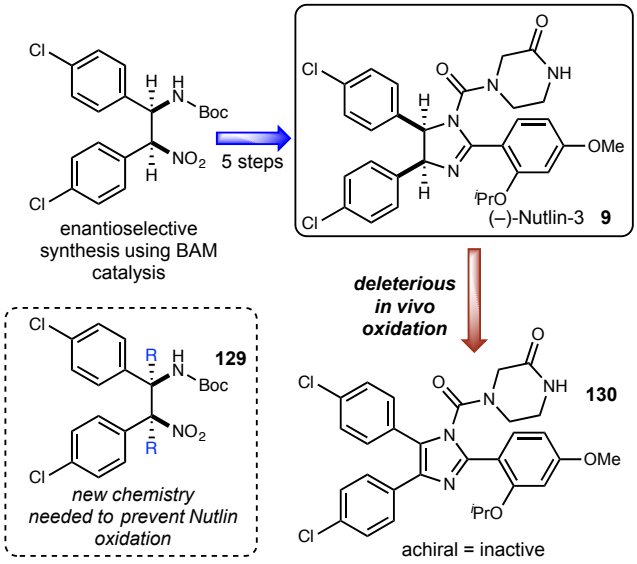
[100] Takeuchi, Y.; Takagi, K.; Yamaba, T.; Nabetani, M.; Koizumi, T. *J. Fluorine Chem* **1994**, *68*, 149. Annedi, S. C.; Li, W.; Samson, S.; Kotra, L. P. *J. Org. Chem.* **2003**, *68*, 1043.
[101] Kwiatkowski, J.; Lu, Y. X. *Org. Biomol. Chem.* **2015**, *13*, 2350.

In an effort to generate α-fluoro amino acid derivatives, the authors again struggled with the reduction of the nitro group to the protected amine **128** (Scheme 35). Yields were similarly very low (20%) using Lindlar's catalyst (Pa/$BaSO_4$, 6 atm H_2) but they were able to obtain the desired amino acid derivative **128** in low dr (3:1 dr). In sum, the chemistry of these α-fluoronitroalkane products is promising, yet much work is needed to truly explore the potential and synthetic applications.

2.4 The aza-Henry Reaction to Access β-Amino-α-Fluoronitroalkanes

Since *bis*(amidine)-based chiral proton catalysis has been so effective in the aza-Henry reaction, we decided to explore the use of fluoronitroalkanes in this content. An additional motivating factor and a long-term goal of the group, is the asymmetric synthesis of (–)-Nutlin-3

Figure 23. Outline of the enantioselective preparation of (–)-Nutlin-3 (**9**). The *cis*-imidazoline core of **9** can oxidize *in vivo* to form the inactive imidazole compound **130**. New asymmetric aza-Henry methods are needed to prevent this biochemical oxidation.

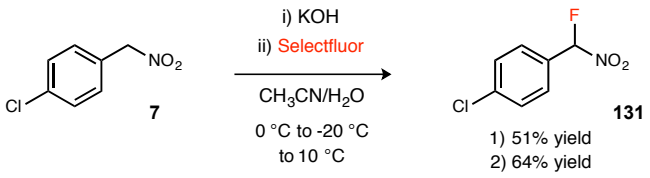


derivatives. Since there is evidence that the *cis*-imidazoline core of the Nutlins can oxidize *in vivo* to the achiral, inactive imidazole **130**, it may ultimately be worthwhile to explore substitution at the 4- and 5-positions of the imidazoline (via **129**) to prevent this deleterious biochemical oxidation event and create a more robust p53-MDM2 inhibitor (Figure 23).

From previous work, *para*-chloro aryl nitromethane (**7**) was readily available and was subjected to monofluorination conditions using Selectfluor (Scheme 36). Gratifyingly, the synthesis of the desired fluoronitroalkane **131** could be prepared in 64% yield on preparative scale. A host of imines were also readily available and were subjected to a typical set of catalysts in order to identify the possibility of enantio- and diastereocontrol.

The initial reaction parameters employed in this case were directly adopted from our past work in the enantioselective addition of aryl nitromethanes to aryl Boc-imines.[102] We surmised

Scheme 36. Successful monofluorination of aryl nitromethane **7**.

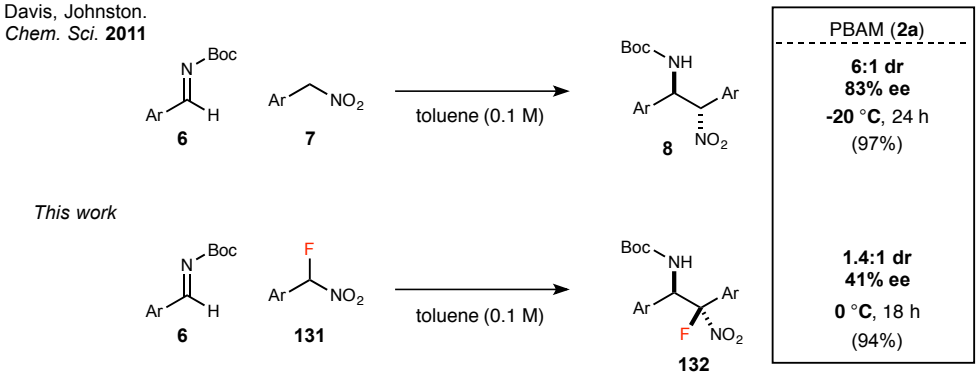


these fluoronitroalkanes to be more Brønsted acidic (and less reactive), due to the additional presence of an electron-withdrawing (electronegative) moiety in the fluorine atom, so a number of less Brønsted basic catalysts were examined. Somewhat surprisingly, the more mild Brønsted basic catalyst H-QuinBAM (**2**) performed very poorly and generated the aza-Henry adduct in low yield, dr, and ee (2:1 dr, 25/24% ee, entry 1, Table 9).

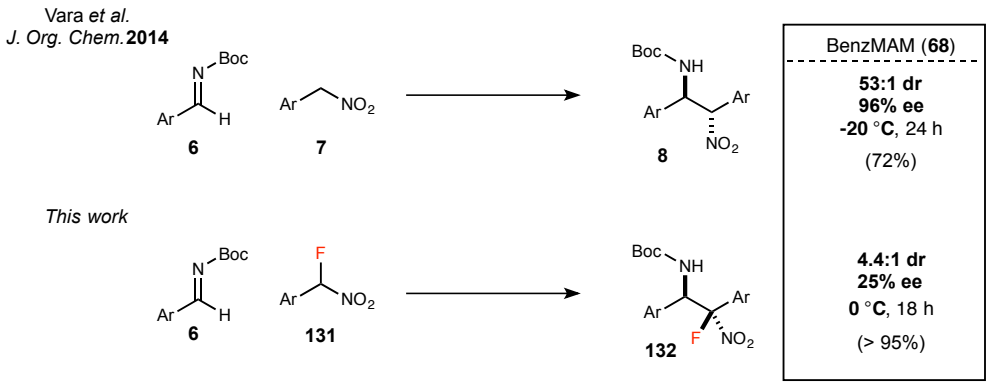
[102] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076. Vara, B. A.; Mayasundari, A.; Tellis, J. C.; Danneman, M. W.; Arredondo, V.; Davis, T. A.; Min, J.; Finch, K.; Guy, R. K.; Johnston, J. N. *J. Org. Chem.* **2014**, *79*, 6913.

It was also immediately evident these nitroalkanes needed warmer temperatures to efficiently react, as conversion was exceptionally slow at temperatures below 0 °C (as a point of comparison, our previous work (*Chem. Sci*. **2011**) with aryl nitromethanes were run at -20 °C and below in order to maintain high levels of stereoselection). The remaining reactions with **131** were conducted at 0 °C for 18 h.

Scheme 37. Reactivity and selectivity comparison of fluoro nitroalkane **131** against non-fluorinated nitroalkane **7** using PBAM (**2a**). Ar = *p*-ClC_6H_4



Scheme 38. Reactivity and selectivity comparison of fluoro nitroalkane **131** against non-fluorinated nitroalkane **7** using BenzMAM (**68**). Ar = *p*-ClC_6H_4



The more Brønsted basic catalyst PBAM (**2a**) also provided the aza-Henry adduct **132** in suboptimal stereoselection (1.4:1 dr, 41/71% ee) but provided a dramatic improvement in conversion, signaling that increased Brønsted basicity is warranted for appreciable conversion

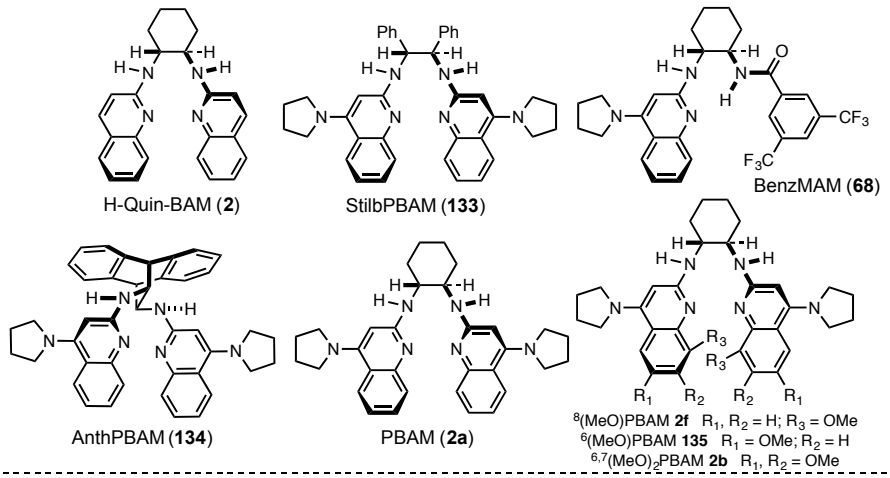
(Scheme 37). Quite strikingly, the mono(amidine) (MAM) amide catalyst BenzMAM (**68**), which worked so well in the identical reaction in the absence of fluorine, provided very poor enantioselection (25/36% ee) and moderate dr at 4.4:1 for **132** (Scheme 38). Based on just these few data points, it was apparent these fluoronitroalkanes behave quite differently from the aryl nitroalkanes previously explored in regards to acidity, nucleophilicity, and overall catalyst recognition.

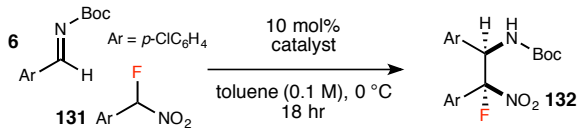
As outlined in Table 9, a range of *bis*(amidine) catalysts containing various chiral diamine backbones, protonation states, and substitutions were evaluated. AnthPBAM (**134**), also highly efficacious in the non-fluorinated version of this aza-Henry reaction (90% ee, 82:1 dr Scheme 84, Chapter 3), provided very poor results (1.6:1 dr, 9/33% ee; entry 4, Table 9). StilbPBAM (**133**) was expectantly incompatible under these conditions (entry 5). ^{6,7}(MeO)$_2$PBAM (**2b**) provided **132** in the highest enantioselection of all the free base BAM catalyst examined (entry 6, Table 9). Improved stereoselection (both dr and ee) when the mono-protonated triflimidic acid salts of the basic chiral ligands were employed (entries 7-13, Table 9). While ^{6}(MeO)PBAM•HNTf$_2$ (**135**•HNTf$_2$) provided **132** adduct in 2.3:1 dr and 86% ee (entry 10), ^{6,7}(MeO)$_2$PBAM•HNTf$_2$ (**2b**•HNTf$_2$) was the most selective, providing the adduct in 4.8:1 dr and 91/86% ee (entry 11, Table 9). The reaction can also be cooled to -20 ºC for improved stereocontrol at the expense of lower yields (entry 14, Table 9).

Even though the diastereoselection was modest, it's notable that both diastereomers maintain high enantioselection in this reaction, on average 6-10% lower ee for the minor diastereomer compared to the major. The beneficial achiral counterion effects observed using **2b**•HNTf$_2$ as compared to free-base **2b** are significant (entries 11 and 6), since the same pair of catalysts provided identical stereoselection with non-fluorinated aryl nitromethanes.

Once the optimal catalyst system was uncovered we briefly explored catalyst loading and concentration of the reaction. Somewhat dramatically, both ee and dr dropped when catalyst

Table 9. Initial experiments examining diverse BAM and MAM organocatalysts in the aza-Henry reaction to obtain high stereoselection employing aryl fluoronitromethane **131** generating adduct **132**.





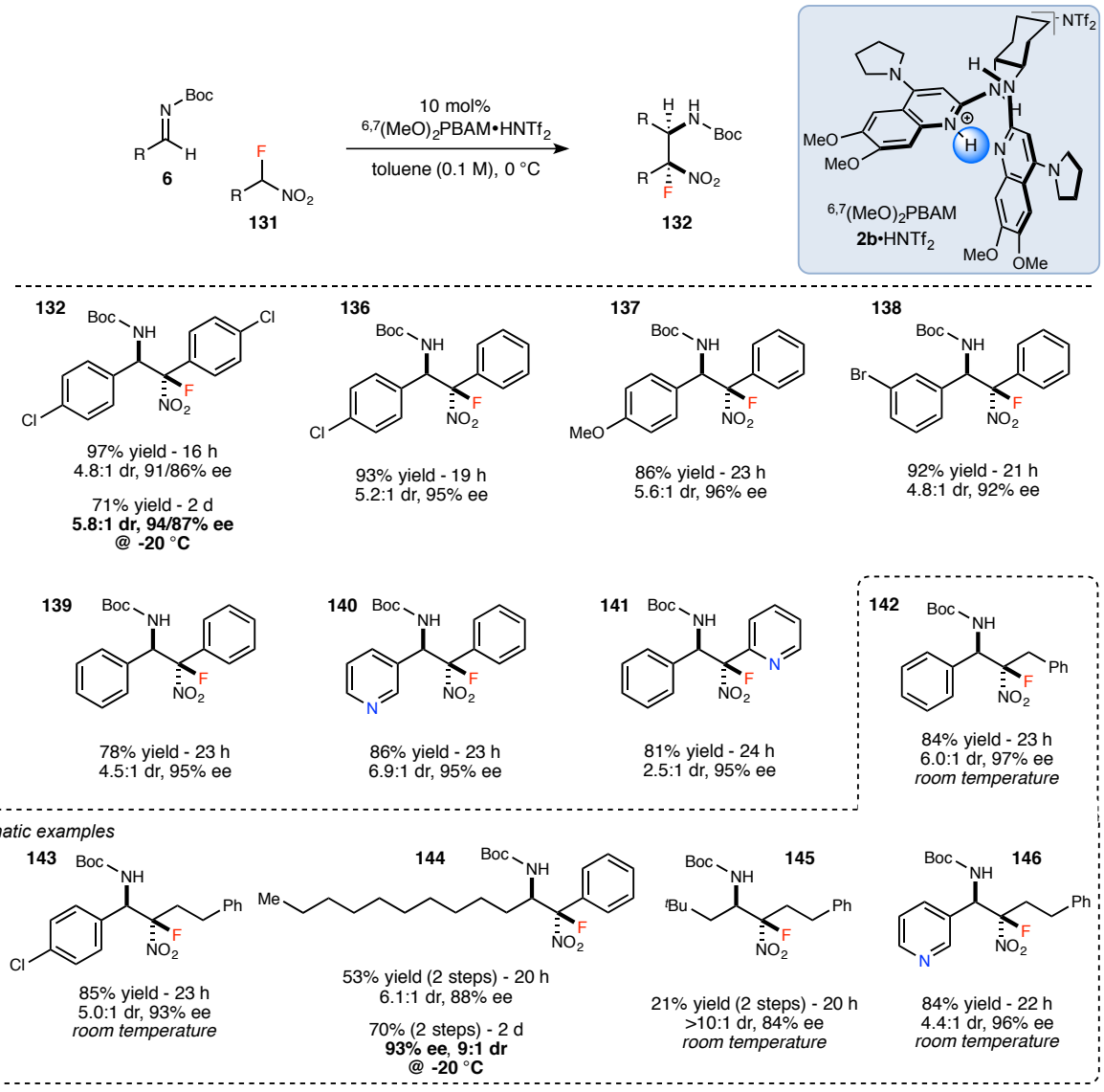
entry	catalyst	acid[a]	yield[c]	d.r.[b]	ee (%)[b]
1	**2**	–	<20	2.1:1	25/24
2	**68**	–	93	4.4:1	25/36
3	**2a**	–	96	1.4:1	41/71
4	**134**	–	95	1.6:1	9/33
5	**133**	–	low	n/a	n/a
6	**2b**	–	84	1.4:1	63/77
7	**2a**	$HNTf_2$	71	1.9:1	83/81
8	**2f**	HOTf	56	1.7:1	57/62
9	**2d**	$HNTf_2$	42	1.6:1	70/71
10	**135**	$HNTf_2$	96	2.3:1	86/84
11	**2b**	**$HNTf_2$**	**97**	**4.8:1**	**91/86**
12	**2b**	$HNTf_2$	73[d]	4.1:1	88/77
13	**2b**	$HNTf_2$	62[e]	3.3:1	86/71
14	**2b**	$HNTf_2$	71[f]	5.8:1	94/87

[a]Catalyst prepared as the 1:1 acid salt. [b]Enantiomeric excess (ee) determined by HPLC using a chiral stationary phase. Reactions are 0.1 M toluene unless otherwise noted. [c]Isolated yield. [d]5 mol catalyst loading. [e]2 mol catalyst loading. [f]Reaction ran at -20 ºC for 40 h.

loading was decreased to 5 and 2 mol % (entries 12 and 13, respectively; Table 9). This is in direct contrast to what was observed in the aza-Henry reactions with non-fluorinated aryl nitromethanes – catalyst loading was decreased to 0.15 mol % (in conjunction with the slow addition of the imine over time) while still maintaining high enantioselection (87% ee).[103]

With satisfactory levels of stereocontrol in hand, generalization of the substrate scope for

Table 10. The scope of the organocatalyzed, enantioselective aza-Henry reaction with fluoronitroalkanes.[a]

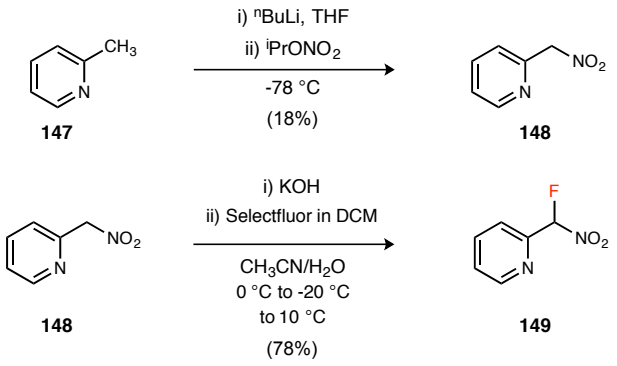


[a]All reactions performed at 0 °C unless otherwise noted and employed 1.1 equiv. of the fluoronitroalkane

[103] Davis, T. A.; Vilgelm, A. E.; Richmond, A.; Johnston, J. N. *J. Org. Chem.* **2013**, *78*, 10605.

this reaction was next examined. A number of diverse aryl Boc-imines were initially employed, and all are very well tolerated using **131** under the robust catalytic system (Table 10). Cooling this reaction down to -20 °C was not dramatically effective in increasing the diastereoselection and hurt conversion somewhat after extending the reaction time to 2 days, although ee marginally increases as expected (**132**, Table 10). Electron releasing *p*-MeO aryl Boc-imine and electron-withdrawing 3-pyridyl imine were effective and their masked-fluoro stilbene amine products (**137** and **140**, respectively) were isolated in good yield and high enantioselection (96% and 95% ee, respectively). This 3-pyridyl imine also afforded **140** in relatively high diastereoselection at 6.9:1 dr. Examining *aryl* fluoronitromethane pronucleophiles further, 2-pyridyl fluoronitromethane performed well in the asymmetric reaction (**141**, 2.5:1 dr, 95/93% ee, 81% yield) considering the proximity of the basic pyridyl-nitrogen to the acidic benzylic position.

Scheme 39. Preparation of the 2-pyridyl fluoronitromethane **149**.



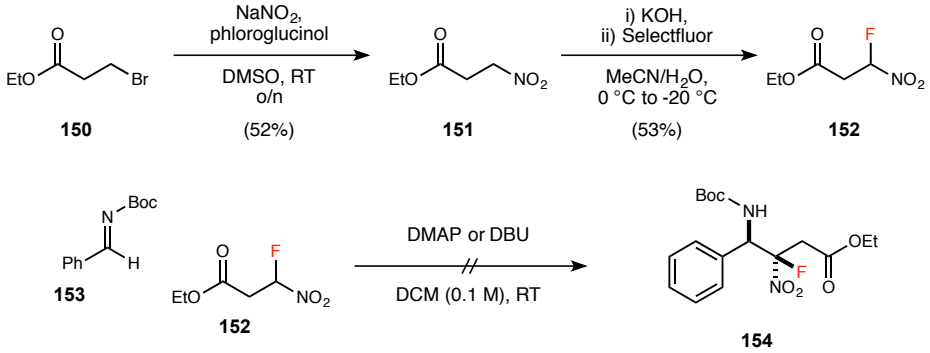
The synthesis of the 2-pyridyl fluoronitromethane **149** was not straightforward yet was able to be achieved using knowledge from similar compounds prepared in the group.[104] As described in more detail in Chapter 1, aryl nitromethanes were typically derived from

[104] For more detailed reports on nitroalkanes see: Davis, T.A. Ph.D. Dissertation, Vanderbilt University, 2011. (Section 2.4)

corresponding benzaldehyde derivatives. 2-Pyridyl nitromethane **148**, perhaps in a most direct approach, was synthesized from 2-methylpyridine **147**. Under basic conditions, the electron-deficient methyl pyridines (or various methylated heterocycles) can be deprotonated and quenched with *i*-propyl nitrate to form the desired aryl nitroalkane in generally good yields. In this case, the unoptimized nitration step to deliver **148** proceeded in low yield (Scheme 39).

Branching away from aromatic coupling partners, the efficacy of aliphatic Boc-imine and aliphatic fluoronitroalkanes under the optimized conditions were next investigated – to our knowledge, aliphatic α-fluoronitroalkanes have never been successfully employed in any enantioselective reaction, despite their relative ease of preparation and potential utility. Lu and coworkers previously failed in this regard using quinine thiourea catalysts.[99] If successful, the potential scope of this reaction could increase exponentially considering the vast library of alkyl bromides (and thus nitroalkanes) that are commercially available.

Scheme 40. Preparation of β-fluoro-β-nitro ester **152** from the corresponding bromoester **150** (synthesis unoptimized).

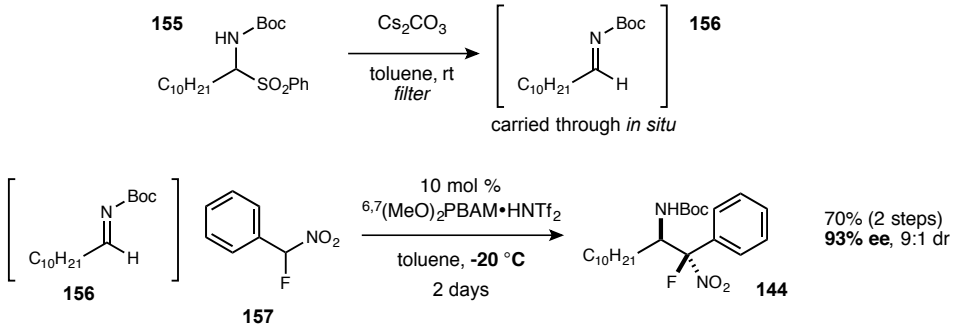


Preparation of the β-fluoro-β-nitro ester **152** in 2 steps from the corresponding bromo ester **150** went smoothly (unoptimized conditions, Scheme 40). The ester would also provide a functionalizable handle for future modifications. Unfortunately after a few reaction attempts with the phenyl Boc-imine, it was evident that conversion to product using DMAP and the more

Brønsted basic DBU was very sluggish, even at room temperature (Scheme 40). Some product was eventually produced using $^{6,7}(MeO)_2PBAM{\bullet}HNTf_2$ but clean material was never isolated. A rational explanation for the incompatibility of **152** in this reaction is not clear.

Simple fluoronitroalkanes could nonetheless be prepared in 2 steps from the corresponding alkyl bromides and can be readily purified on silica gel (> 40% overall yields, 2 steps). Fortuitously, these aliphatic fluoro nitroalkanes are nearly just as effective in this reaction as their arene counterparts in the aza-Henry reaction, in direct contrast to previous reported attempts in the nitro olefin chemistry from Lu (**142**, **143**, **145**, **146**, Table 10). Notably, alkyl fluoronitroalkanes react only at warmer temperatures (24 °C) allowing for facile reaction setup. At room temperature, high levels of stereocontrol can be readily obtained (**143**; 5:1 dr, 93% ee, 85% yield) overnight.

Scheme 41. Aliphatic Boc-imines and their efficacy in the aza-Henry reaction.



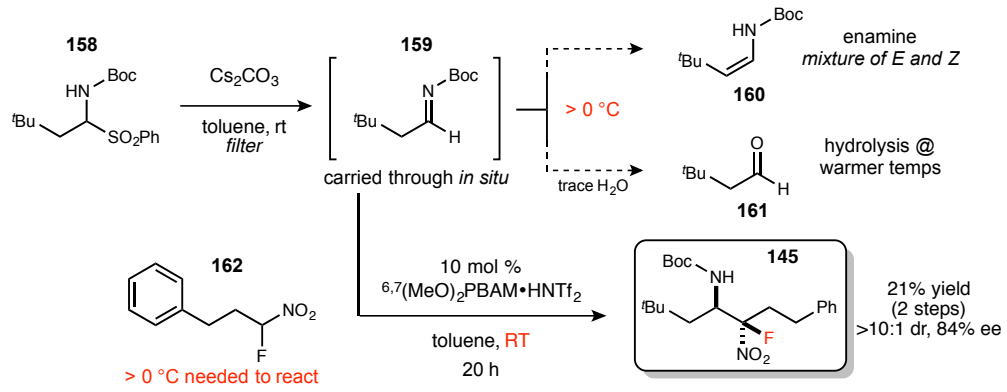
Aliphatic Boc-imines were next examined, as these pose to tautomerize to the *N*-Boc-enamine. An effective synthesis and optimization of aliphatic Boc-imines in the enantioselective aza-Henry reaction with bromonitromethane was recently reported from our group.[105] Using this protocol to generate the unstable imine **156** *in situ* from the isolable α-amido sulfone **155**, the β-

[105] Schwieter, K. E.; Johnston, J. N. *Chem. Sci.* **2015**, *6*, 2590.

alkyl-β-amino fluoronitroalkane product **144** was obtained in good enantioselection and diastereoselection (4.8:1 dr, 88% ee), although in a moderate 53% yield over two steps from **155** at 0 °C (Scheme 41). Improved stereocontrol and yield is nonetheless obtainable at –20 °C (9:1 dr, 93% ee, 70% yield over 2 steps) as a result of decreased imine tautomerization to the unreactive enamine at colder temperatures (Table 10).

The coupling of two aliphatic partners (Boc-imine and fluoronitroalkane) presents a significant challenge given these reagents' reactivity constraints. Of course, at warmer temperatures, enamine tautomerization of the aliphatic Boc-imines will increase substantially, depressing yield of the desired adduct (Scheme 42). Subjecting the hindered *t*-butyl alkyl α-amido sulfone (**158**) to elimination conditions generated the aliphatic Boc-imine **159** *in situ* at room temperature. This mixture was quickly filtered to remove the base and then **2b**•$HNTf_2$ and the fluoronitroalkane **162** were added. At room temperature, good stereocontrol was achieved between these two aliphatic coupling partners (**145**; >10:1 dr, 84% ee), although at the sacrifice of high chemical yield (21%, 2 steps; Table 10). Isomers of the undesired enamine (**160**) were observed in the crude NMR and presumably volatile aldehyde **161** was also generated (Scheme

Scheme 42. Problems associated with the aza-Henry reaction between **159** and aliphatic fluoronitroalkanes – low yields and good stereoselection result.

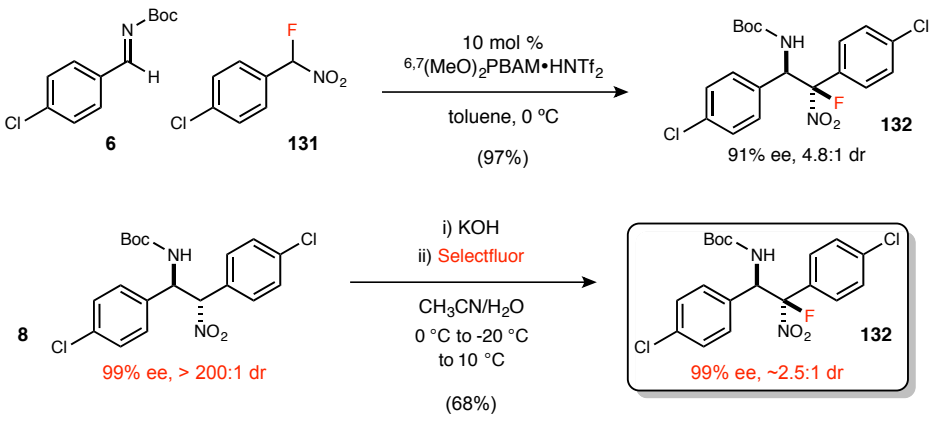


42). These products are versatile synthetic compounds, and enantioenriched fluorinated analogues bearing two orthogonal aliphatic chains are difficult to prepare using any other method.

As a final illustrating example of the diverse electrophile and pronucleophile components, an alkyl fluoronitroalkane can effectively react with a heteroaromatic pyridyl Boc-imine to afford aza-Henry adduct **146** in good levels of stereoselection at room temperature (4.4:1 dr, 96% ee, 84% yield; Table 10). Brønsted basicity of the pyridyl imine seems to have no effect on how the substrates bind the catalyst as revealed by the consistently high enantioselection of the reaction.

This aza-Henry reaction has allowed us to generate enantioenriched β-amino α-fluoronitroalkanes directly from fluoronitroalkanes with good stereocontrol. While this stands as an effective method, we were curious whether the fluorination protocol of nitroalkanes could be directly viable with the saturated β-amino nitroalkane **8**. Submitting **8** to a solution of KOH and Selectfluor afford the fluorinated derivative **132** in 68% yield (Scheme 43). Diastereoselection in this reaction was of specific interest and lower dr (2.5:1) was observed compared to the enantioselective addition of fluoronitroalkane **131**.

Scheme 43. Comparison of the developed aza-Henry reaction to direct fluorination of **8**.

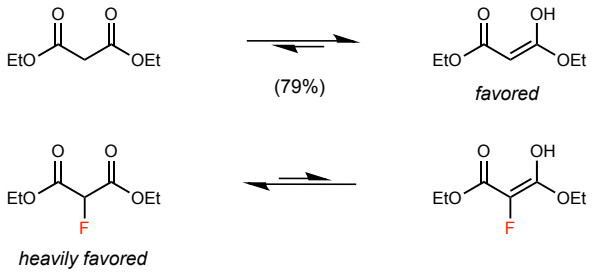


2.5 Reactivity Profiles of Fluoronitroalkanes as Compared to Nitroalkanes

Addressing the sluggish reactivity for the alkyl fluoronitroalkane substrates relative to the aryl fluoronitromethanes exposes a few very interesting scenarios. From the outset of working with these reagents, it was reasonable for one to assume the alkyl fluoronitroalkanes would react faster, since they are by nature more electron rich than the aryl fluoronitromethanes. Based on data presented in this work, that was clearly not the case.

Typically, it is well understood that vinyl/aryl C–F bonds are resonance stabilized from the donation of fluorine's lone pairs, but in electron rich π-systems, destabilization can occur. Comparably, Kumler, Kun, and Shoolery reported an interesting study examining the tautomeric

Figure 24. Experimental effects of fluorine on the tautomerization of diethyl malonate and fluoro diethyl malonate.



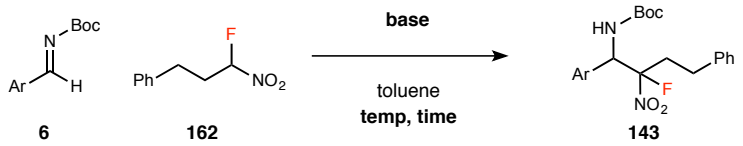
forms of diethyl malonate and fluoro diethyl malonate.[106] Under normal conditions (malonates as oils, room temperature) the enol form of diethyl malonate is favored (79% enolized) whereas fluoro diethyl malonate completely favors the dicarbonyl tautomer (Figure 24). In the enol forms, the π-system is relatively electron-rich due to the presence of the hydroxyl (and ethoxy) group, usually favoring a conjugated π-system. Fluorine, however, destabilizes the enol tautomer

[106] Kumler, W.D.; Kun, E.; Shoolery, J.N.; *J. Org. Chem.* **1962**, *27*, 1165.

– fluorine's lone pairs do not donate into the electron-rich enol system and instead its electronegativity takes precedence stabilizing the dicarbonyl tautomer.

Reports that examine simple fluoronitroalkanes such as fluoronitromethane have shown that they also exhibit *decreased* C–H acidity as compared to nitromethane due to these destabilizing inductive effects on the resulting carbanion or nitronate via electron-electron repulsion.[107] Even comparing α-fluoronitroalkanes to α-chloronitroalkanes, the fluorinated variants are orders of magnitude less acidic than the chlorinated compounds (Adolf)[107]. The α-aryl π-system of the aryl fluoromethylnitronates on the other hand allows for stabilization of the sp^2-hybridized nitronate anion, allowing these to behave more closely to C–H aryl nitromethanes previously explored in our group. The addition of a fluorine atom should theoretically decrease nitronate nucleophilicity, however, based on control experiments we carried out, data show a slower deprotonation (and/or decreased acidity) of the fluoro nitroalkanes to be the root cause for lower reactivity.

Table 11. Reactivity of the alkyl fluoronitroalkane **162** in the aza-Henry reaction. Ar = *p*-ClC_6H_4



6 **162** **143**

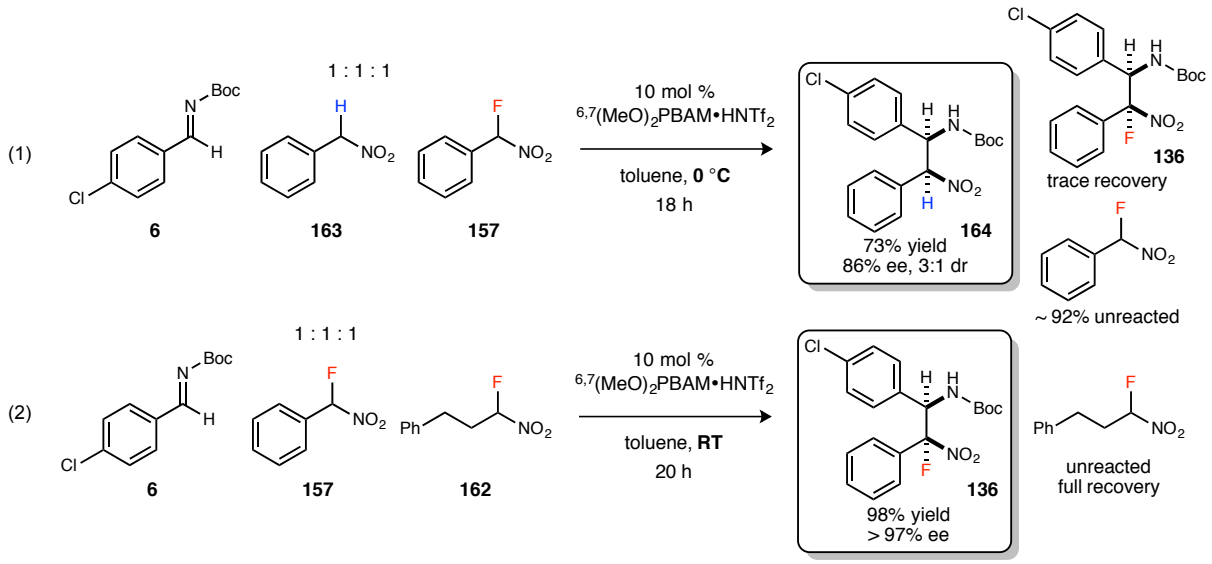
entry	base	temp	time	results
1	DMAP	RT	24 h	SM
2	DMAP	60 °C	o/n	SM(imine also present)
3	**2b**•$HNTf_2$	0 °C	18 h	SM
4	DBU	RT	24 h	> 90% **143**
5	**2b**•$HNTf_2$	RT	18 h	> 90% **143**

[107] Adolph, H. G.; Kamlet, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 4761. Lorand, J. P.; Urban, J.; Overs, J.; Ahmed, Q. A. *J. Org. Chem.* **1969**, *34*, 4176.

We explored this notion experimentally by first reacting the alkyl fluoronitroalkane **162** with the aryl imine **6** using several achiral organic bases. After several attempts using DMAP we could not observe any conversion to the desired aza-Henry adduct **143**, even after heating the reaction mixture at 60 °C overnight (entry 2, Table 11). This was unexpected since most previous aryl (and some alkyl) nitroalkanes we have worked with in the past react very quickly with DMAP at room temperature and below. As outlined previously, even the optimal *bis*(amidine) catalyst $^{6,7}(MeO)_2PBAM{\bullet}HNTf_2$ (**2b**•$HNTf_2$) could not mediate the addition reaction at 0 °C. Finally, DBU at room temperature overnight afforded appreciable conversion to the aza-Henry product **143**.

Collectively, these alkyl fluoronitroalkanes necessitate more strongly Brønsted basic BAM organocatalysts at elevated temperatures to increase the rate of deprotonation as compared to the cinchona thiourea catalysts used by Lu. The deprotonation may be kinetically too slow at 0 °C or below, or simply, the alkyl fluoronitroalkanes are less acidic in accord with Adolf and Lorand's determination of relative pKa's in water. As a result, higher temperatures in

Scheme 44. Competition experiments examining the reactivity (and acidity) of the fluoro nitroalkanes and nitroalkanes in the aza-Henry reaction.

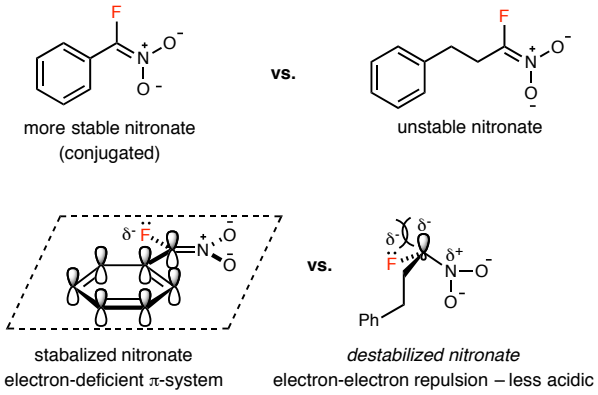


conjunction with a more Brønsted basic catalyst are required to achieve a reasonable rate of conversion.

To drive this point further, a competition experiment between *aryl* nitromethane **163** and the *aryl* fluoronitromethane **157** was examined as shown in Scheme 44 (eq 1). Expectantly, the saturated aryl aza-Henry adduct **164** was the primary product isolated (73% yield, 86% ee). By ^{1}H NMR using an internal standard, roughly 8% of the aryl fluoronitromethane reacted, and only a fraction converted to aza-Henry product. Examining the relative reactivities of the alkyl and aryl fluoronitroalkanes, aryl fluoronitromethane **157** and alkyl nitromethane **162** were subjected to analogous reaction conditions at 0 ºC with the aryl Boc imine **6** in a 1:1:1 molar ratio (eq. 2, Scheme 44). Expectantly, **157** outcompeted considerably the alkyl fluoronitromethane for **9** (98% yield, 97% ee) and unreacted alkyl fluoronitromethane **162** was nearly fully recovered.

As rationalized in this section, the data are consistant with the alkyl fluoronitroalkanes being less acidic than the aryl fluoronitromethanes due to the fluorine lone pair destabilization. Figure 25 depicts these scenarios.

Figure 25. Orbital rationalization for the different reactivity profiles observed for alkyl and aryl fluoronitroalkanes.



2.6 β-Fluoroamines: Applications and their Preparation using BAM Catalysis

β-Fluoroamines are a unique class of fluorinated compounds[108] that display remarkable CNS-penetrant properties – a handful of examples are illustrated in Figure 26. The most illustrious example in this class may be Sofosbuvir, an RNA polymerase inhibitor that is in part responsible for unprecedented high cure rates of the Hepatitis C virus.[109] Furthermore, β-fluoroamines exhibit decreased amine basicity and enhanced binding interactions similar to other fluorinated motifs mentioned at the beginning of this chapter.[110] From a synthetic standpoint, the paucity of direct, enantioselective methods to chiral racemic[111] and non-racemic[112] β-fluoroamines remains enigmatic – one can argue this is circumstantial due to insufficient reaction methods developed and not a general lack of desire.

The BACE and PIM kinase inhibitors outlined in Figure 26 are more recent examples of clinical candidates containing β-fluoroamines used in the treatment of Alzheimer's and cancer, respectively. As is evident, this motif is a highly desirable functionality when targeting an array of disease areas.

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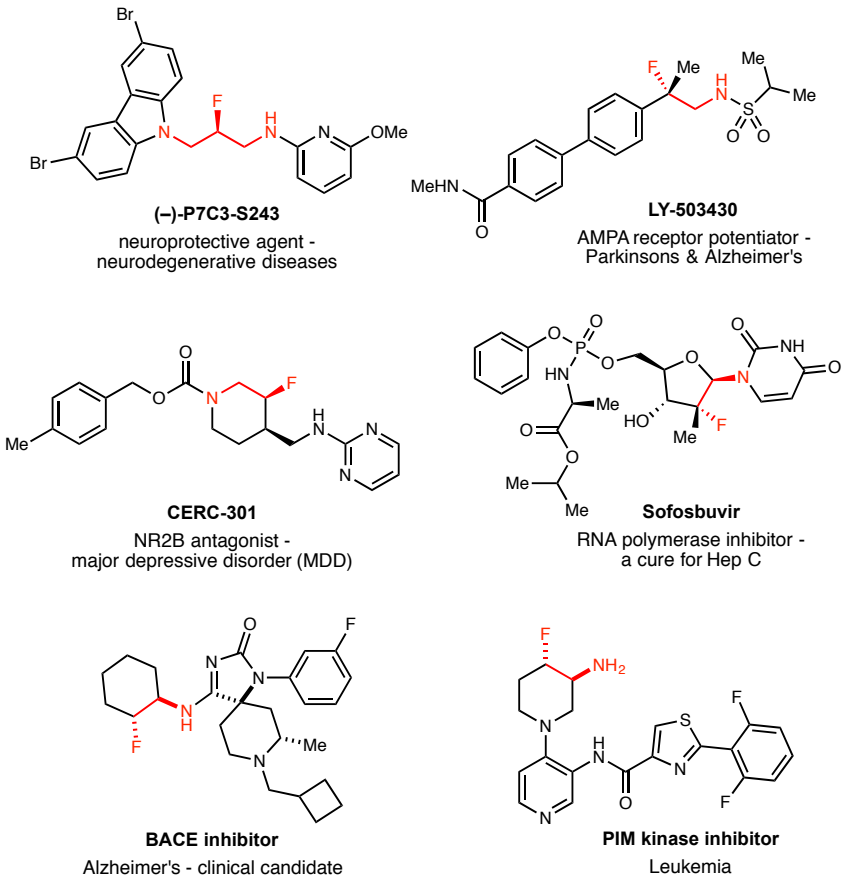
[108] Percy, J. M. *Sci. Synth.* **2006**, *34*, 379.
[109] Clark, J. L.; Hollecker, L.; Mason, J. C.; Stuyver, L. J.; Tharnish, P. M.; Lostia, S.; McBrayer, T. R.; Schinazi, R. F.; Watanabe, K. A.; Otto, M. J.; Furman, P. A.; Stec, W. J.; Patterson, S. E.; Pankiewiez, K. W. *J. Med. Chem.* **2005**, *48*, 5504.
[110] Morgenthaler, M.; Schweizer, E.; Hoffmann-Roder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Mueller, K. *Chemmedchem* **2007**, *2*, 1100.
[111] Alvernhe, G.; Kozlowska-Gramsz, E.; Lacombe-Bar, S.; Laurent, A. *Tetrahedron Lett.* **1978**, 5203. Wade, T. N. *J. Org. Chem.* **1980**, *45*, 5328. Alvernhe, G. M.; Ennakoua, C. M.; Lacombe, S. M.; Laurent, A. J. *J. Org. Chem.* **1981**, *46*, 4938. Hamman, S.; Beguin, C. G. *J. Fluorine Chem.* **1987**, *37*, 191. Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Tyte, M. J. *Org. Lett.* **2010**, *12*, 2936. Kalow, J. A.; Schmitt, D. E.; Doyle, A. G. *J. Org. Chem.* **2012**, *77*, 4177.
[112] Prakash, G. K. S.; Wang, F.; Stewart, T.; Mathew, T.; Olah, G. A. *P Natl Acad Sci USA* **2009**, *106*, 4090. Garcia Ruano, J. L.; Parra, A.; Alonso, I.; Fustero, S.; del Pozo, C.; Arroyo, Y.; Sanz-Tejedor, A. *Chem. - Eur. J.* **2011**, *17*, 6142. Duthion, B.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2010**, *12*, 4620. Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356.

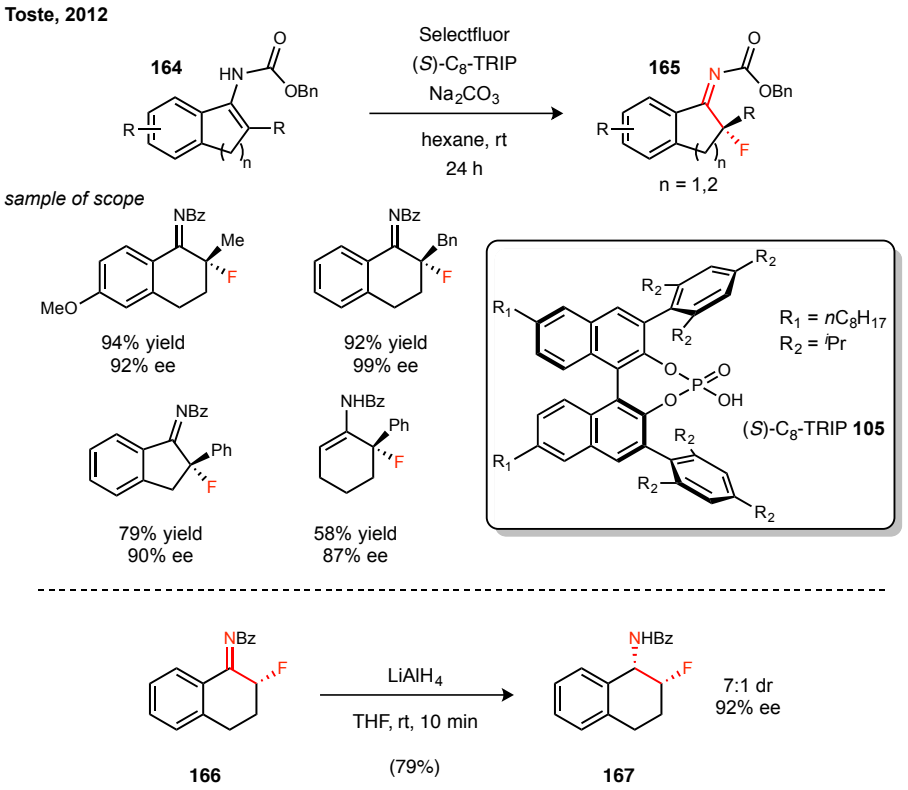
Figure 26. Small molecule therapeutics containing β-fluoroamine motifs that are approved or in the clinic for various diseases. Notably, all are prepared as single stereoisomers.



While enantioselective fluorination reactions have grown by leaps and bounds as previously discussed, the majority of the transformations still require rigorous setup conditions, prefunctionalized substrates, and specially tuned catalysts to selectively deliver this small atom to construct β-fluoroamines.[113] A report from Toste allows for the preparation β-fluoro*imines* from ene-carbamates using the phase transfer phosphoric acid catalyst (*S*)-C_8-TRIP **105** to affect the stereoselective delivery of fluorine (Selectfluor). This work was derived from their previous work in the field discussed in an earlier section. While the mechanistic approach to access these fluoroamine motifs is truly unique and innovative, the substrate scope is primarily restricted to

[113] Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376. Wu, J.; Wang, Y. M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 13729.

Figure 27. Report from Toste and coworkers in the enantioselective synthesis of β-fluorimines from cyclic enamides using phosphoric acid phase transfer catalysis. Derivatization to a β-fluoroamine **166** is also detailed.

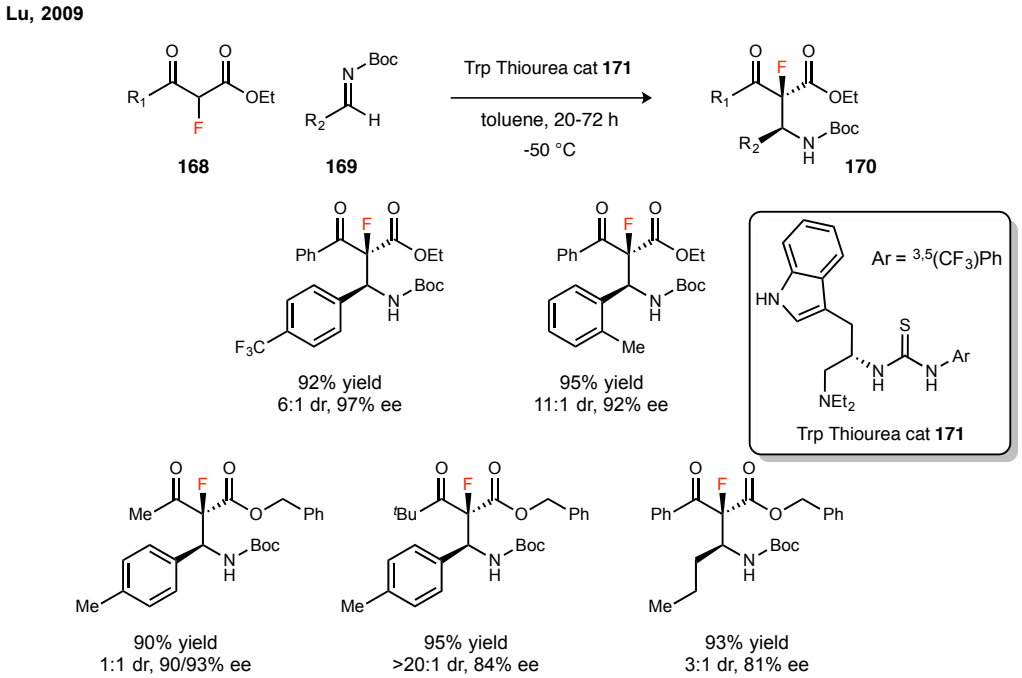


tetralone-derived fluoroimines from cyclic enamides (Figure 27). One example functionalizing the enantioenriched imine adduct **166** to a *cis*-β-fluoroamine was reported, isolating **167** in 7:1 dr and 92% ee.

Lu and coworkers reported an organocatalyzed Mannich reaction in 2009, facilitating the addition of α-fluoro-β-ketoesters **168** into Boc-imines (Scheme 45).[114] While the Mannich additions of β-ketoesters and malonate derivatives have been reported on several occasions using metal and organocatalysts, fluorinated variants are less represented. The novelty in this work is the discovery of the selective tryptophan-derived thiourea catalyst **171**. The scope is quite general, and a pair of *aliphatic* Boc-imines was also tolerated to formally generate an alkyl β-

[114] Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K. W.; Lu, Y. X. *Angew. Chem. Int. Ed.* **2009**, *48*, 7604.

Scheme 45. Organocatalytic, asymmetric Mannich addition of fluoro ketoesters **168** into Boc-imines.



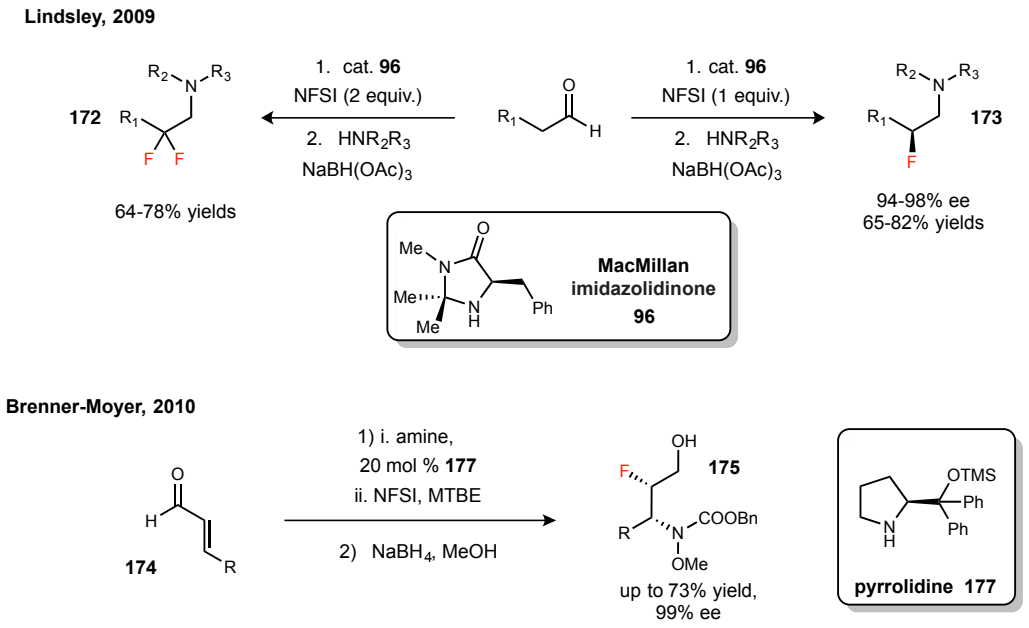
fluoroamine scaffold. These enantioenriched products, containing fluorinated quaternary carbons (**170**), were elaborated further to construct an α-fluoro-β-lactam and an α-fluoro-β-lactone.

Lindsley and coworkers have developed an effective and very practical enantioselective fluorination/reductive amination protocol to access chiral β-fluoroamines in one pot from simple aldehydes (Scheme 46).[115] Condensation of MacMillan's organocatalyst **96** generates the nucleophilic enamine *in situ* followed by a reductive workup of the iminium with $NaBH(OAc)_3$ to construct enantioenriched β-fluoroamines **173** in good ee and yield. β-Difluoroamines (**172**) can be prepared when an excess of NFSI is employed.

Brenner-Moyer in 2010 reported an organocatalytic (**177**), asymmetric olefin aminofluorination reaction of unsaturated aldehydes **174** to construct β-fluoroamines with *vicinal*

[115] Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943. O'Reilly, M. C.; Lindsley, C. W. *Tetrahedron Lett* **2013**, *54*, 3627.

Scheme 46. Organocatalytic, asymmetric fluorination/reductive amination from Lindsley and coworkers, and a later report from Brenner-Moyer.



stereocenters (**175**) in one pot (Scheme 46).[116] These adducts were prepared in good yield and up to 99% ee and 98:2 dr.

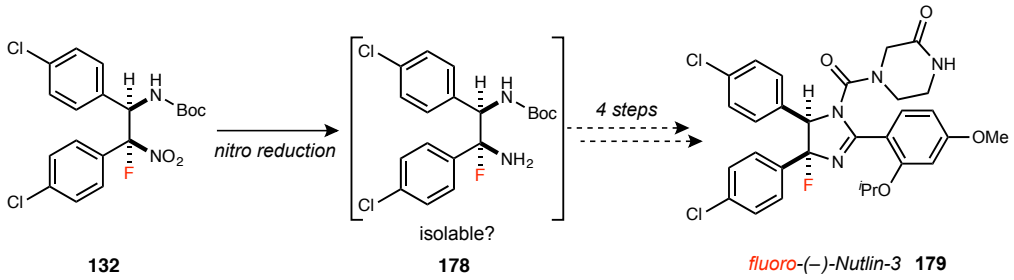
Generally speaking, however, organocatalyzed, asymmetric reactions inducing stereoselection *at both vicinal carbon centers* (C–F and C–N) simultaneously is limited to a small number of reports. Another report from Doyle and coworkers, described the asymmetric desymmetrization of protected aziridines (**115**) using a chiral cobalt fluoride source in moderate levels of enantioselection (up to 84% ee, Scheme 28).[117]

In contrast to enantioselective monofluorinations to access β-fluoroamines, we envisioned accessing these motifs in one step from our enantioenriched β-amino fluoro-nitroalkanes. As mentioned prior, these fluoronitroalkanes can bring tremendous synthetic value to a synthesis, but their chemistry has only been sporadically explored and reported throughout

[116] Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356.
[117] Kalow, J. A.; Doyle, A. G. *Tetrahedron* **2013**, *69*, 5702.

the years. Additionally intriguing, if we can prepare the stilbene α-fluoroamine **178** in good yield and dr from **132**, the fluorinated derivative of (–)-Nutlin-3 **179** should be obtainable (Scheme 48).

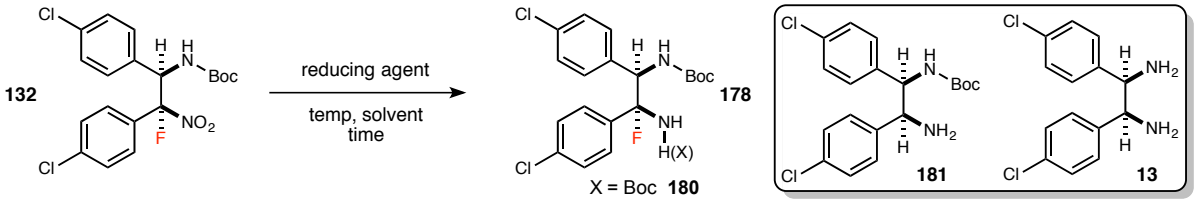
Scheme 47. Proposed route to fluoro-(–)-Nutlin-3 **179**.



132 **178** *fluoro-(–)-Nutlin-3* **179**

Using β-amino α-fluoronitroalkane **132** (Table 12) as a template to test of variety of reduction and functionalization reactions, we were first eager to reduce the nitro-containing compound to the fluoro-α,β-diamine **178**, based off our previous success with the Nutlin intermediates and the hydrogenation conditions reported by Lu in Scheme 35. We first examined metal-hydride donors most familiar to the group (entries 1-3, Table 12). Cobalt(II) chloride and sodium borohydride, which worked well in the Nutlin chemistry, afforded a mixture of byproducts and undesired defluorinated products – nothing significant could be isolated.

Table 12. Attempts to reduce the nitro group to amine **178** (X = Boc amine, **180**). The primary products observed by ^{1}H NMR and ^{19}F NMR did not contain fluorine are also outlined (**181** and **13**).



entry	reducing agent	temp	time	solvent	results
1	$CoCl_2$, $NaBH_4$	0 ºC	2 h	MeOH	mixture
2	$CoCl_2$, $NaBH_4$	RT	3 h	MeOH	mixture
3	$NiCl_2$, $NaBH_4$	RT	3 h	MeOH	mixture+**132**
4	Zn (40 eq.), HCl (40 eq.)	RT	15 min	EtOH	**181**
5	Zn (5 eq.), HCl (40 eq.)[a]	RT	1 h	EtOH	**181**+**132**
6	Zn (40 eq.), HCl (40 eq.)	80 ºC	10 min	EtOH	**13**
7	$Pd/BaSO_4$, H_2 (3 atm), $(Boc)_2O$[b]	RT	3 h	MeOH	**132**
8	$Pd/BaSO_4$, H_2 (6.8 atm), $(Boc)_2O$[c]	RT	o/n	EtOAc	defluoro **181**+**132**
9	Raney Ni, H_2 (1 atm)	RT	6 h	EtOH	30% **181**+**132**

[a]Denotes zinc was washed with HCl prior to use, although did not noticeably affect the reaction. [b]Par shaker used (pressure ceiling of 3 atm). [c]Par reactor used capable of higher pressures.

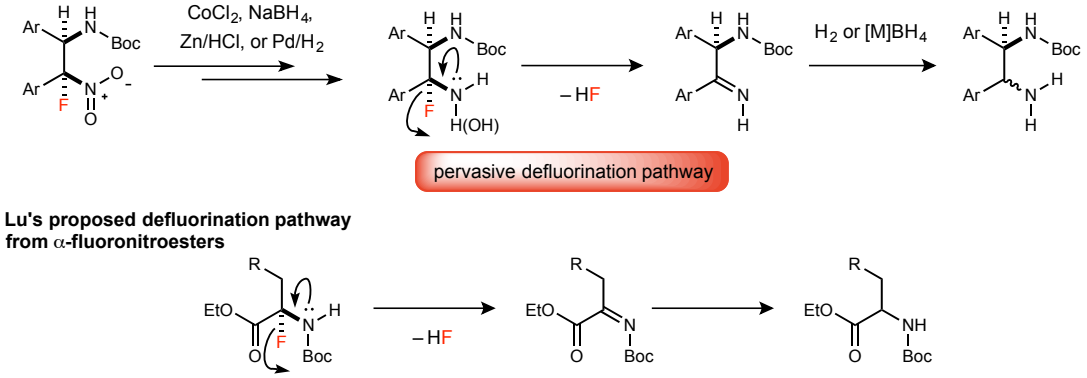
The combination of zinc/HCl seemed to be excessively forceful, initially generating clean defluorinated stilbene diamine **181** (entry 4, Table 12). Curious of the outcome upon heating to 80 ºC, we interestingly observed the *meso* defluorinated *cis*-stilbene diamine **13** in good yield (entry 6). Attempts to temper reactivity were unsuccessful, however, as defluorination seemed to be the lowest energy pathway to product (entry 5).

We were encouraged by the hydrogenation conditions developed by Lu, and since there was precedence for this selective reduction in the presence of an α-fluoro substitution (albeit low yielding), we were hopeful it could be applied to our system. After several attempts using identical and modified conditions to those used by Lu, however, we saw at best trace conversion

to the reduced, protected amine compound **180** and recovered almost entirely **132** (entry 7, Table 12). After several attempts (additional reactions screened not shown), optimal conditions ('a happy medium') could not be obtained. Extending the reaction time under increased pressure (6.8 atm) provided a mixture of undesired defluorinated product **181** and starting material **132** (entry 8, Table 12).

Analogous hydrogenation conditions were examined employing Raney nickel under a balloon of H_2 (1 atm). This reaction was more sluggish compared to the palladium-mediated hydrogenations, yet significant amounts of defluorinated product emerged early on in the reaction (entry 9, Table 12). In sum, a more extensive examination of reducing conditions is needed to prevent the defluorination pathway and selectively reduce/trap the desired amine (Scheme 48).

Scheme 48. The deleterious loss of HF under reducing conditions. Also detailed is the proposed defluorination pathway from work conducted by Lu.[101]

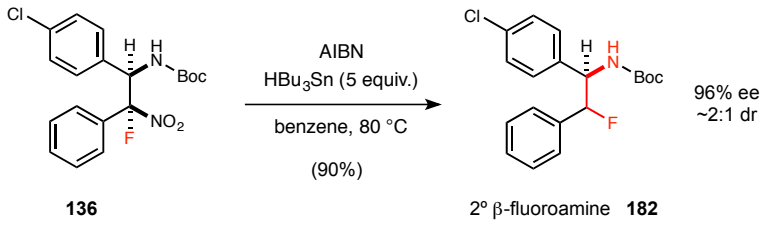


Despite these setbacks, we were confident we could find success in other approaches. It was well known in the literature and within our own work that nitro groups respond well to single electron-mediated substitutions and reductions. The combination of tributyltin hydride ($HSnBu_3$) and azobis(isobutylnitrile) (AIBN) is perhaps the most robust method for the reductive denitration of various substituted 2º and 3º nitro groups. If successful, the products generated

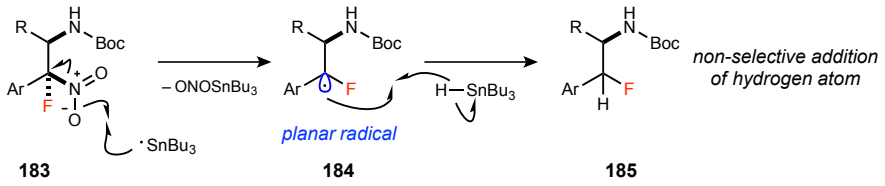
would be highly valued enantioenriched, Boc-protected β-fluoroamines. The primary concern from the outset was retention of diastereoselection, as overcoming epimerization could be a formidable challenge.

Fortunately, we were able to push **136** to the desired denitrated product **182** in nearly full conversion, but was isolated in 90% yield as an inseparable ~2:1 mixture of diastereomers (Scheme 49). Enantioselection of the product was maintained at 96% ee. Obtaining the desired reactivity in this reaction was challenging, and modified denitration conditions were found to be optimal: two separate vials underwent three freeze-pump-thaw cycles. To the vial containing only the substrate in benzene at 80 ºC, was added AIBN and $HSnBu_3$ dropwise as a solution in benzene over the course of 30-40 minutes (see Experimental for additional details).

Scheme 49. Reductive denitration with $HSnBu_3$ affords **182** in ~2:1 dr.



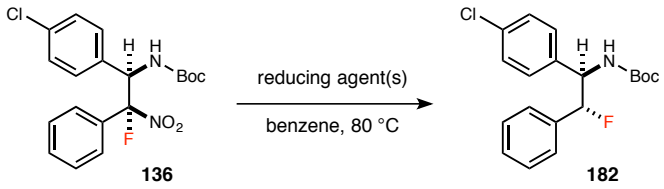
Scheme 50. Proposed pathway for the reductive denitration epimerization.



Mechanistically we do not have a good understanding of why we see an added benefit to the reaction using this modification. It could be that the rate of hydrogen atom transfer or propagation of the carbon-centered radical is slow and the reaction needs to be reinitiated with AIBN. Presumably the reaction operates through a non-stabilized planar radical (**184**, Scheme

51). In which case, the delivery and/or approach of the hydrogen atom would be responsible for the low selectivity observed. In reactions where the $HSnBu_3$ was added to the reaction vial *first*, and AIBN was added later, only starting material was observed after several attempts.

Table 13. Attempts to improve diastereoselection for the reductive denitration to **182**.



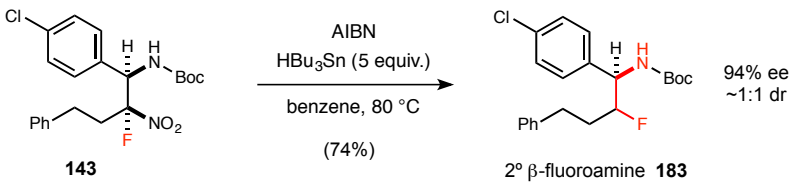
136 **182**

entry	reducing agent	time	results
1	$HSnBu^3$ (1.2 equiv.)	4 h	low conversion: 2:1 dr **182**
2	$(TMS)_3SiH$ (2 equiv.)	2 h	**136**
3	20 mol % PhSeSePh, $HSnBu_3$ (1.5 equiv.)	2 h	2:1 dr **182**

In hopes to improve dr for this reaction, several other reductive conditions were explored. Simply lowering the equivalence of $HSnBu_3$ resulted in sluggish conversion (entry 1, Table 13). Chatgilialoglu's reagent, $(TMS)_3SiH$, was employed as the hydrogen atom donor with AIBN as the initiator – no reaction was observed under these conditions (entry 2). Separately, catalytic amounts of diphenyl diselenide were employed together with tributyltin hydride and AIBN (entry 3). This reaction was setup in the same manner as the optimized reaction with tributyltin hydride and AIBN. After 2 hours only **182** remained, yet 2:1 dr was still observed.

We were naturally curious as to whether the aliphatic β-amino-α-fluoronitroalkanes could

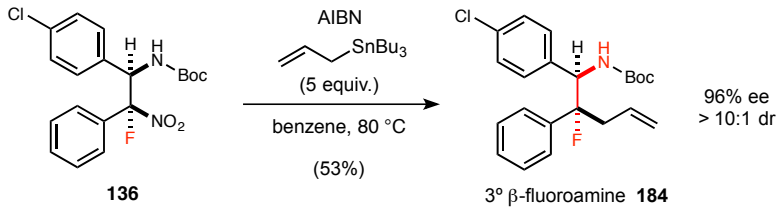
Scheme 51. Reductive denitration of aliphatic substrate **143**.



143 2° β-fluoroamine **183**

be denitrated in a similar manner. The carbon-centered radical generated in this case should be more susceptible to epimerization, also resulting in low diastereoselection. After submitting **143** to the previously optimized denitration conditions, we witnessed clean conversion to the reduced

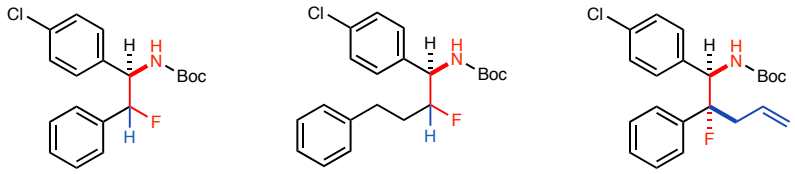
Scheme 52. Reductive allylation with allyl tributyltin affords the 3º β-fluoroamine **184**.



183, which was isolated in 76% yield (Scheme 51). In line with our reasoning, 1:1 dr (94% ee) was observed for this substrate.

Since the radical denitration approach was successful (although product formed in low dr), other organotin reagents were worth exploration. Allyltributyltin was next examined with **136**. Although only moderate conversion was observed after several trials, the desired allylated product **184** was obtained in high dr (>10:1 dr, 96% ee, Scheme 52). Under optimized conditions **184** could be isolated in up to 53% yield. The reasons for low conversion are unclear. This transformation to **184** is notable from a synthetic standpoint because it creates a fluorinated quaternary carbon center, challenging to access by other means. Moreover, the appended allyl group functions as a synthetic handle for additional modifications. Preliminary attempts to further functionalize the allyl group of **184** have proved unfruitful to date, however. Ozonolysis in methanol gave an assortment of products, including defluorinated material by ^{19}F NMR.

Figure 28. Derivatized compounds from enantioenriched β-amino fluoronitroalkanes.



2° β-fluoroamine **182**

96% ee
2:1 dr

2° β-fluoroamine **183**

94% ee
~1:1 dr

3° β-fluoroamine **184**

96% ee
> 10:1 dr

In sum, three derivatized compounds were accessed from the β-amino fluoronitroalkane aza-Henry products in good yields (Figure 28). While the utility of the nitro group remains to be expanded these substrates offer untapped potential and are worth future exploration. Kornblum, Ono, [118]and Koizumi[100,119] over the years have reported very interesting transformations of nitro groups and together are worth examining.

2.7 Target Molecule Synthesis and Future Directions

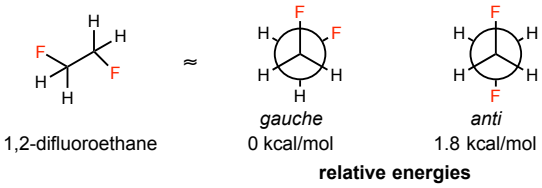
While these β-amino fluoronitroalkanes may be an inherently valuable in their own right, the ability to transform to enantioenriched β-fluoroamines is especially noteworthy. The derivatization reactions highlighted in the previous section demonstrate the ability of the nitro group to function as a synthetic handle, allowing for the incorporation of additional functional groups in a site-specific manner generating substituted β-fluoroamines.

β-Fluoroamines are known to have dramatic biological influences on small molecules in biological systems. This class of organofluorine compounds displays remarkable CNS-penetrant properties through several key features: lipophilicity is often increased (although not

[118] Ono, N. *The Nitro Group in Organic Synthesis.* Wiley-VCH. New York, New York. 2001.
[119] Takeuchi, Y.; Nagata, K.; Koizumi, T. *J. Org. Chem.* **1987**, *52*, 5061. Takeuchi, Y.; Nagata, K.; Koizumi, T. *J. Org. Chem.* **1989**, *54*, 5453.

always), enhancing passive transport into the cell and greater overall bioavailability. Perturbation of pKa of proximal functional groups allows for improved bioavailability and target binding. And finally, molecular conformational changes are often observed upon fluorine substitutions.[64] This is perhaps most pronounced with 1,2-difluoroethane, preferring to adopt a *gauche* conformation instead of the common *anti* conformation (termed gauche effect, Figure 29). The electronegative fluorine anti-bonding orbitals are stabilized through hyperconjugation of the C–H bond, thus adopting a gauche arrangement.

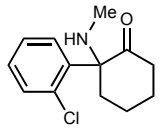
Figure 29. Conformational preference of 1,2-difluoroethane.



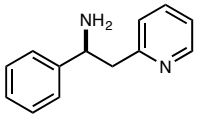
In an effort to illustrate the value of accessing these β-fluoroamine motifs, we sought to prepare β-fluorinated analogues of lanicemine (**186**, AZD6765) – a potent, low-trapping NMDA receptor antagonist containing a chiral phenethylamine motif. Lanicemine entered the clinic in 2006 (PhI-PhIIB, 2006-2010) for the treatment of major depressive disorder (MDD), exhibiting more desirable characteristics than the dissociative anesthetic drug, ketamine (**185**), including limited psychotomimetic and dissociative side effects (Figure 30).[120] Ketamine is also infamously non-selective, hitting other targets including opioid receptors and monoamine transporters.[121] It is for these reasons a number of pharmaceutical companies continue to pursue more efficacious and selective CNS-penetrant agents targeting depression.

[120] Sanacora, G.; Smith, M. A.; Pathak, S.; Su, H. L.; Boeijinga, P. H.; McCarthy, D. J.; Quirk, M. C. *Molecular Psychiatry* **2014**, *19*, 978.
[121] Kohrs, R.; Durieux, M. E. *Anesth Analg* **1998**, *87*, 1186.

Figure 30. NMDA receptor antagonists: Ketamine, used in the treatment of depression, among a variety of ailments. Lanicemine **186** is a low-trapping antagonist.



NMDA antagonist (non-selective)
Ketamine
185

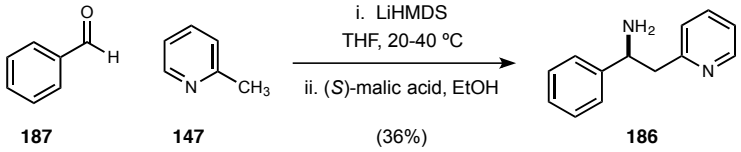


low-trapping NMDA antagonist
Lanicemine (AZD6765)
186

An optimized process patent[122] from AstraZeneca reports a one step synthesis (using LiHMDS to generate the TMS-imine from **187** *in situ*) and chiral resolution using (*S*)-malic acid, yielding the single enantiomer of lanicemine (**186**) in 36% yield over the two steps (Scheme 53).

While β-fluoroamines are known to have dramatic influences on blood-brain barrier penetrant small molecules, there is no concrete way to predict the conformational effects of a F-

Scheme 53. Synthesis of lanicemine **186** reported in a patent from AstraZeneca.



187 **147** (36%) **186**

lanicemine derivative from the outset, especially considering the gauche conformational influence of β-fluoroamines when protonated at physiological pH (Figure 31).

[122] Giles. M.E. *et al.* U.S. patent WO00/63175 US006518432B1, 2003

Figure 31. Potential conformational changes upon of the installation of fluorine in F-lanicemine ((*R*,*S*)-F-lanicemine pictured), as compared to lanicemine.

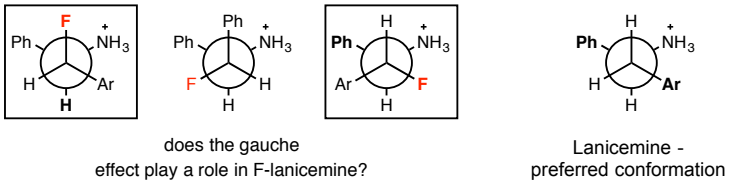
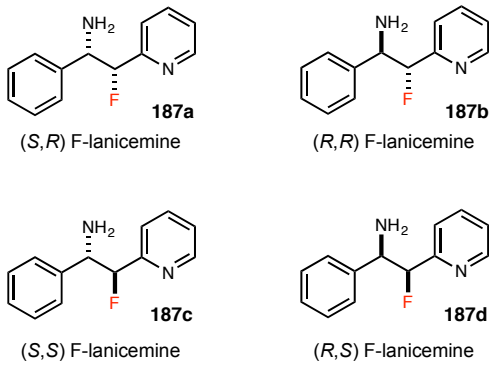
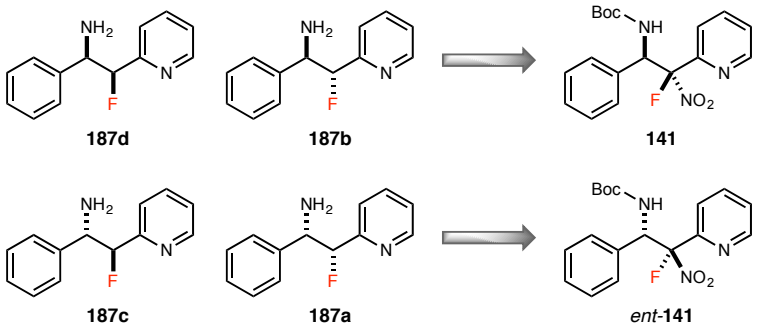


Figure 32. All four stereoisomers of F-lanicemine targeted for synthesis.



Using our developed methodology, we envisioned preparing then screening all four stereoisomers of F-lanicemine (**187a-d**, Figure 32) in NMDA-based assays prepared by David Weaver here at Vanderbilt University to assess activity and viability. As proven in our substrate scope, pyridines are well tolerated under the optimized conditions, a necessary aspect in order to prepare the four stereoisomers. Retrosynthetically, using both antipodes of $^{6,7}(MeO)_2PBAM{\bullet}HNTf_2$ organocatalyst, from the (*R*,*R*) and (*S*,*S*) cyclohexane diamine

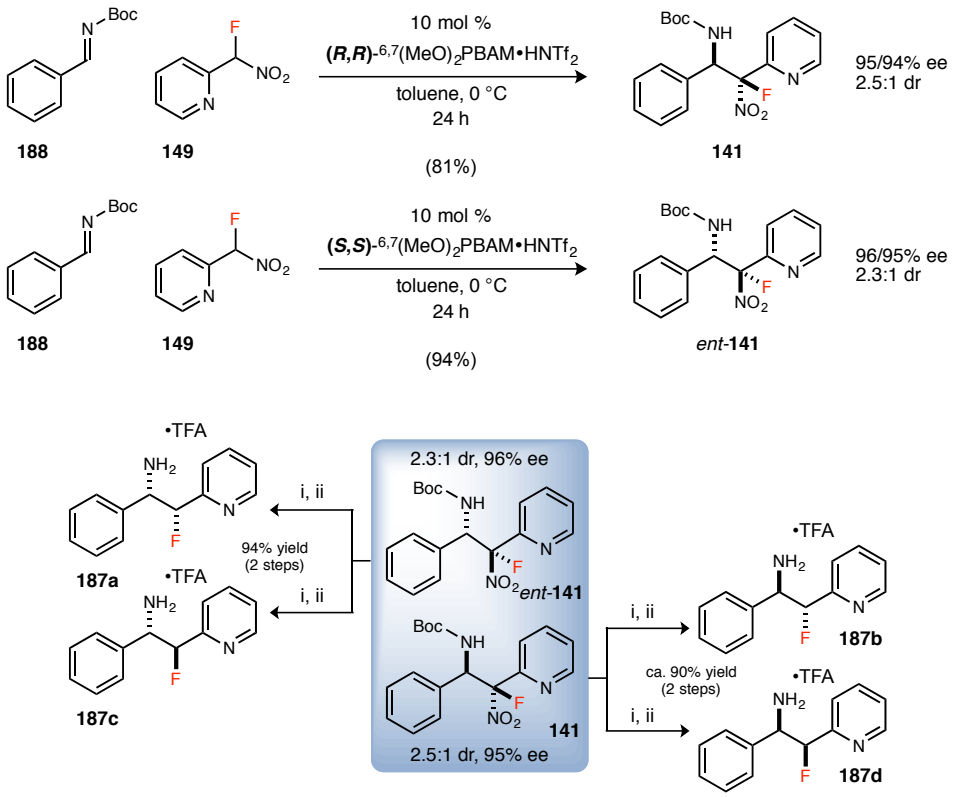
Scheme 54. Retrosynthesis of F-lanicemine stereoisomers.



backbone, both enantiomers of the fluoropyridyl aza-Henry products **141** could be obtained in high ee. Reductive denitration (non-selective) followed by Boc-deprotection should arrive at all four stereoisomers of F-lanicemine (Scheme 54).

In the forward sense, aza-Henry adduct **141** with *R*-configuration at the benzylic amine stereocenter was prepared in good yield and enantioselection (81% yield, 2.5:1 dr, 95% ee). Following the four-step synthesis of the (*S*,*S*)-^{6,7}(MeO)$_2$PBAM•HNTf$_2$ catalyst, the enantiomer *ent*-**141** was prepared in 94% yield (2.3:1 dr, 96% ee, Scheme 55). Fortunately, high dr of this material is not critical considering the subsequent steps.

Scheme 55. Synthesis of all four F-lanicemine stereoisomers from the enantioenriched β-amino fluoronitroalkanes.

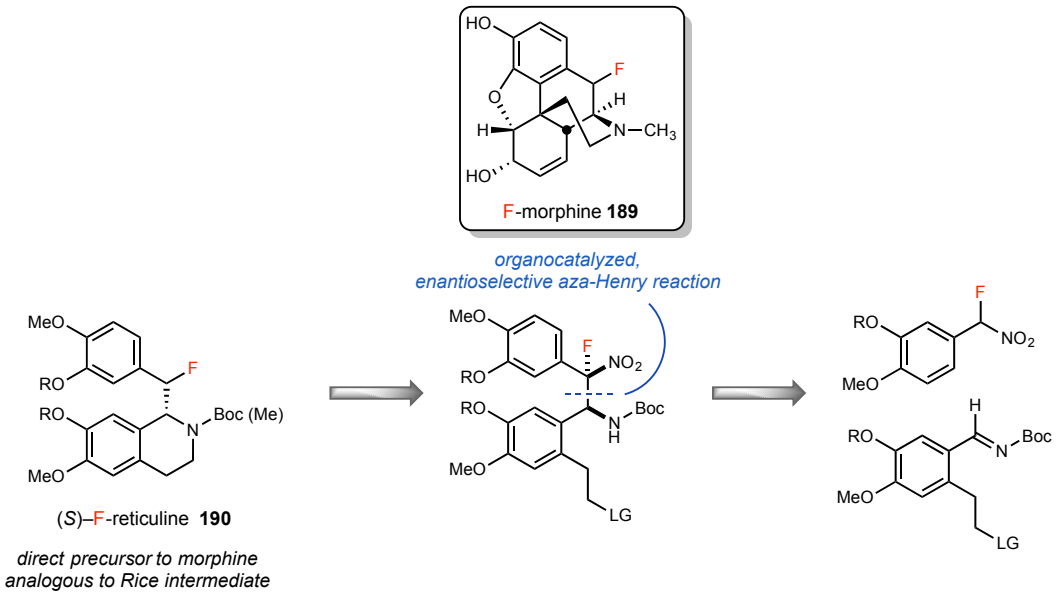


i) $HSnBu_3$ (5 equiv.), AIBN, benzene, 80 ºC, 4 h; ii) TFA (40 equiv.), DCM, 2 h, separated by reverse phase prep HPLC

Reductive denitration went smoothly to afford the Boc-protected 2º β-fluoroamines in good yields (see Experimental for additional details). Several silica gel purifications were attempted at this stage in order to separate diastereomers, but clean separations were never obtained and the material was carried forward as a ~2:1 mixture of diastereomers. In the final step, trivial Boc-deprotections with trifluoroacetic acid (TFA) afforded the desired F-lanicemine TFA salts. While the crude material from the deprotection step afforded clean **187**, these TFA adducts could be readily separated via reverse phase preparatory HPLC. Thus, all four F-lanicemine stereoisomers were isolated and characterized as their TFA salts. Notably, these β-fluoroamines salts can be converted to the stable free amines – no aziridine formation was observed by ^{1}H and ^{19}F NMR.)

In sum, the organocatalyzed, asymmetric Mannich reaction employing fluoronitroalkanes developed in this work was readily extended to the synthesis of β-fluoroamine containing F-lanicemine derivatives in two additional steps. While synthesizing all four stereoisomers does not require the implementation of a highly enantioselective organocatalyst, we have set the stage

Scheme 56. Proposed retrosynthesis to **190** (en route F-morphine **189**) implementing the enantioselective aza-Henry reaction with the corresponding aryl fluoronitromethane.



for an efficient asymmetric synthesis should a single enantiomer be highly potent as a novel NMDA antagonist. While this document was under preparation, biological data on the four molecules submitted was not yet available.

Additional projects are underway in the group utilizing fluoronitromethanes in the aza-Henry reaction. Since this work has proven β-fluoroamines are readily accessible, F-morphine (**189**) has been targeted for formal (total) synthesis, featuring the aza-Henry reaction as the key enantiodetermining step to access the reticuline-type intermediate (**190**) targeted by Kenner Rice[123] in his original elegant synthesis (Scheme 56). Morphine, one the most widely prescribed opioid painkillers, is a highly effective analgesic, yet can be highly addictive along with many opioids in this class. For various reasons, it would be worthwhile to investigate the effects of a β-fluoroamine analogue of morphine from an activity and pharmacological perspective.

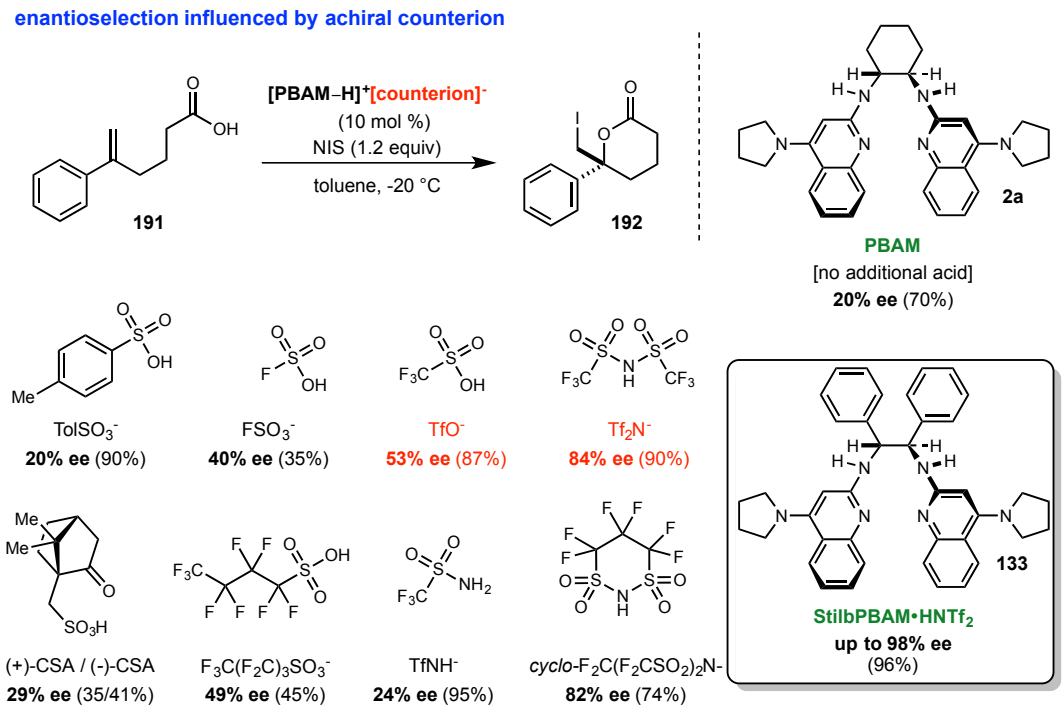
[123] Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135.

III. Brønsted Acid/Base-Catalyzed Halocyclizations and Carbon Dioxide-Fixation

3.1 History of Organocatalyzed, Asymmetric Halocyclizations

A recent report from our group detailed a novel enantioselective iodolactonization reaction using commercially available *N*-iodosuccinimide (NIS) and a chiral *bis*(amidine)

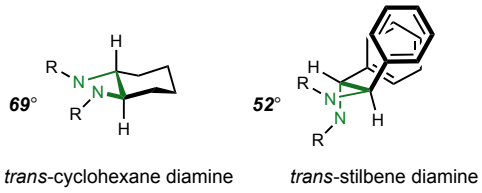
Scheme 57. Initial report from the Johnston Group detailing the achiral counterion effects on stereoselectivity in the iodolactonization reaction. Figure adopted from Mark Dobish's Ph.D. dissertation.



(BAM) acid salt, to arrive at structurally unique iodo-γ-lactones in good yield and up to 98% ee.[124] A more significant aspect of this work was the finding that an *achiral* acid and a chiral Brønsted basic ligand dramatically affected the enantioselectivity of the halocyclization reaction (Scheme 57). The chiral Brønsted base ligand used in this study originated from the PBAM (**2a**) scaffold (Scheme 57) and achiral counterions were tested using this ligand system. Not only was the counterion effect crucial for this specific transformation, the catalyst backbone was also tuned, and the *trans*-stilbene diamine showed the highest efficacy in terms of both enantioselection and yield. This catalyst was dubbed StilbPBAM (stilbene pyrrolidine *bis*(amidine), **133**) and was the first example of this catalyst being successfully employed in an asymmetric reaction in the Johnston group (Scheme 57).

trans-Stilbene diamine is reported to have a smaller N-C-C-N dihedral angle as compared to *trans*-cyclohexane diamine (52° compared to 69°, respectively),[125] and may present the polar-ionic hydrogen bonding network in a more constrained and rigid manner (Figure 33). Soon after this reaction was developed, Dobish extended this methodology to substrates derived from

Figure 33. NCCN Dihedral angles of the two common chiral diamine backbones determined by density functional theory (DFT) calculations.[125]

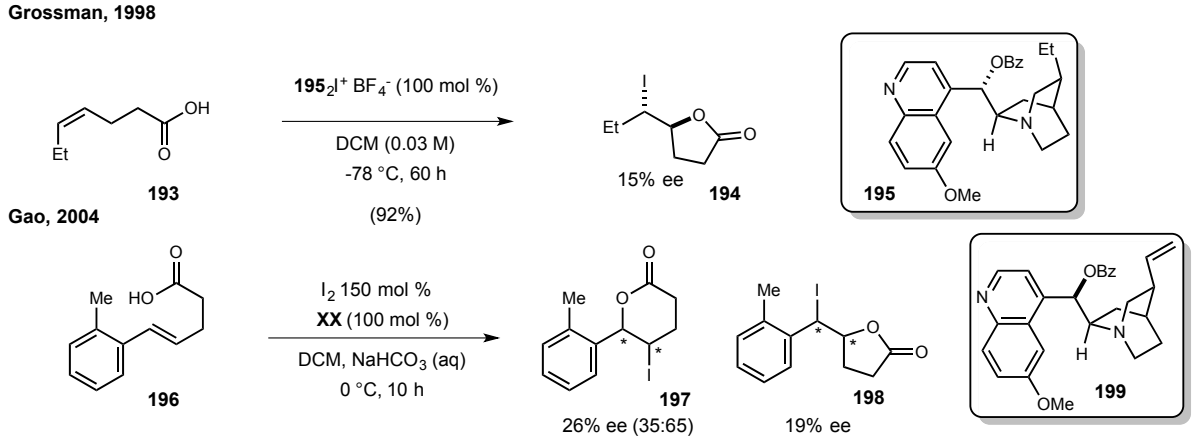


[124] Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068.
[125] These dihedral angles were derived computationally: Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239.

unactivated 1,2-disubstituted (internal) *E*-alkenes instead of 1,1-disubstituted alkenes. In this study, 6-membered lactones resulted from high catalyst-controlled regioselectivity favoring the 6-*endo* cyclization over the competing 5-*exo* cyclization.[126]

The first organocatalyzed, enantioselective iodolactonization was reported by Grossman in 1998 and presented the first reagent-controlled enantioselective halolactonization, although enantioselection was very low (15% ee, Scheme 58). Looking to expand the work of Grossman, Gao in 2004 investigated the use of cinchona-based alkaloid (**199**) as stoichiometric, chiral halogen equivalents in reagent-controlled asymmetric iodolactonizations – providing additional proof that this class of reactions can be stereochemically controlled using an organocatalyst

Scheme 58. Seminal publications detailing the asymmetric halolactonizations of unsaturated acids mediated by organocatalysts.



(Scheme 58).[127] The highest enantioselectivity (19% ee) for the γ-lactone (5-exo, **198**) was obtained from the *ortho*-tolyl analog **196** (though it only formed with 2:1 regioselectivity). Since then, similar halocyclization reactions employing organocatalysts have traditionally suffered from suboptimal stereoselectivity, regioselectivity (if applicable), and higher than ideal levels of catalyst loading.

[126] Dobish, M. C., Johnston, J. N. *unpublished results*
[127] Lu, X.-B.; Liang, B.; Zhang, Y.-J.; Tian, Y.-Z.; Wang, Y.-M.; Bai, C.-X.; Wang, H.; Zhang, R. *J. Am. Chem. Soc.* **2004**, *126*, 3732.

More broadly, the field of alkene halo alkene-difunctionalization chemistry using organocatalysts has progressed at a relatively slow pace since pioneering efforts in the early 2000's.[128] In 2010, the Jacobsen group first reported the highly enantioselective iodolactonization reaction employing a tertiary aminourea derived organocatalyst.[129] Other notable developments in this field over the past 5-7 years have examined chloro- and bromolactonizations,[130] haloaminations,[131] and even fluoroetherifications.[132]

The field has received increased attention as of late as catalysts advance, for widening synthetic utility of the products, and challenges associated with such a transformation from a growing number of groups including Borhan, Denmark, Jacobsen, Toste, Johnston, and Yeung (*vida infra*). New approaches to this class of reactions have been the result, many exploring novel and creative methods for activating the (pro)nucleophile, alkene nucleophile, and/or the terminal electrophile. Mechanistically, following olefin activation with a suitable electrophile in the presence of a chiral organocatalyst, various nucleophiles can be employed (primarily in intramolecular fashion) to set at least one stereocenter. Specific examples are illustrated in Figure 34. In 2012, Toste and coworkers optimized a highly unique set of conditions to afford bromocyclization products (**201**) with good enantioselection.[133] The authors invented an interesting and unique electrophilic brominating reagent **202** that can be employed under phase transfer conditions in the presence of the chiral (and bulky) phosphoric acid catalyst **203** to afford highly selective cyclized product in high ee.

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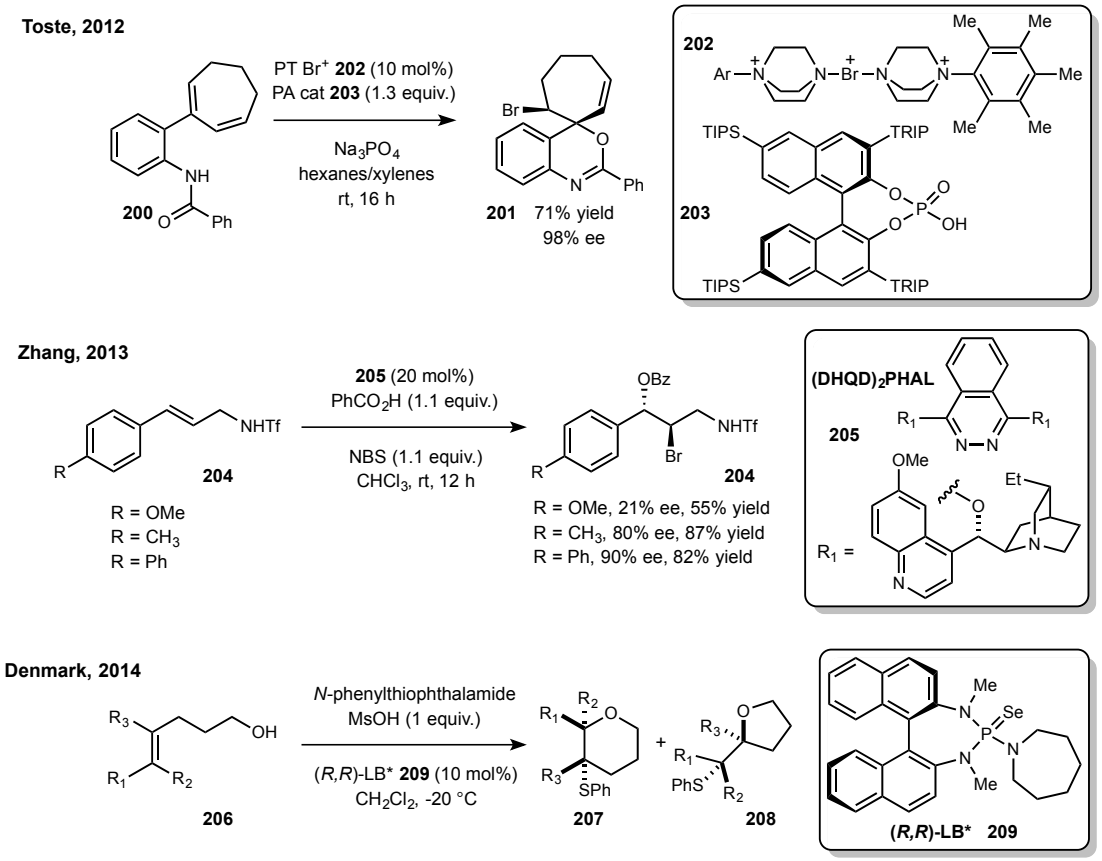
[128] Fang, C.; Paull, D. H.; Hethcox, J. C.; Shugrue, C. R.; Martin, S. F. *Org. Lett.* **2012**, *14*, 6290. Tungen, J. E.; Nolsoe, J. M. J.; Hansen, T. V. *Org. Lett.* **2012**, *14*, 5884.
[129] Veitch, G. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 7332.
[130] Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. Yousefi, R.; Whitehead, D. C.; Jaganathan, A.; Jamalifard, F.; Borhan, B. *Abstr. Pap. Am. Chem. Soc.* **2010**, *239*. Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 608.
[131] Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164.
[132] Lozano, O.; Blessley, G.; del Campo, T. M.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 8105.
[133] Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928.

Another innovative approach involves expanding the use of various terminal electrophiles as can be seen in the heavily mechanism-driven field of "Lewis base activation of a Brønsted acid" pioneered by Scott Denmark[134] (Figure 34). 'Unactivated' alkenes (**206**) are granted this namesake for the simple reason that the π-electrons of the alkene are weakly nucleophilic, and an activated electrophile is often needed to overcome this barrier of addition. Common pre-

Figure 34. Reports from Toste, Zhang, and Denmark detailing each group's respective reactions and modes of asymmetric catalysis.



[134] Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752. Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655. Collins, W. R.; Swager, T. M.; Denmark, S. E. *Abstr. Pap. Am. Chem. Soc.* **2010**, *240*.

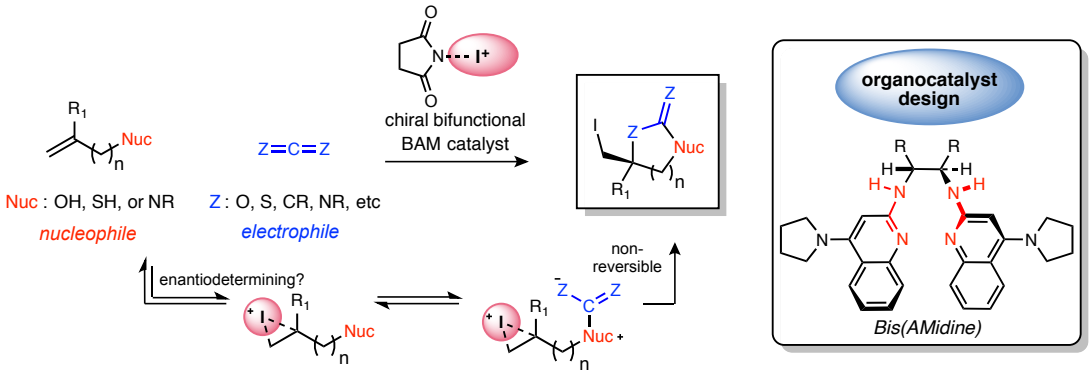
activated halogenated electrophiles are traditionally used, such as bromine[135] (Br_2), NBS (*N*-bromo succinimide), and *N*-iodo-4-fluorophthalimide (Jacobsen[129]) – the latter of which is additively activated due to the presence of an electron-withdrawing fluorine atom on the phthalimide's aromatic ring. Denmark has mechanistically examined various Lewis base additives and catalysts to activate relatively sluggish main group electrophiles such as sulfur and selenium, in hopes of extending the breadth of electrophiles used in such a reaction. Another strong trend in the field is *double activation* of both the nucleophile and electrophile components with Brønsted acids or bases.

Figure 34 shows an example of a Lewis basic catalyst developed by Denmark appended to a chiral BINAM diamine backbone (*R*,*R*)-LB* **209**. In the presence of a suitable Brønsted acid, a seleniranium[136] or thiiranium[137] activated ion pair is generated with the catalyst and the alkene can entrain the electrophile in this enantiodetermining step. Olefin to olefin transfer of these activated electrophiles is cited as a common process promoting non-selective additions not only Denmark's chemistry, but in the halo alkene-difunctionalization field as a whole. Demark has successfully navigated around the issue by incorporating stronger Brønsted acids, but a full equivalent of an acid additive is often needed to observe desirable effects.[138] Despite the pivotal advances in catalyst design and mechanistic understanding of these reactions, enantioselection in Denmark's chemistry is modest to good at best, and extending this approach to other useful electrophiles is still in its infancy.

3.1.2 Efforts Towards a Multicomponent, Asymmetric Halocyclization Reaction

[135] Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.
[136] Denmark, S. E.; Collins, W. R.; Cullen, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 3490.
[137] Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308.
[138] Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

Scheme 59. Proposed 3-component, one-pot enantioselective iodocyclization. Although the enantiodetermining step is unclear, a 3-component process should mechanistically be feasible.



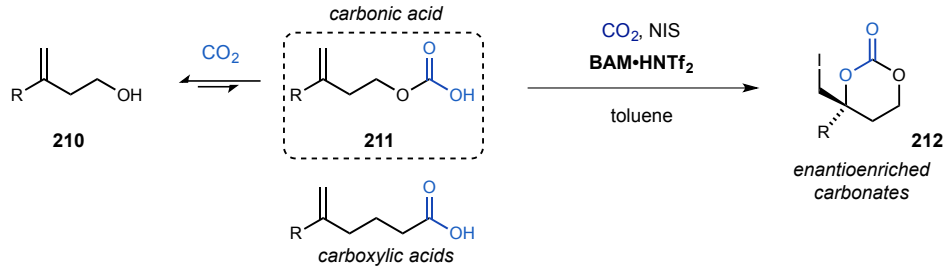
While halocyclization reactions have experienced much success and attention in recent years as previously discussed, an area mysteriously absent or perhaps unexplored is a *multicomponent* (3 or more)*, alkene activation-trap-halocyclization* reaction. In such a reaction, greater increase in complexity could be achieved in a single pot using readily available reagents. Scheme 59 depicts possible components an asymmetric 3-component reaction may entail. Conceptually, the catalyst should be able to control the order of addition between all reaction components as well. A major driving force for a productive sequence may be the assembly of a thermodynamically-favored halocyclized product – non-productive reaction intermediates are in equilibrium and could revert to starting material.

Although we cannot say definitively where or when the enantiodetermining step is occurring using chiral BAM catalysts in Johnston group chemistry (Scheme 59), such as in the iodolactonization chemistry, we have evidence selectivity is dependent on *both* the carboxylate group and the hydrogen-bond accepting carbonyl of NIS (dual activation) in the iodolactonization chemistry that is responsible for stereocontrol. This has been shown in a number of experiments initially conducted by Dobish and others illustrating the fact that those two components are essential for stereocontrol. To date, other iodine sources and carboxylate

ester moieties (i.e. *tert*-butyl ester or Boc group) result in lower ee or racemic product with almost no exception.

These data set the stage to explore carboxylate surrogates in the enantioselective halocyclization reaction, cognizant of the ultimate goal to uncover an asymmetric, three-component reaction. As outlined in Scheme 60, carbon dioxide via the carbonic acid (**211**) initially seemed like a reasonable substitute for a carboxylic acid, however optimizing CO_2 as an electrophile in an organocatalyzed reaction could be challenging. If this hypothesis were to be supported, we would expect to see enantioselection under similar reaction conditions.

Scheme 60. Proposed carbon dioxide capture in the halocyclization reaction.



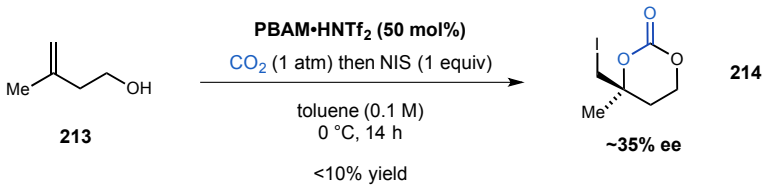
3.2 Initial Studies Towards a Bifunctional Brønsted Acid/Base Catalyzed, Enantioselective CO_2-Fixation Reaction

A visiting summer undergraduate pursued initial experiments using carbon dioxide as the preliminary electrophile in the iodocyclization reaction.[139] Drawing analogies to previous work with carboxylic acids, capturing CO_2 with an alcohol would generate a carbonic acid *in situ* (pKa of ≈ 4-6) and could be recognized by the Brønsted basic BAM catalyst, in which case

[139] Mark Dobish and Weiwei Wang

stereochemical induction could ensue in the presence of NIS. One of the main challenges herein lies is the fact that weakly nucleophilic alcohols and carbon dioxide are highly unstable upon addition, heavily favoring the lower energy starting alcohol and gaseous CO_2 (*vida infra*).

Scheme 61. Preliminary results: iodocarboxylation of homoallylic alcohol **213** (Weiwei Wang).



Early attempts to generate cyclic carbonates were met with mixed success by combining 2-methyl-3-butene-1ol (**213**), NIS, CO_2 at 1 atm and PBAM•$HNTf_2$ (**2a**•$HNTf_2$) at 0 °C (Scheme 61). The desired iodo-δ-carbonate **214** was isolated in low yield (<10% yield) but encouraging enantioselectivity (35% ee) for a first attempt, supporting the idea that a carbonic acid can be a surrogate for a carboxylic acid. Notably, it became apparent tha use of solely Brønsted basic ligands (i.e. PBAM, DMAP or DBU) resulted in no reaction indicating (at least at present) that a Brønsted acid, bifunctional Brønsted acid/base system, or more complex hydrogen bonding network was necessary for a productive enantioselective, multicomponent reaction.

Outlined hereafter, we have successfully validated this design[140] by the development of a carboxylation/alkene functionalization reaction of homoallylic alcohols to produce chiral cyclic carbonates. Moreover, this carbon dioxide fixation formally allows for the replacement of toxic phosgene as a source of carbonate protecting group in this preparation of protected chiral 1,3-diols.

[140] Vara, B. A.; Struble, T. J.; Wang, W. W.; Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2015**, *137*, 7302.

3.2.2 Background: Carbon Dioxide and its Use as an Electrophile in Organic Synthesis and Enantioselective Catalysis

Carbon dioxide (CO_2) has received the lion's share of attention in research and the media over the past couple of decades as environmental and governmental concerns about its accumulation in the atmosphere have steadily increased. The discussion of CO_2 as a greenhouse gas in conjunction with other 'chemical pollutants' elicits fascinating and dynamic debates, many of which are instrumental in altering policies at the intersections of science, governments, and economics. This brief yet important introduction aims at addressing the cost-benefit analysis of environmental policies, and how chemical research can shape futures discussions.

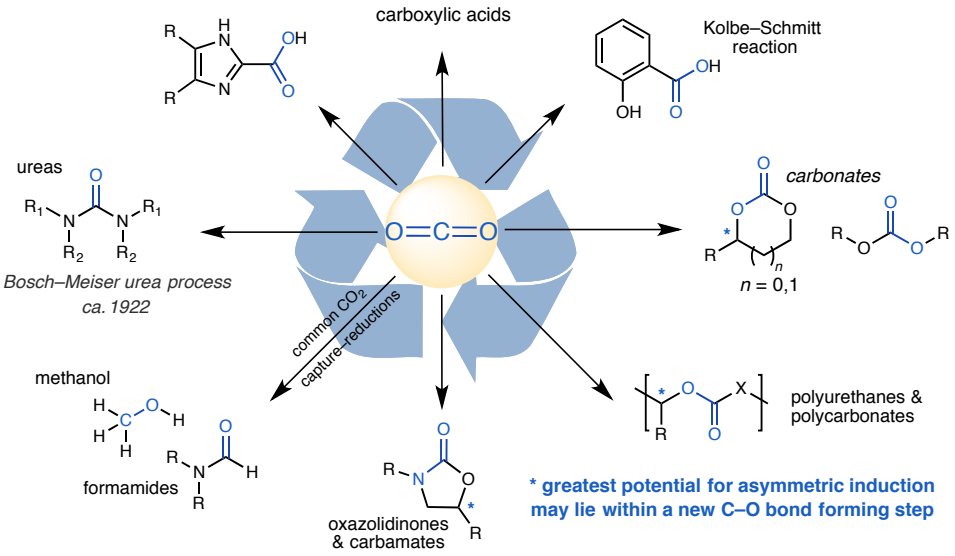
Since the birth of the industrial revolution in the early 1900's in the U.K. and Americas, CO_2 accumulation has grown exponentially in the earth's atmosphere. Technological advances developed around the turn of the 20^{th} century have allowed scientists to monitor these levels throughout the decades, and this noted upsurge of CO_2 levels in the atmosphere is in close connection with the world's consumption of fossil fuels needed to power a thriving, mobile globalized economy – one can argue there has been a direct correlation between humanity's improved quality of life and increasing atmospheric CO_2 levels.

Many have speculated that CO_2 emissions from the combustion of fossil fuels and organic material has sparked a massive shift in the earth's climate, termed global warming, that threatens the very existence of mankind on earth in generations to come. Although much research is still needed to determine the root cause and effect of CO_2 in the atmosphere, the planetary buildup of CO_2 is largely undisputed, and has inspired many governing bodies across

the world to implement strict CO_2 emission policies[141] (such as tradable emissions permits), in a showcase of strength and in hope of change. Carbon dioxide accumulation has had dramatic trickledown economic implications as well. Somewhat paradoxically, government-mandated limits on CO_2 production are on the rise and have recently pressured academic and corporate firms alike to pursue "green, renewable, and energy-efficient" infrastructure projects and research, often at the expense of growth or consumer-fronted taxation. The takeaway message as proposed by Fullerton and Stavins, is that "no specific policy instrument, or even set of policy instruments, is a panacea".[142] To change the status quo for the betterment of markets and the environment, new technologies and scientific innovations are needed to fundamentally change the way current processes function.

Across numerous chemical research disciplines, CO_2 research has found the most success (or popularity, arguably) in the areas of carbon-capture engineering, materials and polymer

Figure 35. The common uses of carbon dioxide as a reagent in chemical synthesis.

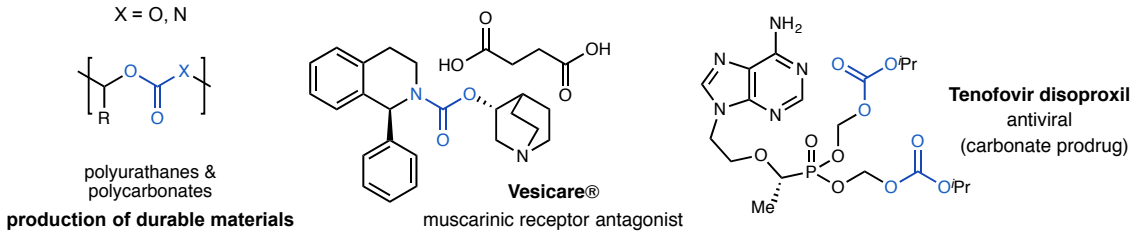


[141] Arrow, K. J.; Cropper, M. L.; Eads, G. C.; Hahn, R. W.; Lave, L. B.; Noll, R. G.; Portney, P. R.; Russell, M.; Schmalensee, R.; Smith, V. K.; Stavins, R. N. *Science* **1996**, *272*, 221.
[142] Fullerton, D.; Stavins, R. *Nature* **1998**, *395*, 433.

chemistry, and CO_2-reduction chemistry. The threat of carbon dioxide accumulation as a greenhouse gas has motivated these innovative sequestration strategies, but this gaseous reagent holds immense potential value as an abundant and nontoxic C1–building block[143] for carbon-carbon bond formation and carbon-heteroatom functionalization reactions in chemical synthesis.[144] The Bosch-Meiser urea process developed in 1922 famously uses amine feedstocks and carbon dioxide to form ureas on the industrial level (Figure 35).

Unfortunately, the underlying features that contribute to carbon dioxide's low general toxicity and ease of handling render it relatively inert as a chemical reactant.[145] This is punctuated by the contrasting abundance of *enantioselective* chemical reactions using hydrogen (H_2),[146] oxygen (O_2),[147] and even carbon monoxide (CO). Despite the virtues of high temperature and/or pressure to address poor reactivity, transformations employing CO_2 as a reagent are typically

Figure 36. CO_2 and CO_2-surrogates found among polymer and pharmaceutical chemistry.



[143] Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. Additional uses of CO_2 as a feedstock: Lindsey, A. S.; Jeskey, H. The Kolbe-Schmitt Reaction. *Chem. Rev. (Washington, DC, U. S.)*, **1957**, *57*, 583-620. Greenhalgh, M. D.; Thomas, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 11900. Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109. Reduction of CO_2 for commodity-based chemical production: Studt, F.; Sharafutdinov, I.; Abild-Pedersen, F.; Elkjær, C. F.; Hummelshøj, J. S.; Dahl, S.; Chorkendorff, I.; Nørskov, J. K. *Nat Chem* **2014**, *6*, 320. Graciani, J.; Mudiyanselage, K.; Xu, F.; Baber, A. E.; Evans, J.; Senanayake, S. D.; Stacchiola, D. J.; Liu, P.; Hrbek, J.; Sanz, J. F.; Rodriguez, J. A. *Science* **2014**, *345*, 546. For recent advances adapting CO_2 in continuous flow synthesis: Kozak, J. A.; Wu, J.; Su, X.; Simeon, F.; Hatton, T. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 18497.

[144] Tsuji, Y.; Fujihara, T. *Chem. Commun.* **2012**, *48*, 9956. Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kuhn, F. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 8510.

[145] Omae, I. *Coordination Chemistry Reviews* **2012**, *256*, 1384.

[146] Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.

[147] Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Cham. Rev. (Washington, DC, United States)* **2005**, *105*, 2329.For a metal-free example, see: Yang, Y.; Moinodeen, F.; Chin, W.; Ma, T.; Jiang, Z.; Tan, C.-H. *Org. Lett.* **2012**, *14*, 4762.

limited to either Lewis basic substrates with sufficient nucleophilicity to react with the poorly electrophilic CO_2, or metal-based reagents to increase the rate of CO_2 incorporation, often through a metal carboxylate intermediate.[148]

Despite the inherent challenges, CO_2 integration (via gaseous CO_2 or other CO_2 equivalents such as phosgene) into synthetically useful molecules can be found in the assembly of cyclic and linear carbonates and carbamates, among others. These compounds have applications in lithium ion batteries, pharmaceuticals (Vesicare, Figure 36), polymers (polycarbonates and polyurathanes), and natural product synthesis.[149]

From a synthesis perspective, organic carbonates have also been shown to undergo a variety of chemical transformations – the methylenation forming a ketene acetal en route to the octalactin natural products is an excellent example.[150] Additionally, the use of carbonates in total synthesis to access stereo-defined alcohols can be seen in the synthesis of leukotriene B and olivomycin by Corey[151] and Roush,[152] respectively. Carbonates and carbamates are broadly deployed as masking agents in total synthesis where upon cleavage (either chemically or *in vivo* by esterase enzymes) often unveil chiral hydroxyl and/or amine functionalities – this unique ability may help explain their growing implementation as prodrugs (i.e. Tenofovir disoproxil, Figure 36) in a variety of small molecule pharmaceuticals, often improving lipophilicity and even metabolism.[153]

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[148] Decortes, A.; Castilla, A. M.; Kleij, A. W. *Angew. Chem. Int. Ed.* **2010**, *49*, 9822. Maeda, C.; Miyazaki, Y.; Ema, T. *Cat. Sci. Tech.* **2014**, *4*, 1482.
[149] Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878.
[150] O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194.
[151] Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 7986.
[152] Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.
[153] Rautio, J.; Kumpulainen, H.; Heimbach, T.; Oliyai, R.; Oh, D.; Jarvinen, T.; Savolainen, J. *Nat. Rev. Drug Discov.* **2008**, *7*, 255.

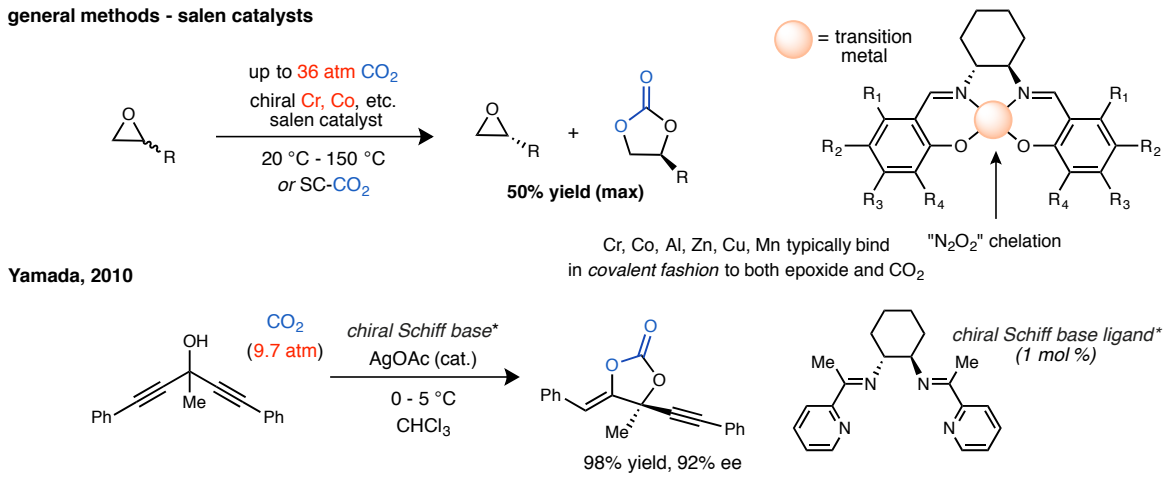
We sought a reagent, ideally a catalyst, that could both overcome these barriers to reactivity and/or unfavorable equilibria while simultaneously controlling stereoselection. Chemical technologies that preferentially form one enantiomer of a chiral molecule have direct application to drug development and new materials.[154]

Following our initial results obtaining the desired iodocarbonate in 35% ee and less than 10% yield, we posited that a properly balanced Brønsted acid-Brønsted base bifunctional catalyst might lower the barrier to CO_2 incorporation and/or assist in the stabilization of the resulting adduct as a prelude to its use as an oxygen nucleophile in a subsequent enantioselective carbon-oxygen bond-forming step. Interesting to note, organic carbonic acids are notoriously challenging to isolate and even generate *in situ*, and to our knowledge, concrete spectroscopic evidence of their formation has only been reported on a few occasions – their production is limited by an equilibrium that generally favors free CO_2 and the corresponding organic alcohol.[155] Nonetheless, if this acid formation could be achieved using a metal-free catalyst – an organocatalyst – the virtues of minimalism (cheap goods, low temperature, atmospheric pressure, near-neutral pH) would apply, suggesting broad impact.

The most fruitful methods developed to date in this field employing CO_2 as a reagent has been in the area of CO_2-epoxide coupling reactions. These reactions are non-enzymatic, metal-based systems inserting CO_2 into activated epoxides to generate almost exclusively 5-membered

[154] Xu, Z. R.; Tice, C. M.; Zhao, W.; Cacatian, S.; Ye, Y. J.; Singh, S. B.; Lindblom, P.; McKeever, B. M.; Krosky, P. M.; Kruk, B. A.; Berbaum, J.; Harrison, R. K.; Johnson, J. A.; Bukhtiyarov, Y.; Panemangalore, R.; Scott, B. B.; Zhao, Y.; Bruno, J. G.; Togias, J.; Guo, J.; Guo, R.; Carroll, P. J.; McGeehan, G. M.; Zhuang, L. H.; He, W.; Claremont, D. A. *J. Med. Chem.* **2011**, *54*, 6050.
[155]Gassensmith, J. J.; Furukawa, H.; Smaldone, R. A.; Forgan, R. S.; Botros, Y. Y.; Yaghi, O. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 15312.

Scheme 62. Reports generating 5-membered cyclic carbonates in racemic and enantioselective fashion.



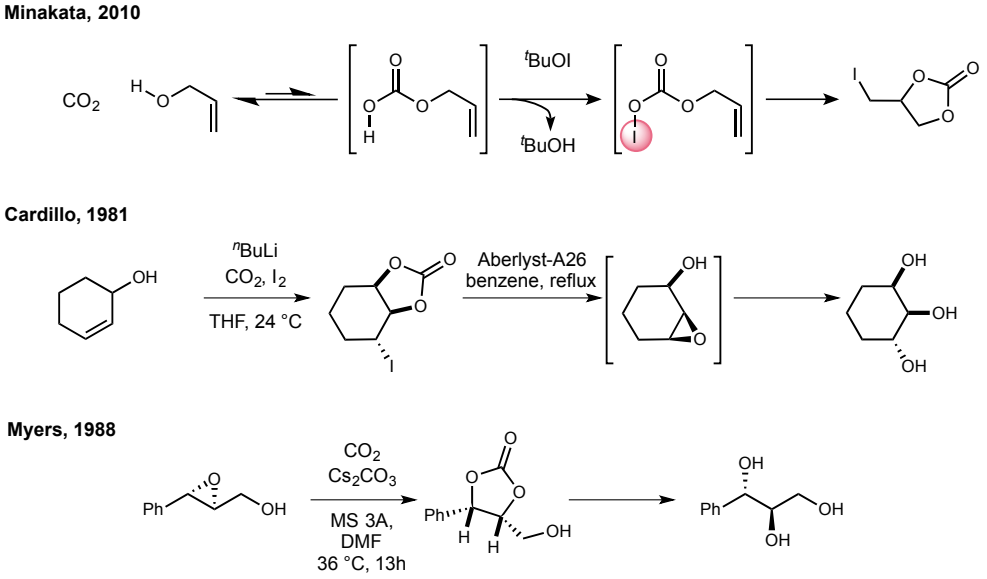
cyclic carbonates. In recent years, these methods have evolved to include enantioselective kinetic resolutions using metal-salen derived catalysts.[156]

These reactions (Scheme 62) have been successful at the industrial level, coupling CO_2 with epoxides (almost always mono-substituted propylene oxide derivatives) at high pressures and temperatures assembling enantioenriched carbonate monomers and polymers (polycarbonates). Separately, Yamada has elegantly reported a silver(I)-based alcohol desymmetrization using carbon dioxide at high pressure (Scheme 62).[157]

The basic capture/cyclization between various *alcohols* and CO_2 has been previously reported,[158] although enantioselective variants have never been published (Scheme 63). A relatively recent report from Minakata and coworkers elegantly synthesized 5- and 6-membered cyclic carbonates employing CO_2 (1 atm), *tert*-butylhypochlorite and sodium iodide – notably

[156] Lu, X.-B.; Liang, B.; Zhang, Y.-J.; Tian, Y.-Z.; Wang, Y.-M.; Bai, C.-X.; Wang, H.; Zhang, R. *J. Am. Chem. Soc.* **2004**, *126*, 3732. Paddock, R. L.; Nguyen, S. T. *J. Am. Chem. Soc.* **2001**, *123*, 11498. Berkessel, A.; Brandenburg, M. *Org. Lett.* **2006**, *8*, 4401. Luinstra, G. A.; Haas, G. R.; Molnar, F.; Bernhart, V.; Eberhardt, R.; Rieger, B. *Chem. Eur. J.* **2005**, *11*, 6298.
[157] Yoshida, S.; Fukui, K.; Kikuchi, S.; Yamada, T. *J. Am. Chem. Soc.* **2010**, *132*, 4072.
[158] Myers, A. G.; Widdowson, K. L. *Tet. Lett.* **1988**, *29*, 6389. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc. Chem. Comm.* **1981**, 465.

Scheme 63. Diastereoselective iodocarbonation reports detailing the use of CO_2 as a reagent.



none of the more common electrophilic iodine source (NIS, I_2, and IPy_2BF_4) produced any product.[159]

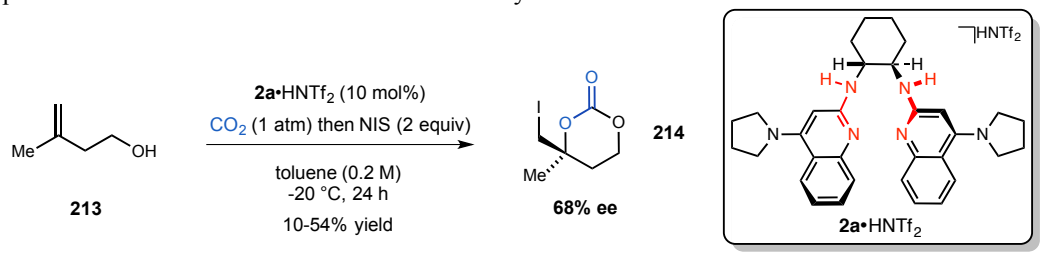
In this work, Minakata proposes a stabilization event upon the formation of iodous carbonic acid, which then forms the iodonium and cyclic carbonate upon cyclization (Scheme 63). Two older examples employing 1 atm of CO_2 by Cardillo and Myers show nice utility of iodocarbonates and epoxy alcohols, respectively, to generate triols (Scheme 63). Although these carbonates are isolated as their racemates, high diastereoselectivity and chemoselectivity are achieved through substrate control.

[159] Minakata, S.; Sasaki, I.; Ide, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 1309.

3.2.3 Optimization of the First Catalytic Enantioselective, Iodocarbonation Reaction

After the initial finding that iodocarbonation with homoallylic alcohol **213** and PBAM•$HNTf_2$ (Scheme 64) was modestly effective in this present work, solvent conditions, reaction time, temperature, iodine sources, and levels of CO_2 infusion were next investigated in my hands. Based off the prior knowledge that PBAM•$HNTf_2$ (**2a**•$HNTf_2$) was the optimal pairing for counterion and carboxylic acid for iodolactonization chemistry, extensively screening different catalysts or achiral counterions was not immediately pursued.

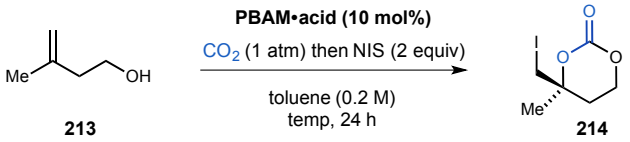
Scheme 64. Improved reaction conditions and enantioselectivity.



Using readily available **2a**•$HNTf_2$, an improved 68% ee was eventually obtained under the devised reaction conditions – lower catalyst loading, more concentrated reactions, and less NIS (2 equiv.) proved optimal at present. Additionally from the outset, it was apparent that these iodocarbonate adducts were not the most stable compounds, thus running the reaction at -20 °C (or lower) was necessary to eliminate decomposition pathways and byproducts. Isolated yields at this point hardly ever exceeded 54%, and additionally puzzling, conversion was very inconsistent from one reaction to the next. More intense examination of the reaction conditions would be needed in order to improve enantioselection and conversion to the desired carbonates.

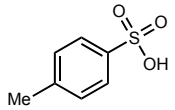
The next set of experiments to improve ee involved examining various achiral Brønsted acids while employing **2a** as the chiral ligand. As previously mentioned, we assumed an optimal achiral counterion had been found in $HNTf_2$ (pKa = –11.9, 1,2-DCE),[160] though this was never

Table 14. Evaluation of achiral counterions with **2a** (10 mol% catalyst loading) and **213**.



entry	acid (1:1)	temp (°C)	yield (%)[a]	ee (%)[b]	notes
1	HOTf	-20	8	51	-
2	FSO_3H	-20	n/a	30	-
3	*cyclic*-$C_3F_6NTf_2$	-20	45	40	-
4	$LiNTf_2$	-20	78	48	MS 4A
5	(±)-CSA	-20	47	40	-
6	$HBArF_{24}$	-20	decomp	n/a	-
7	$C_4H_2F_4O_4$ (2:1)	-20	22	20	MS 4A
8	H_2NTf	-20	49	28	MS 4A
9	$HNTf_2$	-20	73	63	MS 4A
10	0.5 mol% $HNTf_2$	-40	15	49	MS 4A

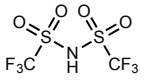
Catalyst prepared as the 1:1 acid salt, except entry 7. MS denotes molecular sieves 4A, employed at a concentration of 1 g/mmol relative to the alcohol. [a]Isolated yield. [b]Enantiomeric excess (ee) determined by HPLC using a chiral stationary phase.



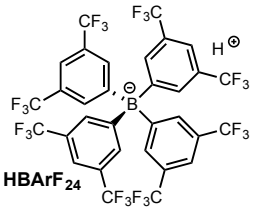
^{p}TolSO$_3$H

FSO$_3$H

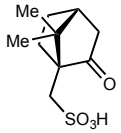
TfOH



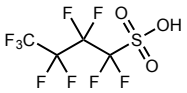
Tf$_2$NH



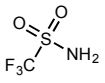
HBArF$_{24}$



(+)-CSA / (-)-CSA



F$_3$C(F$_2$C)$_3$SO$_3$H



TfNH$_2$

***cyclic*-C$_3$F$_6$NTf$_2$**

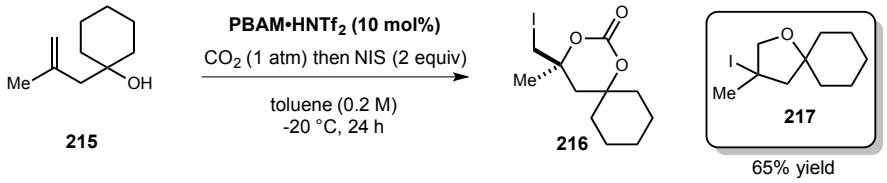
confirmed for this particular system. An evaluation of achiral counterions using the PBAM ligand can be found in Table 14. As the table reveals, no significant improvement in ee was

[160] A. Kütt. *J. Org. Chem.* **2011**, *76*, 391

observed with any of the common achiral Brønsted acids, and triflimidic acid seems optimal for this system. Entries 7 and 8 (Table 14) gave the cyclic carbonate **214** in very low ee (<30% ee). Entry 8 is notable case because of the substantial effect in ee switching from triflamidic acid to triflimidic acid (entry 9, Table 14). In Dobish's work, he uncovered an important trend where increased acidity of the achiral counterion generally correlated with increased enantioselection.[161] Unfortunately, the HBArF salt of **2a** (entry 6) gave only decomposition.

A few early attempts to enhance ee in the iodocarbonation reactions were pursued but saw little success. A variety of electronically and structurally diverse homoallylic alcohols were targeted with the expectation that it might improve alcohol nucleophilicity and enantioselectivity.

Scheme 65. Unexpected cyclic iodoether byproduct from the attempted iodocarbonation afforded **217** in good yield.



None of these structural differences resulted in improved ee. We've learned from these studies however, that the devised catalyst system is quite robust and tolerable to many substrate modifications (in addition to alcohol additives screened, such as benzyl amine, phenol, and nitrobenzene). Notably, in an effort to probe sterics of the alcohol substrate, spiro alcohol **215** was prepared and led to the 5-*endo* ether product **217** instead of the desired cyclic carbonate **216**, presumably due to increased Thorpe-Ingold effect (Scheme 65). Unfortunately, this 5-*endo* iodoetherification reaction lacked any enantioselection in the presence of the chiral catalyst.

Homoallylic alcohol **222** then became the basis for developing a tandem alcohol carboxylation–alkene iodocarbonation reaction due to the past success of the 1,1-disubstituted

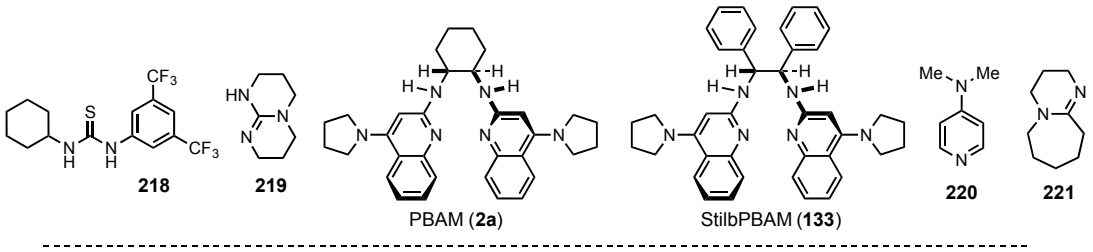
[161] Text and supporting information therein: Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068.

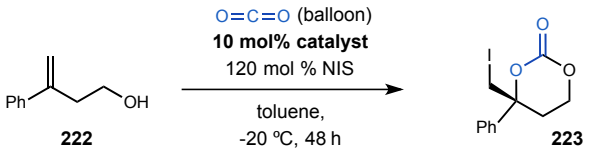
alkene in the carboxylation chemistry (Table 15). This can be readily prepared in a one step hydroarylation reaction from the phenyl boronic acid and homopropargyl alcohol catalyzed by palladium(0) tetrakis.

From the outset, we wanted to understand reactivity and necessary reactions parameters. The standard reaction to which others are compared involved chilling (-20 °C) a toluene solution of homoallylic alcohol (**222**, 0.4 M) prior to addition of *N*-iodosuccinimide (entry 1, Table 15) and carbon dioxide (balloon). These catalyst-free conditions returned starting material following a 48 h reaction period. Compared to an otherwise identical reaction, addition of a strong base (sodium hydride, entry 2, Table 15) delivered **223** but in only 16% yield. Substitution of a more polar solvent (e.g. THF) for toluene increased the yield marginally (entry 3, Table 15). Based on precedence for Brønsted basic amines to react directly with carbon dioxide, or CO_2/H_2O combined, several amine bases were examined (entries 4-5, Table 15), as well as hydrogen bond-donor/acceptor amines (e.g. TBD, entry 6, Table 15) in an attempt to accelerate the desired reaction.

These extensive attempts generally provided three outcomes: 1) return of unreacted homoallylic alcohol, 2) formation of apparent iodoetherification products, or simply 3) low yields (<15%) of the desired carbonate. As previously mentioned, we proposed a good hydrogen-bond donor complex was essential to activation and/or stabilization of the carbonic acid intermediate. However, good hydrogen bond-donors, such as TFA or thiourea **218** (entries 7-8, Table 15) and acetic acid (not shown) failed to deliver any significant amount of carbonate. These data suggest the underlying framework of our *bis*(amidine)/counterion system is far superior in this context to other, more readily available hydrogen-bond donors or Brønsted acid/base combinations.

Table 15. Development of an enantioselective CO_2-capture reaction using homoallylic alcohol **222** to afford iodocarbonate **223**.





entry	ligand (base)	acid[a]	notes[b]	yield[c]	ee (%)[d]
1	none	–	–	0%	–
2	none	–	NaH[e]	16%	–
3	none	–	NaH (THF)[e]	25%	–
4	DMAP (**220**)[f]	–	–	trace	–
5	DBU (**221**)[f]	–	–	trace	–
6	TBD (**219**)[f]	–	–	11%	–
7	TFA[f]	–	–	6%	–
8	**218**[f]	–	MS	4%	–
9	PBAM (**2a**)	–	–	18%	39
10	StilbPBAM (**133**)	–	–	33%	36
11	**133**	–	MS	35%	60
12	**133**	HOTf	MS	62%	74
13	**133**	H_2NTf	MS	52%	62
14	**133**	$F_6C_3(SO_2)_2NH$	MS	70%	86
15	**133**[g]	**$HNTf_2$**	**MS, 0.4 M**	**95%**	**91**
16	**133**	$HNTf_2$	MS, 0.2 M	51%	89
17	**133**	$HNTf_2$	MS, 0.1 M	10%	79
18	**218**[f]	–	–	trace	–
19	**219**[f]	–	MS	30%	–
20	**133**[f]	–	MS	13%	–
21	**133**[f]	½ $HNTf_2$	MS	4%	–

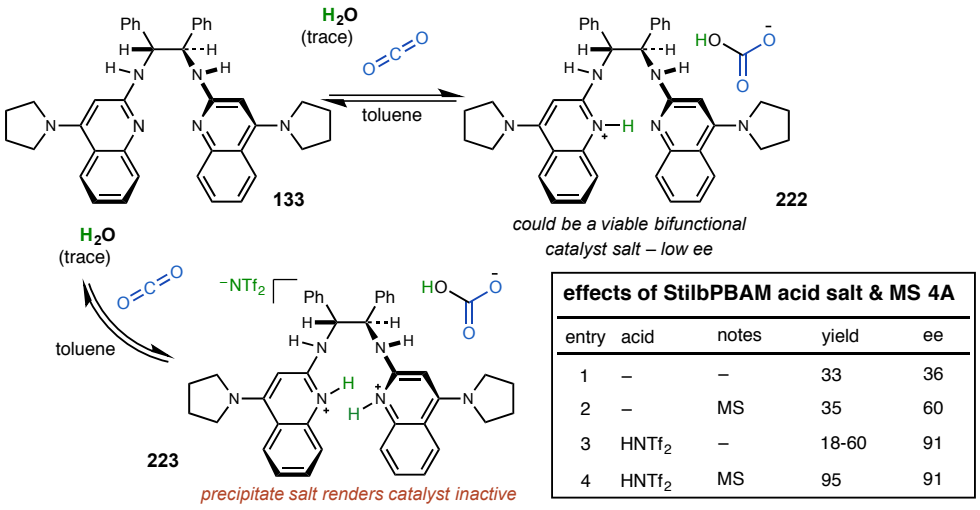
[a]Catalyst prepared as the 1:1 acid salt, except entry 21. [b]MS denotes molecular sieves 4A, employed at a concentration of 1 g/mmol relative to the alcohol. [c]Isolated yield. [d]Enantiomeric excess (ee) determined by HPLC using a chiral stationary phase. Reactions are 0.4 M toluene unless otherwise noted. [e]Reaction carried at 0 °C. 3-Methyl-3-buten-1-ol was converted in 60% yield under identical conditions. [f]20 mol % catalyst employed. [g]5 mol % catalyst employed, with results analogous to those using 10 mol % catalyst.

Our ultimate goal was to explore the ability of a *bis*(amidine) Brønsted acid/base combination to promote the reaction. Use of *bis*(amidine) free base **2a** (PBAM) resulted in an 18% yield of **223**, however the carbonate was still formed in 39% ee (entry 9, Table 15) at -20 °C. The analogous catalyst incorporating *trans*-stilbene diamine StilbPBAM (**133**) instead of

trans-cyclohexane diamine provided the product in 33% yield and similar ee (36% ee, entry 10, Table 15). Interestingly, no significant change in ee was observed with the free base of these two chiral Brønsted basic ligands. It was also noted in these early experiments that the addition of molecular sieves (MS 4A) resulted in more consistent reactions as judged by conversion and/or yield (entry 11, Table 15).

In reactions without sieves, formation of a precipitate appeared to correlate with lower yields, although enantioselectivity was only marginally affected. As depicted in Figure 37 we believe the observed precipitate, through a number of control experiments, may correlate with the formation of a doubly protonated catalyst salt (**223**) in the presence of H_2O and CO_2, generating carbonic acid (H_2CO_3). Accordingly, in the presence of molecular sieves when water should not be present, carbonic acid is unable to form and the reaction may proceed forward as desired.

Figure 37. Catalysts deactivation pathway by carbonic acid from water and carbon dioxide.

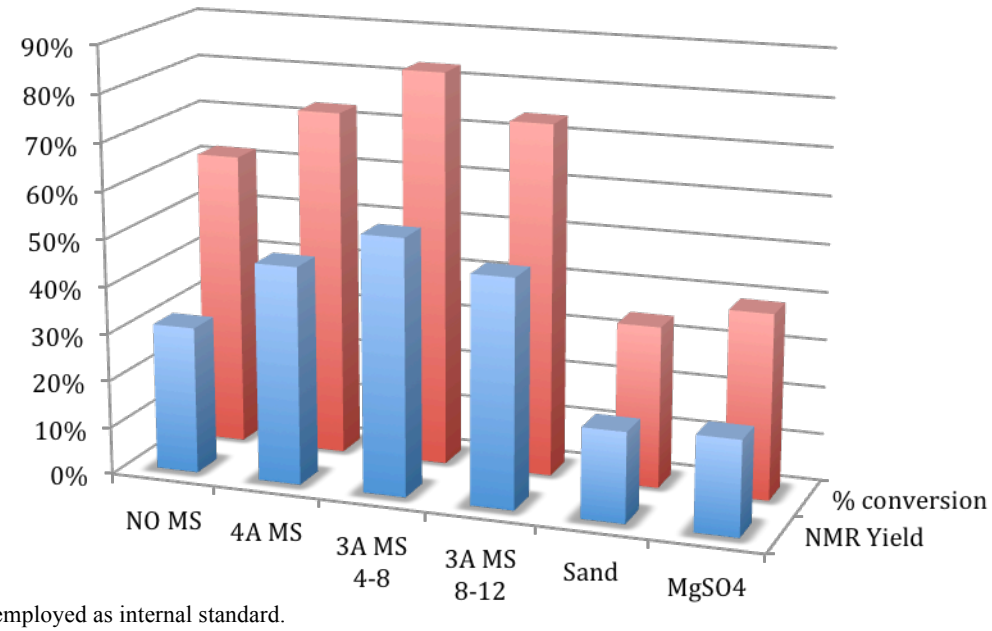


effects of StilbPBAM acid salt & MS 4A

entry	acid	notes	yield	ee
1	–	–	33	36
2	–	MS	35	60
3	$HNTf_2$	–	18-60	91
4	$HNTf_2$	MS	95	91

As outlined in Chart 3, other common desiccants were examined and performed in line with MS 4A – MS 3A performed slightly better in terms of product conversion (82% conversion after 38 hours) to product than MS 4A (75% conversion). MS 4A were ultimately employed due to higher availability in our lab setting. Aluminosilicates (i.e. MS 4A) in general are known to *adsorb* gaseous species, many of which include SO_2, CO_2, H_2S, C_2H_4, C_2H_6, and C_3H_6, and the pH of aluminosilicates (in a "5% aqueous slurry solution") is 10.5 – reasonably basic which

Chart 3. The Effect of Desiccants on the Conversion of the Catalytic, Enantioselective Iodocarbonation Reaction after 38 Hours[a]



[a]CH_2Br_2 employed as internal standard.
Reactions did not go to completion (>48 h) and each entry was run in duplicate.

elicits interesting additional hypotheses into their exact function in this reaction.[162] In addition to aluminosilicates, another desiccant magnesium sulfate ($MgSO_4$) was examined. Interestingly, this additive provided the desired carbonate (**223**) in far lower yield and conversion than any of

[162] R. V. Siriwardane, M. S. Shen, E. P. Fisher. *Energy Fuels* **2005**, *19*, 1153.

the aluminosilicate desiccants previously examined. Sand was also employed as a control (a high surface area solid), but had no detectable effect.

Next, the exploration of strong achiral Brønsted acid additives (1:1 ligand:acid) finally resulted in moderate differences in enantioselection (Table 15, entries 12-15), with catalyst complex **133**·$HNTf_2$ providing **223** with 91% ee (Table 15, entry 15). Some sensitivity of both yield and selectivity to concentration was noted, with lower concentrations leading to depressed yield and selectivity (Table 15, entries 16-17). Interestingly, the electrophile NIS is sparingly soluble under the optimized concentration in toluene (0.4 M) and never fully dissolves, suggesting possible phase-transfer like activation of NIS by the soluble catalyst, as previously observed by Jacobsen in his iodolactonization chemistry.[163]

With the optimized conditions in hand, we took the time again to reinvestigate several achiral amine bases to address just how unique (or not unique) this catalyst system was at producing carbonate product – with or without stereoselectivity. While these chiral *bis*(amidine) catalysts are essential to promoting high enantioselection, we believed the high chemical yield of this largely unprecedented transformation was remarkable and attempts to mimic this robust system were explored.

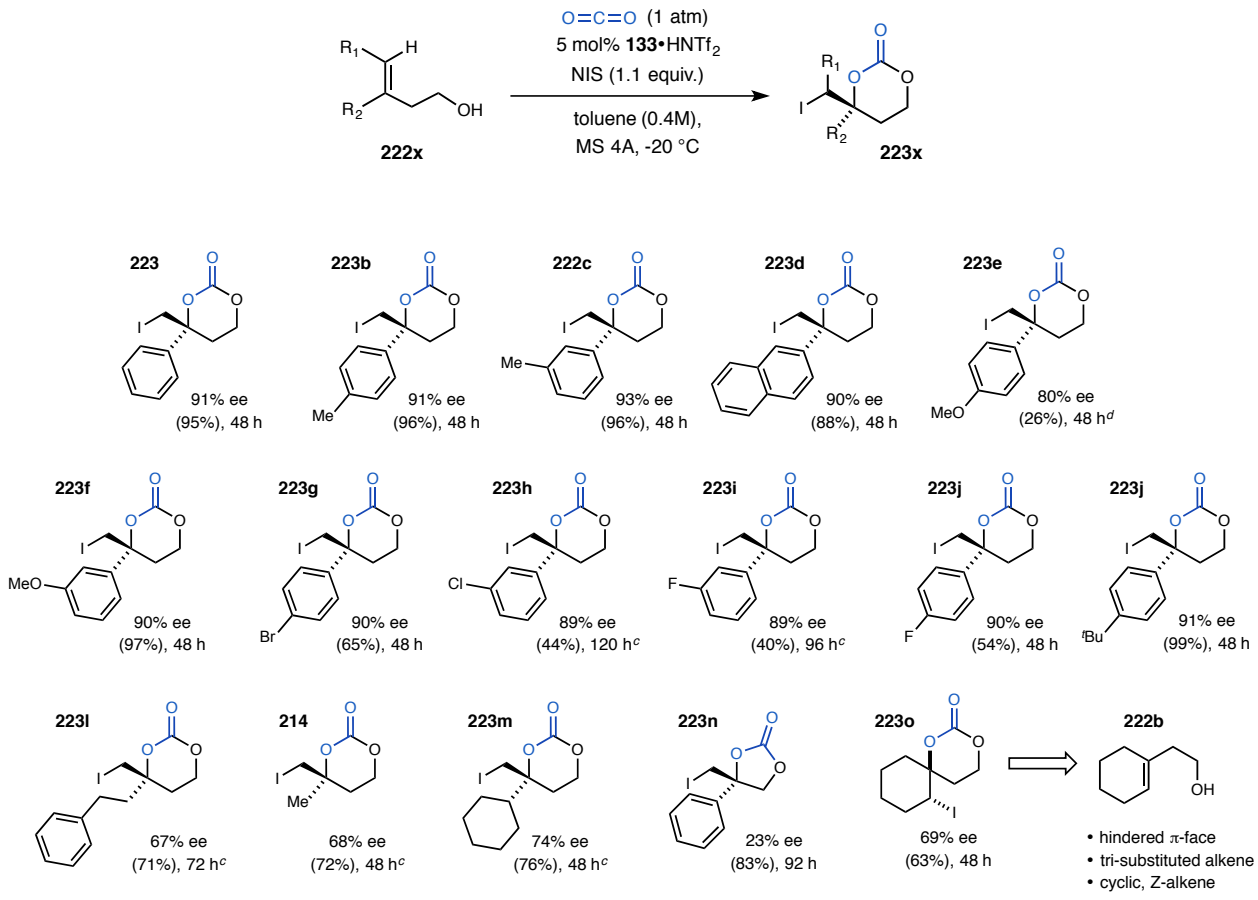
After screening a host of common organic amine bases and hydrogen-bond donors, we witnessed low to very moderate yields (entries 18-21, Table 15). Experiments simulating the Brønsted acid/base character of catalyst **133**•$HNTf_2$ using achiral monobasic amines in combination with varying amounts of Brønsted acid were investigated (e.g. entry 21, Table 15), none resulting in significant improvement of yield (DBU•1/2$HNTf_2$, 4% yield). Collectively, these results suggest an underlying order to the hydrogen bonding network in the key selectivity-

[163] Brindle, C. S.; Yeung, C. S.; Jacobsen, E. N. *Chem. Sci.* **2013**, *4*, 2100.

determining step, if not unique reactivity associated with the proper positioning of a Brønsted acid and base in the same molecule, in this carbon dioxide–fixating reaction.

Optimized conditions for homoallylic alcohol **222** were applied to a range of similar substrates outlined in Table 16. α-Substituted styrene derivatives were scrutinized using the mild conditions developed to afford a range of carbonates (**223a-q**, Table 16). Nominal substitution of the aromatic ring led to equally positive outcomes, with **223a-223c** formed in 91-93% ee, and high chemical yield (95-96% yield). Increasing the reaction temperature to 0 °C led to complex

Table 16. Development of an enantioselective CO_2-capture reaction using a homoallylic alcohol.[a]



[a]Enantiomeric excess (ee) determined by HPLC using a chiral stationary phase. Reactions are 0.4 M in toluene. Isolated yields are listed. See SI for complete experimental details. Absolute configuration for **2a** assigned using X-ray analysis, remaining examples assigned by analogy. A single diastereomer was observed (NMR) for **2q**. [b]6.8 mmol (1.0 g) substrate was employed under the optimized conditions (1 atm CO_2) utilizing 3.0 mol % for 48 h, providing a 79% yield of **2a** (89% ee). [c]10 mol % catalyst loading. [d]Reaction temperature was -50 °C.

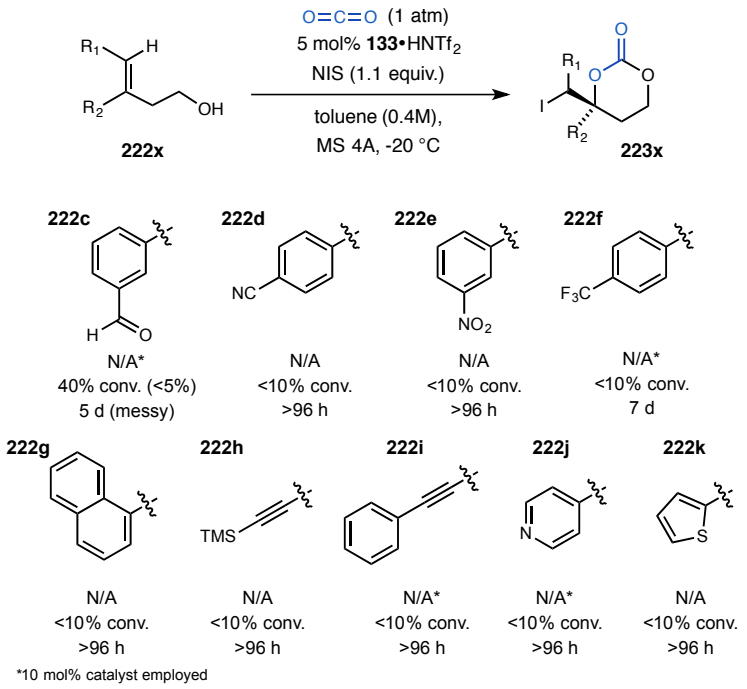
mixtures suggestive of competing intermolecular iodoetherification. However, a β-naphthyl-substituted alkene led to good enantioselection and yield (**223d**, 90% ee, 88% yield).

Anisole derivatives (*meta*- and *para*-substituted) provided generally good enantioselectivity (80-90% ee) and higher chemical yield (97%, **223e-f**). Halogen-substituted arenes led to a range of results, mostly related to reactivity; while selectivity remained high, some reached only partial conversion despite extended reaction times. Halogen substitution *meta* and *para* to the alkene provided conversion with consistently good enantioselection (89-90% ee). Reactivity varied greatly among **223g-223j**, however, and suggested that the alkene nucleophilicity might be a key determinant of reactivity.

Alkenes bearing aliphatic substituents are often regarded as challenging substrates in stereoselective difunctionalization reactions.[164] 3,3-Dialkyl butenols leading to **223l-223m** and **214** were prepared and converted to carbonates with promising levels of enantioselectivity (up to 74% ee, Table 16). Iodocarbonate **214**, derived from the sterically-unencumbered 3-methyl-3-butane-1-ol (**213**) previously employed and a widely available isoprenyl feedstock, still formed in a moderate 68% ee and was not improved from previous attempts. Allylic alcohols reacted sluggishly and were quite challenging and unique in this work and may be worth exploration in future studies. Many homoallylic alochols tested exhibited good yield after extended reactions times although lower enantioselection (c.f. **223n**, **223a**). Finally, a trisubstituted alkene (**222b**) was examined, and despite the increased steric hindrance, it behaved similarly to aliphatic alkenes. The immediate product, spirocycle **223o** was formed in 69% ee, and this material could be enriched through fractional recrystallization (Table 16).

[164] Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

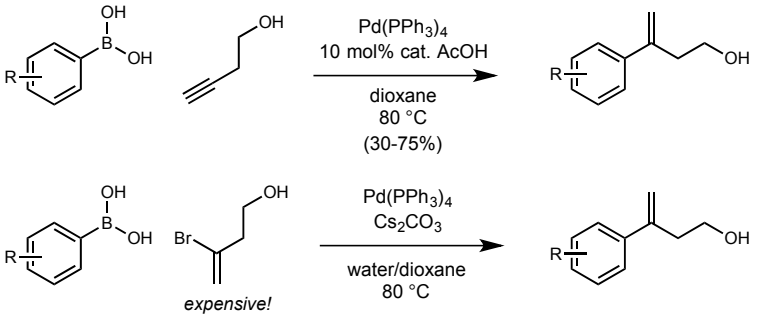
Table 17. 1,1-Disubstituted homoallylic alcohols tested that behaved poorly under optimized conditions.



In addition to the variety of homoallylic alcohols that worked well under these catalytic conditions, there were many substrates (**222c-k**) that were not successful (Table 17). The majority of these substrates would have provided welcomed diversity to the substrate scope as well as potential future applications in target molecule synthesis. A number of electron withdrawing groups were not tolerated to any extent – the 1,1-disubstituted alkene must be sufficiently electron rich in order to react. Interestingly, 1-ene-2-yne systems **222h**-**222i** were not tolerated as well for reasons unclear, only returning unreacted starting material. Heteroaromatic styrenyl compounds (**222j**-**222k**) were not compatible under these conditions, and significant decomposition was noted, perhaps due to competing non-selective iodination by NIS.

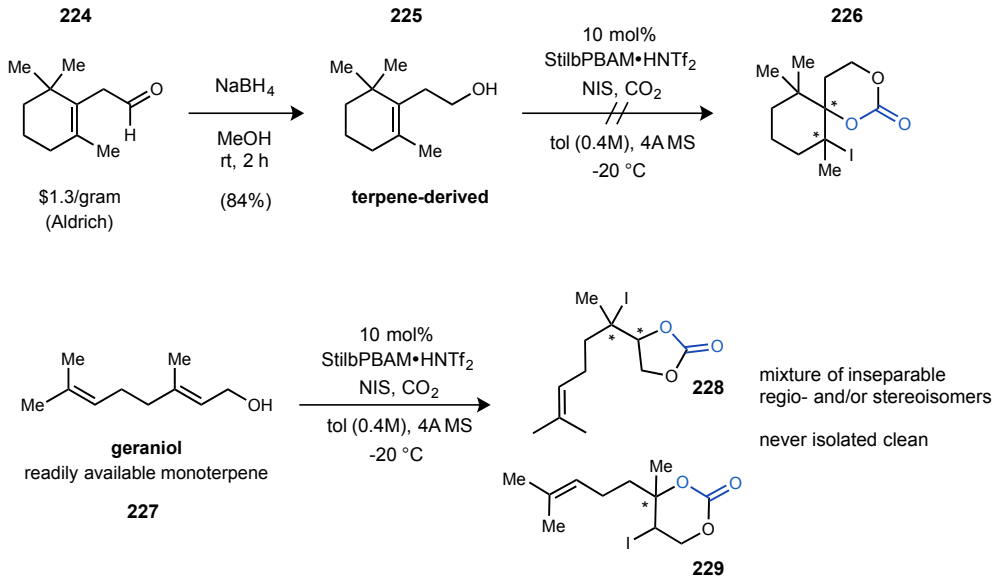
All of these substrates were prepared predominantly using two methods – the hydroarylation reaction of homopropargyl alcohols and Suzuki reactions between a boronic acid and the vinyl bromide (Scheme 66). For practicality, we mostly favored the hydroarylation reaction due to ease of preparation and availability of coupling partners.

Scheme 66. Syntheses of the styeneyl homoallylic alcohols via hydroarylation and a Suzuki coupling reaction.



Various homoallylic alcohols could conceivably undergo the enantioselective iodocarbonation reaction. Naturally occuring alcohols are attractive for a number of reasons, most notable is their potential utility in complex molecule synthesis (Scheme 67). Commercially

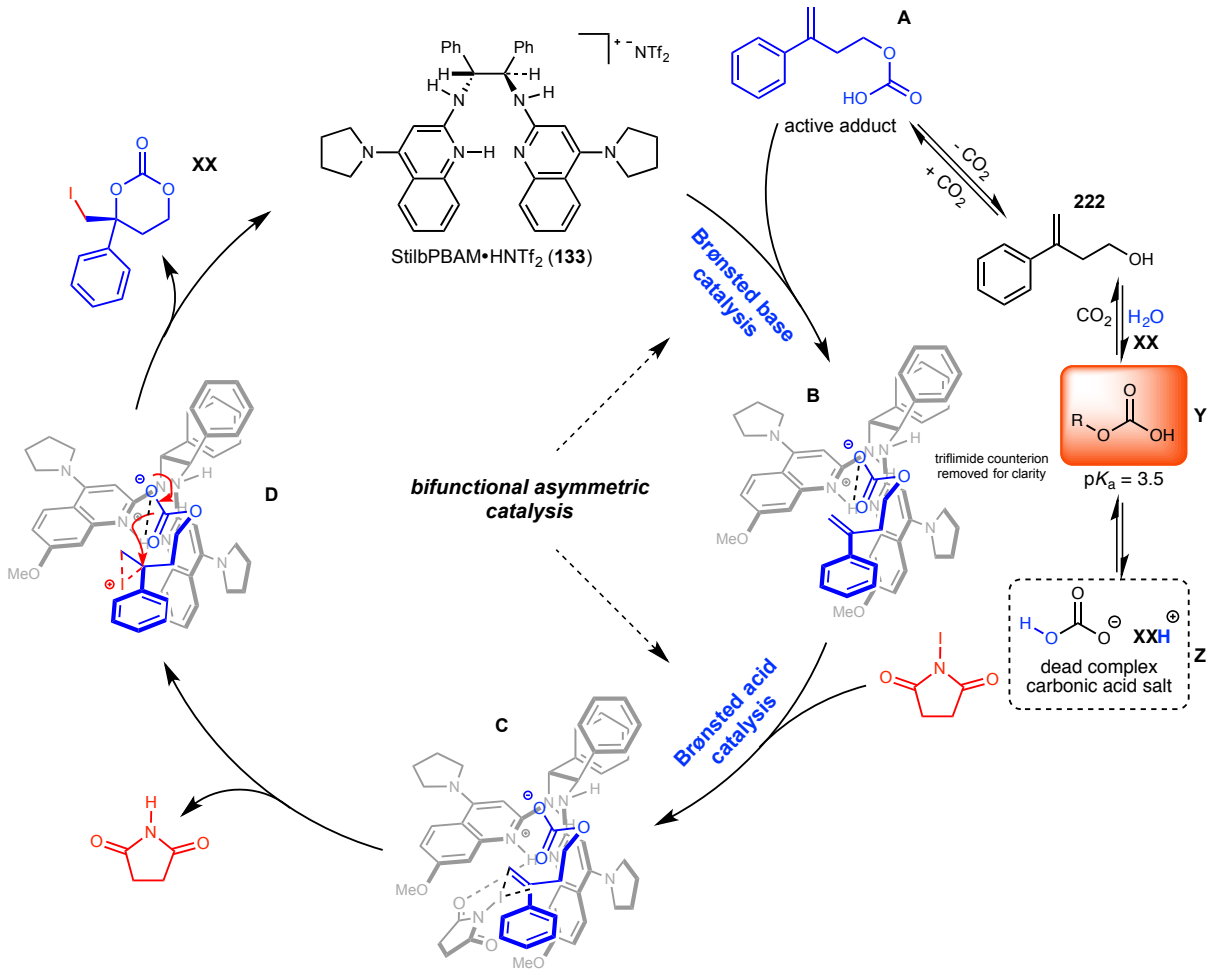
Scheme 67. More challenging alcohol substrates tested in the iodocarbonation reaction.



available terpene-derived aldehyde **224** was reduced to homoallylic alcohol **225** with $NaBH_4$. This alcohol is interesting for the following reasons: it is a readily available terpene feedstock, and it bears a very hindered, trisubstituted alkene – the most hindered we have explored. Additionally, the product would generate a sterically hindered spirocyclic motif (**226**). Combined, these characteristics make **225** a very attractive candidate for this enantioselective chemistry and would put this methodology to the ultimate test. Following numerous attempts employing optimal and modified conditions, however, conversion was very poor and primarily starting material was recovered. We believe the π-face of this alkene is simply too hindered.

Similarly, geraniol (**227**) is a common monoterpene and the precursor in a host of natural

Scheme 68. Proposed catalytic cycle of carbon dioxide-fixation and bifunctional Brønsted acid/base interactions with the generated alkyl carbonic acid.



product syntheses[165] disclosed in the past and is the proposed biosynthesis precursor[166] to taxol (Scheme 67). This substrate bears many similarities to alcohol **225** previously attempted although it is acyclic. This geraniol alkene was reactive in the reaction, although yield was low and two regioisomers predominated (5-*exo* and 6-*endo*) making purification difficult (Scheme 67). Chemoselectivity improved at -50 ºC but clean material could not be isolated.

A catalytic cycle derived from these observations is broken down in Scheme 68. The high degree of enantioselection observed indicates the catalyst (**133**•$HNTf_2$) is involved directly in the cyclization step (**C→D**). It may also accelerate the carbon dioxide capture step by increasing the alcohol nucleophilicity through a hydrogen bond-acceptor (HB-A, catalyst) and hydrogen bond-donor (HB-D, alcohol) interaction. Additionally, the intermediate carbonic acid (**A**) can be stabilized through the same combination (**B**, HB-A/HB-D), shifting the equilibrium more in favor of carbonic acid formation when the catalyst is present.

Several experimental observations are worth mentioning that help assess the order of mechanistic events. Foremost among these, use of a carbon dioxide balloon establishes that the steady-state carbon dioxide concentration is significant in chilled toluene and could be reached within 40 minutes – far shorter than the time to complete conversion (confirmed by in situ IR).[167] The rate of CO_2 absorption was affected insignificantly by most every factor examined, including temperature, the presence of MS 4A, and stirring rate.

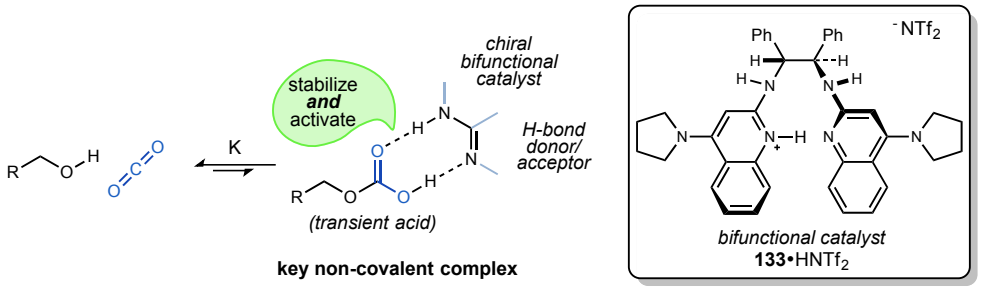
The correlation between high chemical yield and molecular sieves can be explained by the formation of a complex between the catalyst (**Z**, Scheme 68), water, and carbon dioxide, which we hypothesize to be the carbonic acid salt. This complex **Z** precipitates from the reaction mixture when using **133**•$HNTf_2$, but its formation appears reversible, reverting to active catalyst

[165] Denmark, S. E.; Kobayashi, T.; Regens, C. S. *Tetrahedron* **2010**, *66*, 4745.
[166] Rubenstein, S. M.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 7215.
[167] Struble, T.J.; Johnston, J.N. unpublished results

when a desiccant (MS 4A) is added. Although a non-covalent complex is hypothesized in our work, some nucleophlic amines can form a covalent adduct with CO_2.[168] This sensitivity to water is most pronounced with catalyst **133**•$HNTf_2$ and poorly nucleophilic alcohol substrates. When not in competition with water, the alcohol substrate (**222**) can entrain carbon dioxide, forming an intermediate and transient alkyl carbonic acid with the bifunctional catalyst salt **B**. This intermediate, in reaction with NIS, forms a complex [NIS•**C**], which then collapses to the cyclic carbonate **D** either stepwise or directly.[169]

More simply, we believe the hydrogen bond donor/acceptor complex initiated by the organocatalyst StilbPBAM•$HNTf_2$ (Scheme 69) is essential to shifting the equilibrium (*K*) towards productive carbonic acid formation – the key intermediate precursor for enantioselective cyclization. Complementary contacts between the catalyst hydrogen bond-donor (amidinium) and acceptor (amidine) functionalities with their counterparts in the intermediate carbonic acid *and* NIS are all critical to high enantioselection.

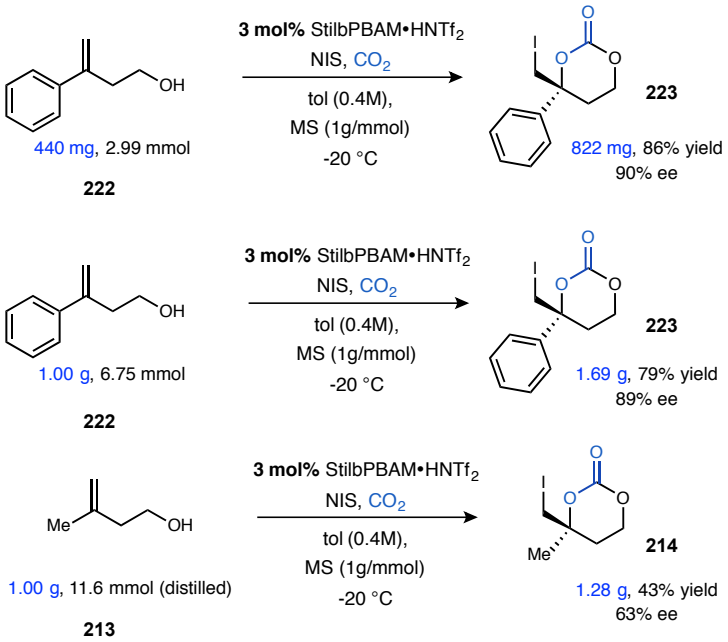
Scheme 69. The key non-covalent hydrogen-bonding complex responsible for carbonic acid stabilization.



[168] Villiers, C.; Dognon, J.-P.; Pollet, R.; Thuéry, P.; Ephritikhine, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3465. Heldebrant, D. J.; Jessop, P. G.; Thomas, C. A.; Eckert, C. A.; Liotta, C. L. *J. Org. Chem.* **2005**, *70*, 5335.
[169] Wu, J.; Wang, Y. M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 13729. Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232. Müller, C. H.; Rösner, C.; Hennecke, U. *Chem. Asian J.* **2014**, *9*, 2162. Yousefi, R.; Ashtekar, K. D.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. *J. Am. Chem. Soc.* **2013**, *135*, 14524.

Many organocatalysts do not perform as well in reactions at larger scale. In fact, Eric Jacobsen alluded to this poor scalability phenomenon in his work with urea and thiourea catalysts.[170] BAM catalysts, however, have been scaled at a number of opportunities. When attempting to run the iodocarbonation reaction on larger scale (up to 1 gram **222**), we saw success with several substrates. Carbonates **223** and **214** were still prepared in both good yield and ee employing just 3 mol % of the catalyst (Scheme 70). Recrystallization of the iodocarbonates on scale was also explored but gave mixed results. The phenyl iodocarbonate **223** could be enriched to 99% ee from diethyl ether (Et_2O), although recovery was low (<40%). Methyl-substituted carbonate **214** was enriched to 84% ee, but again, recovery was very low.

Scheme 70. Validation that the enantioselective iodocarbonation reaction is amenable to scale.

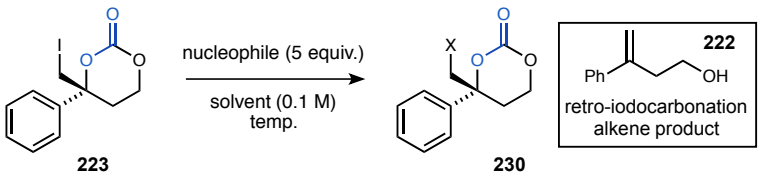


[170] Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678.

3.2.4 Exploring Useful Chemical Transformations of the Enantioenriched Iodocarbonates

From this simple and robust protocol for generating enantioenriched cyclic iodocarbonates, we next set out to establish useful transformations of these chemicals. The ability to use an inexpensive and readily accessible organocatalyst in conjunction with such a cheap, plentiful oxygen source like carbon dioxide could have wide synthetic implications and impact on the community. One can envision transforming these products into other chemical building blocks, pharmaceuticals, or agrochemicals. While these carbonates may be valuable in their own right, we envisioned their derivatization into unique (and oxygenated), chiral building blocks based on both known and less precedented methods in order to broaden their immediate

Table 18. Substitution attempts for the neopentyl iodide employing a range of nucleophiles.

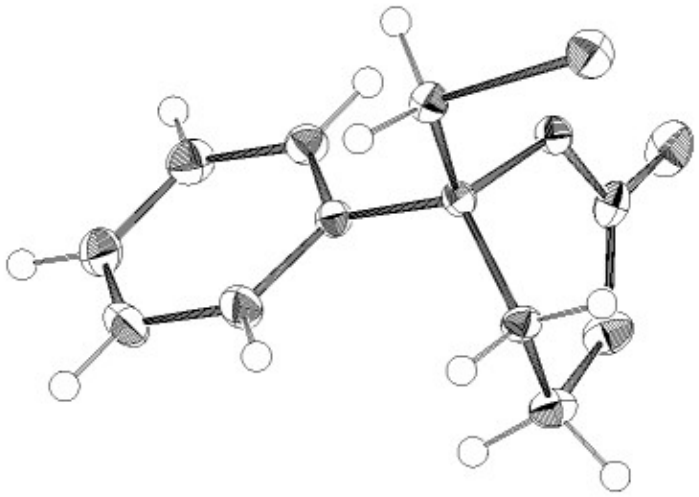


entry	Nucleophile(s)	solvent	temp (ºC)	time	result
1	NaN_3	DMSO	80	8 h	**223**
2	AgCN	DMSO	80	24 h	**223**
3	$MeNO_2$	neat	80	24 h	**223**
4	AgOAc	DMSO	80	24 h	**223**
5	NaN_3	DMSO	110	18 h	1:1 **222**:**230**
6	$AgNO_2$/$MeNO_2$	neat	110	18 h	1:1 byproduct:**223**
7	AgOAc	H_2O	110	18 h	unfamiliar byproduct
8	**NaN_3**	**DMF**	**110**	**18 h**	**~1:1 222:230**
9	NaN_3	MeCN	110	5 d	**223**
10	NaN_3 (15 equiv.)	DMSO	110	18 h	**222**
11	NaN_3 (2 equiv.)	DMSO	110	18 h	**223**, trace **230**
12	NaN_3 (2 equiv.)	DMF	110	18 h	~1:1 **222**:**230**
13	NaN_3/Ag_2CO_3	DMF	110	3 h	1:1:1 **222**:**223**:**230**

utility.

Derivatization attempts were initially focused on substituting a number of nucleophiles for the pendant iodide – conceivably feasible using small, strong nucleophiles such as ^{-}CN, $^{-}N_3$, etc. An array of nucleophiles tested is listed in Table 18. Substitution attempts at this carbon largely failed and primarily resulted in retro-iodocarbonation product (**222**). Due to the steric congestion and sheer size of the iodine atom (via assumptions made from the resolved crystal structure of **223**, Figure 38), even small nucleophiles presumably have trouble accessing the C–I anti-bonding orbital, and instead attack the more accessible (electrophilic) iodine. Silver(I) salts (halophiles) were also explored in hopes of polarizing the carbon-iodine bond to promote substitution and/or departure of iodide, but this approach also failed (entries 2,4/6-7, Table 18). The best overall result obtained in these experiments was employing NaN_3 in DMF at 110 °C (entry 8, Table 18), which resulted in 40% conversion to the desired azide adduct – although yield was incurably low and never exceed 25%. It was soon evident that substitution on the neopentyl iodide would be a significant challenge.

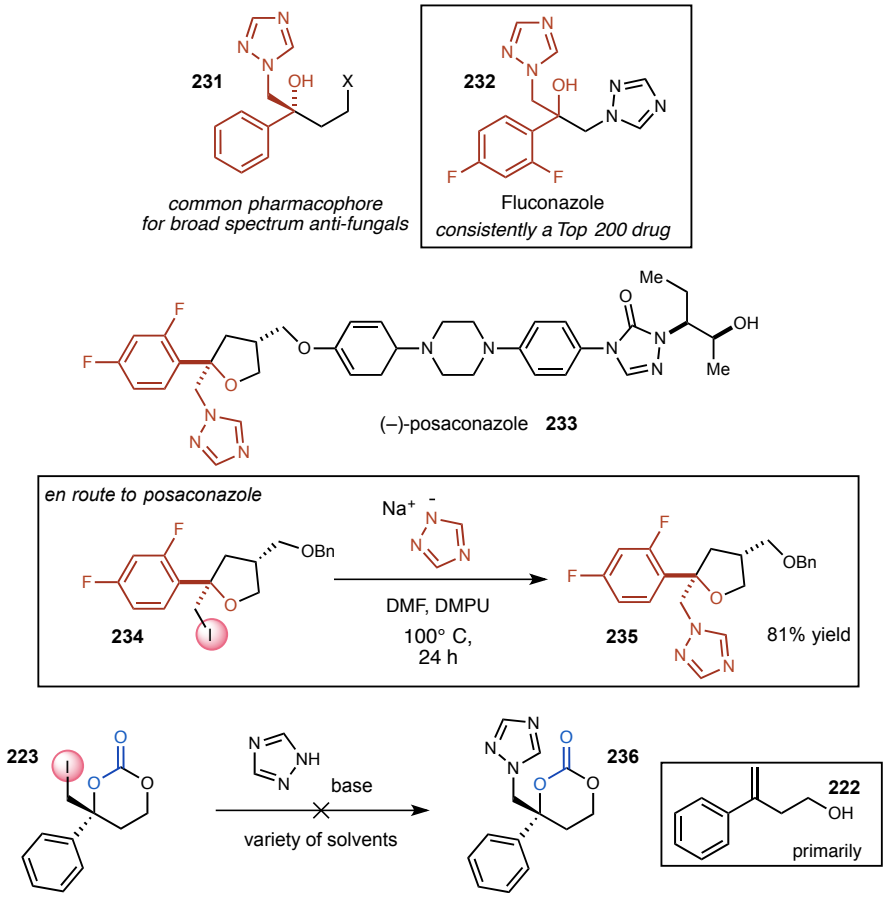
Figure 38. Single X-ray crystal structure of iodocarbonate **223** (courtesy of Maren Pink, Indiana U.).



Also evident was the possibility of assembling chiral tertiary alcohols beginning from these enantioenriched carbonates. Well known is a class of antifungal drugs known simply as the 'triazole and imidazole antifungals' (**231**, Scheme 71) – largely important to the global health community for treating a variety of parasitic and fungal infections.

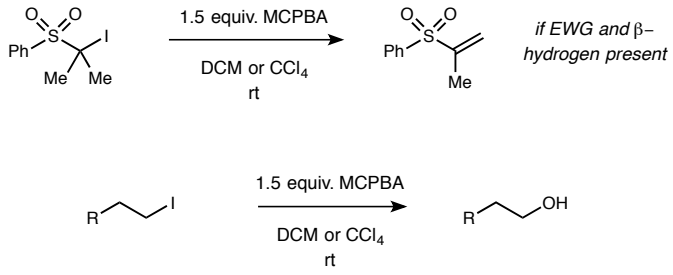
Posaconazole (**233**) may be one of the more unique and structurally complex antifungals in this class and is also prescribed to treat Chagas disease (Scheme 71). It is marketed by Schering-Plough and the key synthetic step introducing the triazole ring is via displacement of a

Scheme 71. The common pharmacophore belonging to the triazole antifungals: tertiary alcohol, substituted arene, and pendant triazole are all necessary for activity. Literature precedence to posaconazole and our failed attempts to install the triazole.



neopentyl iodide[171] to give **235** as outlined in Scheme 71. Based on this scaffold and synthetic precedence, 1,2,4-triazole was employed in the substitution chemistry employing a range of bases, additives, and solvents. Similar to other small nucleophilic species previously attempted, these triazole nucleophiles were also not tolerated with this system, and primarily resulted in retro-iodocarbonation alkene product. Conceivably, any amine-based nucleophile that cooperates with these substrates could arrive at a similar, nitrogenated heterocycle needed to furnish the active triazole pharmacophore.

Scheme 72. Literature precedent of alkyl iodine activation using peracids (MCPBA).



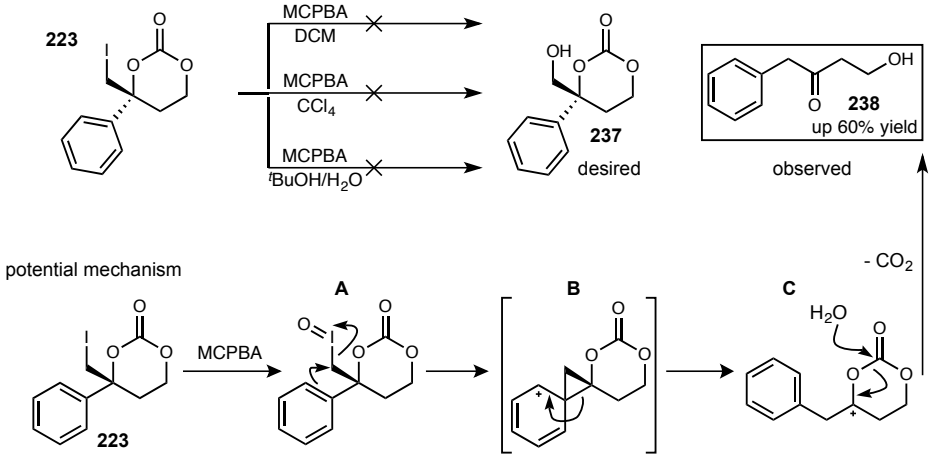
It has been reported that oxidants, specifically peracids like *m*-chloroperoxybenzoic acid (MCPBA), can react with alkyl (often primary) iodides and generate iodoso compounds *in situ*.[172] In the reported work, the generated iodoso compounds undergo *syn* elimination to form alkenes from the loss of hypoiodous acid (IOH). In the absence of a suitable electron-withdrawing group, primary alcohols can be isolated from primary iodides in good yield as well (Scheme 72). It's reasonable to postulate that upon iodoso formation, various nucleophiles may be introduced at this time promoting a substitution reaction. In our system, we saw a variety of interesting results. Firstly, it was apparent the desired iodoso intermediate was forming in the reaction by TLC, what occurred following this event varied significantly.

[171] Saksena, A. K.; Girijavallabhan, V. M.; Wang, H.; Liu, Y. T.; Pike, R. E.; Ganguly, A. K. *Tet. Lett.* **1996**, *37*, 6821.
[172] Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888.

Under the standard literature conditions using CCl_4 or DCM, we witnessed low conversion to the desired primary alcohol, but dominant conversion to an achiral, rearranged compound **238** (Scheme 73). Mechanistically, we understand this to occur by the formation of the iodoso intermediate **A**, followed by the π-donation of the aromatic ring resulting in the phenonium ion cyclopropane intermediate **B**. At this stage, the phenonium ion is quenched to relieve ring strain through cyclopropane fragmentation and the resulting α-oxycarbocation (in **C**) is neutralized upon carbonate hydrolysis generating the achiral ketone. A recent report using a fluoro hypervalent iodine reagent proposes an analogous mechanism for a similarly rearranged product isolated.[173]

With these results in hand, it was apparent the intramolecular arene addition to the iodoso

Scheme 73. Attempts to access iodoso intermediate **A**, and its possible role in formation of achiral ketone **238**.



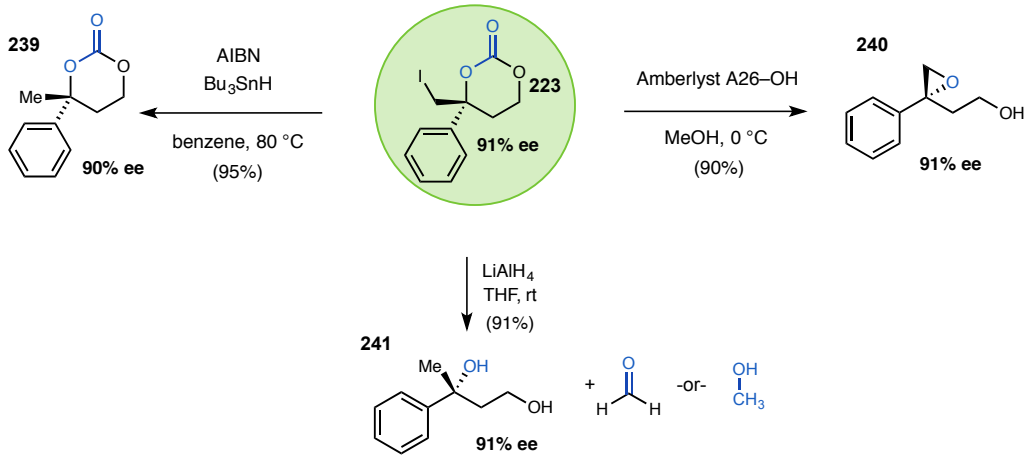
carbon was fast and outcompeting the desired pathway of water/nucleophile addition to afford the alcohol product. We explored a variety of other solvents and conditions to no avail. Additionally, other nucleophiles such as anisole (employed as a solvent) and fluoride (KF) were

[173] *Intramolecular Fluorocyclization of Unsaturated Carboxylic Acids with a Stable Hypervalent Fluoroiodane Reagent*. *Angew. Chem. Int. Ed.* **2015**, Ahead of Print, DOI: 10.1002/anie.201507790

examined resulting in unreacted starting material or undesired alkene. In summary, the nucleophiles and conditions employed were insufficient at displacing the generated iodoso intermediate. From these data, it is clear the combination of a neopentyl iodide and a vicinal carbonate narrowed the possible product transformations. Our focus then turned to the fragmentation of the carbonates taking advantage of these destabilizing features.

The primary iodide of iodocarbonate **223** can be reduced with $HSnBu_3$ to generate **239** in good yield – notably little if any decarboxylation is observed (Scheme 74). Despite the success of this radical approach, other single electron donors (generated through light, thermally, or chemically) were not explored. The styrene-derived enantioenriched epoxide **240** was also formed under mild hydrolysis conditions using Amberlyst A26-OH in methanol.[174] This is

Scheme 74. Successful derivatizations of iodocarbonate **223** constructing enantioenriched, oxygenated compounds. Ee is maintained throughout.



significant from the viewpoint that carbon dioxide is effectively used as an equivalent to epoxidation, which normally requires an electrophilic source of oxygen (such as a peracid or dioxirane). As a further comparison and testament to the power of this derivatization approach,

[174] Together with Thomas Struble

enantioselective epoxidations of 1,1-disubstituted alkenes are notoriously challenging and have only been reported on a few occasions by Shi, but in suboptimal enantioselection.[175] Similarly, under reducing conditions with lithium aluminum hydride ($LiAlH_4$) in THF, the enantioenriched tertiary diol **241** was formed (Scheme 74). Enantioenriched tertiary alcohols are also challenging to prepare by other more direct asymmetric methods such as Gringard/cuprate additions to ketones and aldol reactions. This CO_2-fixation method therefore offers a two-step alternative to metal-free oxidations of homoallylic alcohols, for which CO_2 is reduced and converted to either dialkyl carbonate (using Amberlyst) or methanol. The high levels of enantioselection are conserved in all of the transformations in Scheme 74.

3.3 An Enantioselective Approach to Chroman Natural Products via CO_2-Fixation

This robust enantioselective CO_2-fixation transformation was next envisioned to be a viable approach to access tocopherol or chroman/chromene natural products based on many of the aforementioned derivatizations of the iodocarbonate intermediates. The results discussed hereafter are largely preliminary and require optimization of the enantioselective iodocarbonation using aliphatic homoallylic alcohols.

Over the past few decades, the number of biologically active natural products isolated that contain chroman and chromene units has increased dramatically. While their structures have fascinated chemists, their biological activity has provided hope that additional and better

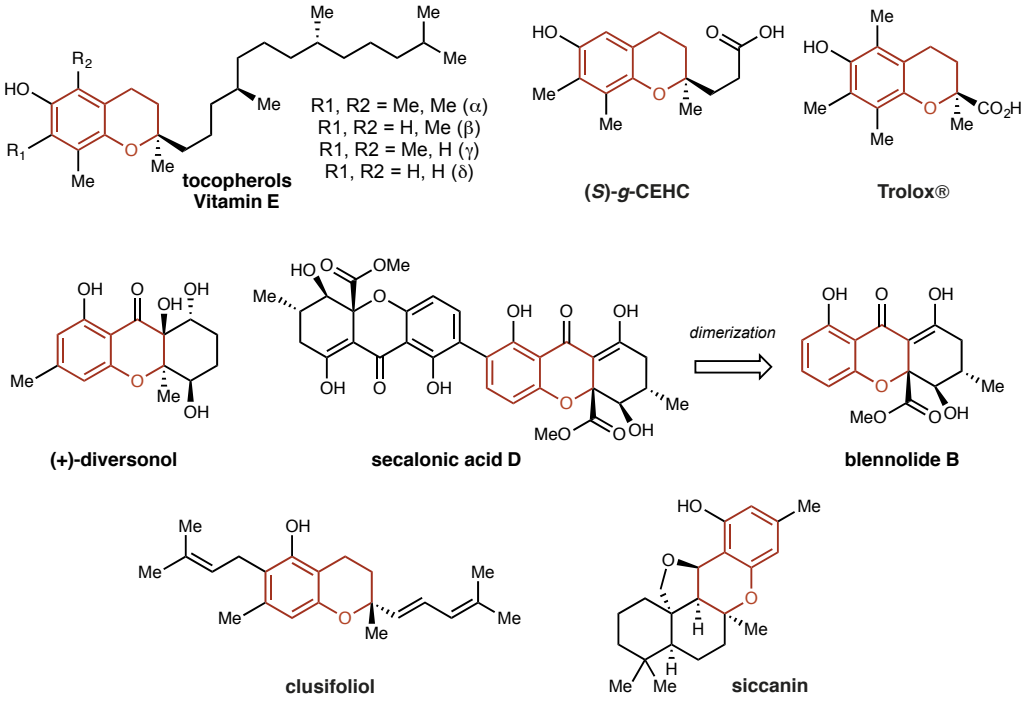
[175] Wang, Z. X.; Shi, Y. A. *J. Org. Chem.* **1997**, *62*, 8622. Wang, B.; Wong, O. A.; Zhao, M. X.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 9539. Wang, Z. X.; Shi, Y. A. *J. Org. Chem.* **1997**, *62*, 8622.

treatments for diseases may arise from their production and study. However, the study of their biological activity is oftentimes hampered by the lack of availability of these structurally diverse natural products from isolation alone. This fact has naturally prompted efforts to expand synthetic methods to access this structurally demanding scaffold, particularly using enantioselective means.

The chroman and chromene classes of natural products are vast, and are characterized by the presence of a highly substituted benzo tetrahydropyran (BTHP) core (highlighted in maroon, Figure 39) often containing one or more oxygenated stereocenters.[176] The most common chiral chromans belong to the tocopherol class – vitamin E is probably the most abundant and well studied compound in this family and exists as several constitutional isomers including α-, β-, δ-, γ-tocopherol (Figure 39).[177] These lipid-soluble compounds are constructed to function as robust single electron reductants – excellent radical traps or scavengers for harmful free radicals, including singlet oxygen species, in biological life as a result of oxidative metabolism in both plants and animals. γ-Tocopherol is the most common tocopherol of vitamin E in the North American diet. Vitamin E can be isolated in large quantities form natural sources, often collected and isolated to serve as food additives or vitamin supplements. Furthermore, tocopherols show physiologically diverse properties, including anti-tumor, anti-inflammatory, anti-atherosclerosis, and cell-signaling activities.[178]

[176] Shen, H. C. *Tetrahedron* **2009**, *65*, 3931.
[177] Netscher, T. *Vitam Horm* **2007**, *76*, 155.
[178] Blatt, D. H.; Pryor, W. A.; Mata, J. E.; Rodriguez-Proteau, R. *J. Nutr. Biochem.* **2004**, *15*, 380. Tomasetti, M.; Neuzil, J. *Vitam. Horm.* **2007**, *76*, 463. Howard, A. C.; McNeil, A. K.; McNeil, P. L. *Nat. Commun.* **2011**, *2*. Howard, A. C.; McNeil, A. K.; Xiong, F.; Xiong, W. C.; McNeil, P. L. *Diabetes* **2011**, *60*, 3034.

Figure 39. Tocopherol and chroman-containing natural products.



Trolox is a truncated derivative of vitamin E and is also widely used as a lipid-soluble antioxidant, especially in laboratory settings.[179] Clusifoliol was a component isolated decades ago from *Peperomia* species which have been used to treat malignant tumors.[180] Siccanin (Figure 39) is a potent antifungal agent and used clinically in Asia.[181]

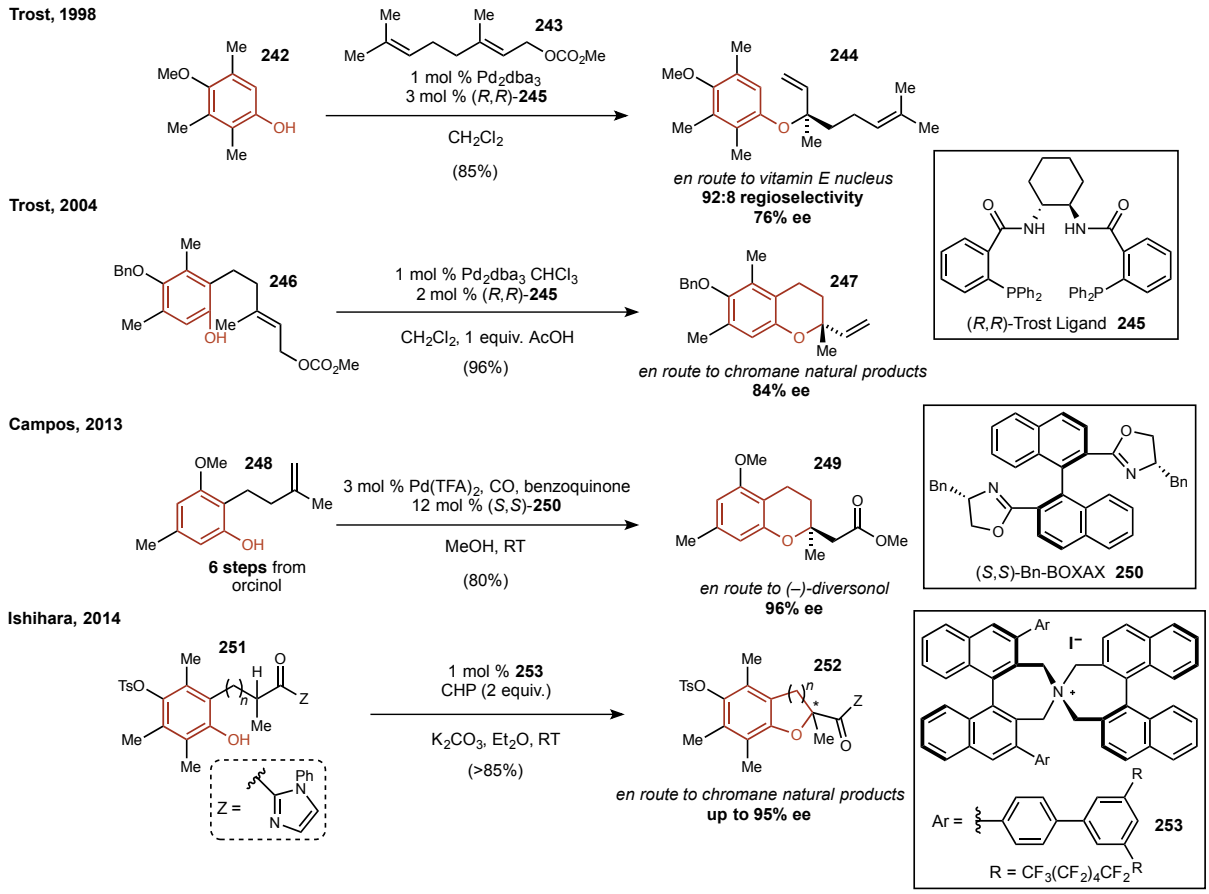
The key structural feature of chromans and tocopherols, both synthetically and biologically, are the relative and absolute configurations around the chiral tertiary ether moiety. While many syntheses have been reported to access these classes of natural products, the overarching challenge from a chemical assembly point of view is still the asymmetric construction – and preservation – of the chiral ether group. The enantiomeric configuration of the ether chiral center (*R* or *S*) is critical to biological activity, and certain enantiomers are not

[179] Terao, K.; Niki, E. *J. Free Rad. Biol. Med.* **1986**, *2*, 193.
[180] Seeram, N. P.; Jacobs, H.; McLean, S.; Reynolds, W. F. *Phytochemistry.* **1998**, *49*, 1389.
[181] Isabashi, K. *J. Antibiot. Ser. A* **1962**, *15*, 161.

accepted or recognized by the tocopherol transfer protein.[178] A number of elegant asymmetric reports to access the chiral BTHP cores are outlined in Scheme 75.

Trost and coworkers in the late 1990's used a unique approach (at the time) employing palladium catalysts, phosphine ligands (now widely recognized as the Trost Ligand. **245**), and allyl carbonates to afford chiral BTHP cores via the asymmetric allylic alkylation (AAA) of substituted phenols (**244**). Initially developed was the convergent, intermolecular asymmetric

Scheme 75. Pioneering and more recent, elegant examples detailing enantioselective preparations of chiral chroman cores.



phenolic alkylation, where both regio- and enantioselectivity had to be controlled.[182] Yield and enantioselection were generally good (up to 98% ee) and a number of diverse allyl carbonates (such as readily available geranyl carbonate **243**, Scheme 75) were tolerated to access the chiral

[182] Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9400.

ether functionalities. This initial report in 1998 from Toste and Trost opened the field for many other, very useful methods to access this challenging motif.

An extension of Trost's pioneering asymmetric alkylation work can be fully realized in the groups' full article expanding the synthetic scope and probing the mechanism, pH, and olefin geometry of this robust transformation.[183] Arguably more efficient, the method was extended to include *inter*molecular asymmetric allyl alkylations (**246**), resulting in the enantioselective synthesis of vitamin E and the first total syntheses of (+)-clusifoliol and (–)-siccanin (Trost, 2004; Scheme 75). This intermolecular, tethered approach has since been the gold standard to construct these compounds. Despite the broad applications and high enantioselection reported in these works, the synthetic steps needed to obtain the asymmetric reaction precursors can be many, up to 9 steps from commercially available materials.

Campos and coworkers in 2013 reported a clever asymmetric, domino Wacker/carbonylation/methoxylation reaction from an unsaturated precursor (**248**) similar to the phenol derivatives prepared by Trost.[184] In the presence of benzoquinone, 1 atm of carbon monoxide, and a Pd catalyst/ligand combination (Pd/**250**), high enantioselection was observed (up to 96% ee; Scheme 75). This enantioenriched intermediate **249** was further translated to the total synthesis of (–)-diversonol – a fungal metabolite isolated from various fungi including *Penicillium diversum*. K.C. Nicolaou and Li prepared *rac*-diversonol in 2008.[185]

The most recent catalytic, asymmetric reaction advancement to access this chroman core was reported by Uyanik and Ishihara in 2014 in the journal *Science* (Scheme 75).[186] While the

[183] Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J. P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966.
[184] Tietze, L. F.; Jackenkroll, S.; Raith, C.; Spiegl, D. A.; Reiner, J. R.; Campos, M. C. O. *Chem. Eur. J.* **2013**, *19*, 4876.
[185] Nicolaou, K. C.; Li, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 6579.
[186] Uyanik, M.; Hayashi, H.; Ishihara, K. *Science* **2014**, *345*, 291.

oxidative hypoiodite organocatalyst was reported previously in similar work,[187] the primary advance here is the broad utility, scope, and high catalytic performance (turnover frequency, TOF of ~ 200). Only Ishihara has reported this distinctive, oxidative approach to these antioxidant (ironically enough) molecules and is quite a mechanistically intriguing and innovative approach. Analogous to previous syntheses to access these molecules in enantioselective fashion, these unsaturated substrates (**251**) require many steps to prepare (7-10 steps from commercially available phenols) and a tailored auxiliary group (formimidazole group) is needed for high ee. Notably however, this developed protocol is suitable to construct *both* BTHP and benzo dihydrofuran core in high enantioselection, making this a very attractive advance to a broad number of natural and non-natural chroman or tocopherol products.

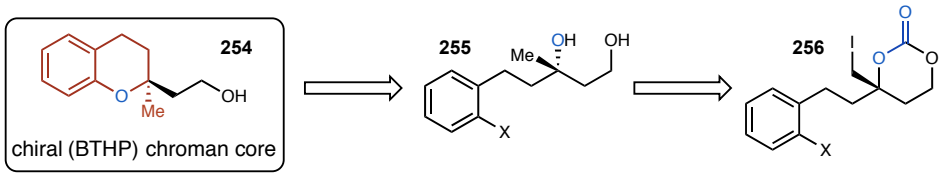
3.3.2 A Novel Route to Access Enantioenriched Chiral Chromans via Carbon-Capture Methodology

By examining the various iodocarbonates and derivatized products prepared from our enantioselective, CO_2-fixation reaction,[188] it was soon apparent the aliphatic variants in this chemistry could in principle, be transformed into chromans while maintaining ee throughout. From the outset, unfortunately, the aliphatic homoallylic alcohols needed for this conversion only afforded iodocarbonates in lower ee, topping out at 68% ee under optimized conditions. Thus a more selective and reliable catalytic system would need to be developed in order to increase enantioselectivity to more synthetically useful levels.

[187] Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376.
[188] Vara, B. A.; Struble, T. J.; Wang, W. W.; Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2015**, *137*, 7302.

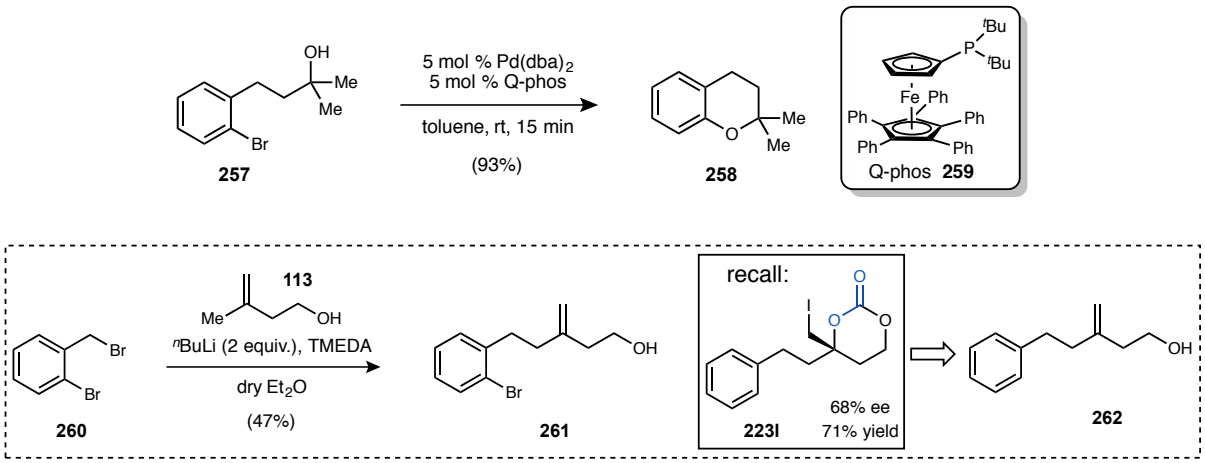
Retrosynthetically, our devised approach to obtain the chiral chroman scaffold is outlined in Scheme 76. First, we previously showed the iodocarbonates can be reduced ($LiAlH_4$) to afford the enantioenriched tertiary alcohols – **255** would stand as the key oxygenated intermediate en route to the desired chroman. From here, cyclization of **255** (6-membered cyclization favored over the 8-membered) onto the pendant aryl group (though C-H activation or by some other means) furnishes the BTHP (**254**), while presumably maintaining the stereochemical integrity of the chiral center. Also worth noting using this approach, is the conceptual notion of the oxygen

Scheme 76. Retrosynthetic analysis to prepare chroman **254** from chiral iodocarbonate **256**.



atom (highlighted in blue) from carbon dioxide contained in the carbonate would be incorporated into the final chroman core, effectively *utilizing CO_2 as an oxygen source* or formal oxidative reagent to access a natural product – an appealing notion from a "green chemistry" perspective. Furthermore, the resulting chroman ethanol **254** (Scheme 76) presents a useful handle for additional synthetic manipulations.

Scheme 77. Pertinent aryl etherification reaction. Successful synthesis of bromo alcohol **261** and previous enantioselection iodocarbonation results.



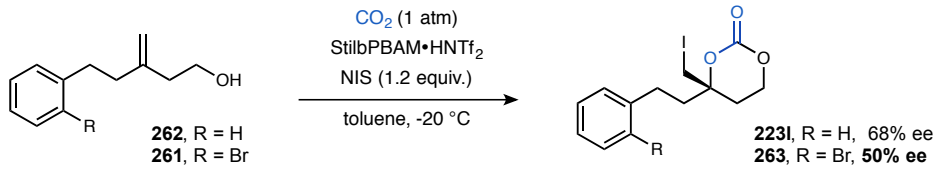
Known etherification methods are reported in the literature to access chroman/chroman-type heterocycles forging new aryl C-O bonds. One approach uses electrophilic 1,3-diiodo-5,5-dimethylhydantoin (DIH) to promote the electrophilic aromatic substitution followed by the pendant oxygen displacement of the aryl iodide. Alternate approaches use aryl bromides to complete the aryl C-O etherification cross-coupling reaction using transition metal catalysis. One report uses copper[189] while another report developed by Hartwig uses palladium and a ferrocenyl phosphine ligand known as Q-Phos (**259**, Scheme 77).[190]

Although ee for the desired substrates was low at this juncture, we first needed to test this proposed synthesis for feasibility, efficiency, and practicality. We elected to attempt one of the transition metal coupling conditions using an aryl bromide tether. While substrate **223l** (Scheme 78) had been previously prepared in 68% ee, *ortho*-bromo alcohol **261** was analogously prepared in moderate yields from 2-bromobenzyl bromide (**260**). This double-deprotonation method employing an excess of *n*-BuLi is effective, although rigorous exclusion of water is needed to achieve moderate yields.

[189] Niu, J.; Guo, P.; Kang, J.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2009**, *74*, 5075.
[190] Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

When **261** was initially subjected to the enantioselective iodocarbonation conditions with StilbPBAM•$HNTf_2$, an unexpected *drop in ee* of roughly 15%, relative to the debromo substrate **262** was observed with the installment of the bromine atom in the 2-position of the arene (from 67% ee when R = H, to 50% ee when R = Br) – although the yield was in line (64%) with similar

Scheme 78. Similar alkyl homoallylic alcohol substrates **261** and **262** in the enantioselective iodocarbonation reaction.

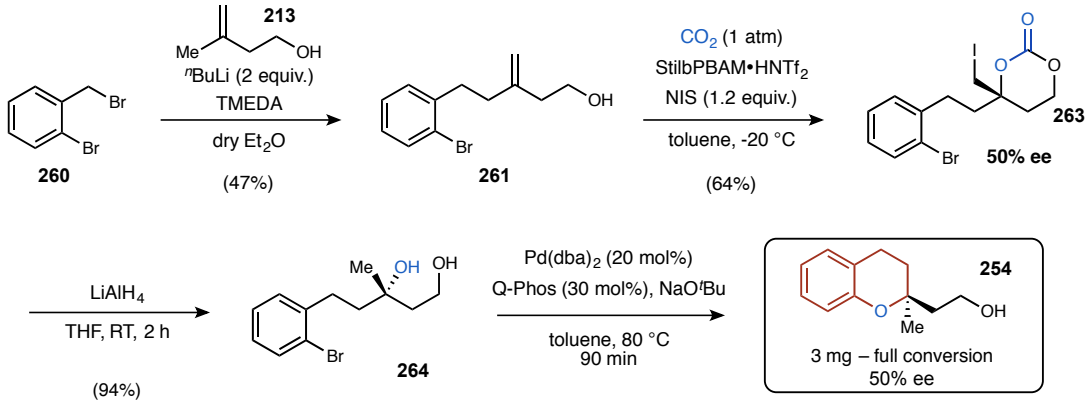


aliphatic substrates at -20 ºC (Scheme 78).

Optimization of the enantioselective iodocarbonation reaction remains needed, yet carbonate **263** (50% ee) was prepared to carry through to the final chroman. Reduction of this material with $LiAlH_4$ in dry THF went smoothly at room temperature, affording the desired diol in 94% yield (Scheme 79).

From this enantioenriched tertiary alcohol intermediate **264**, we first attempted the Hartwig conditions using palladium at room temperature. We were confident in this method since the authors explored a very similar substrate (Scheme 77), containing a tertiary alcohol and aryl bromide forming the tetrahydropyran in good yield. The developed protocol called for 5 mol % $Pd(dba)_2$ and 5 mol % Q-Phos (**259**), however, this failed to yield any product after several attempts (Scheme 79). After careful scrutiny, catalyst loading for palladium and Q-Phos was increased (20 and 30 mol%, respectively), NaO^tBu was increased (3 equiv.) and the reaction was heated at 80 °C for 90 minutes – full conversion was observed under the modified protocol. Chroman ethanol **254** (Scheme 79) was compared to its racemate (also synthesized using this

Scheme 79. Completion of the chiral BTHP core (**254**) via the enantioselective iodocarbonation reaction.



method) via chiral HPLC confirming enantioselection was maintained at 50% ee. Additional data acquired (NMR, IR) matched that of the previously reported compound.[191]

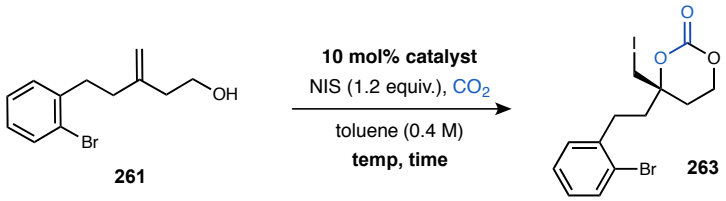
From commercially available starting materials, the enantioenriched chromane **254** can be reached in four synthetic steps using 1 atm of CO_2, a chiral non-racemic organocatalyst, and a final transition metal catalyzed etherification in overall good yield. In summary, the synthetic route (unoptimized) outlined in Scheme 79 illustrates the potential of this enantioselective approach to installing the critical tertiary ether moiety of BTHP natural products, in moderate to good yields and offers a complementary approach to literature precedent.

3.3.3 Optimization Attempts Employing Aliphatic Homoallylic Alcohols in the Enantioselective Iodocarbonation Reaction to Access Chromans

[191] Saito, N.; Ryoda, A.; Nakanishi, W.; Kumamoto, T.; Ishikawa, T. *Eur. J. Org. Chem.* **2008**, 2759.

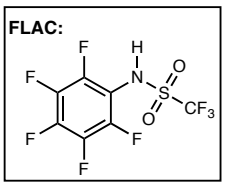
While we were able to successfully achieve the synthesis of the basic enantioenriched chroman scaffold from the chiral iodocarbonate precursor in 50% ee, significant reaction optimization for these aliphatic homoallylic alcohols was necessary to provide the needed iodocarbonate intermediates in higher levels of enantioselection in order to be synthetically applicable. Considering the extensive optimization events carried out at the beginning of this project using 3-methyl-3-buten-1-ol, approaching these aliphatic substrates as a general class

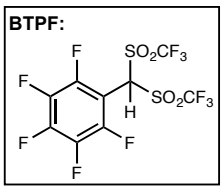
Table 19. The study of catalyst ligand, acid, and temperature combinations in order to increase ee for carbonate **263**.[a]

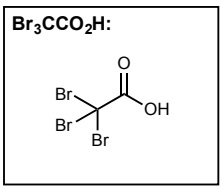


entry	ligand+counterion	temp (°C)	yield (%)[a]	ee (%)	rxn time (d)
1	StilbPBAM•$HNTf_2$	-50	23 (iso.)	70	6
2	StilbPBAM•$HNTf_2$	-20	67 (iso.)	50	3
3	PBAM•$HNTf_2$	-20	56	35	2
4	^{5}MeStilbPBAM•$HNTf_2$	-20	70	25	2
5	^{7}(MeO)StilbPBAM•$HNTf_2$	-20	60	20	2
6	StilbPBAM	-20	60	21	2
7	StilbPBAM•FLAC	-20	44	21	2
8	StilbPBAM•$C_3F_6NTf_2$	-20	60	41	2
9	StilbPBAM•BTPF	-20	65	40	4
10	StilbPBAM•Br_3CCO_2H	-20	95	42	4

[a]NMR yield was determined by the use of the internal standard, CH_2Br_2. 1 atm CO_2 employed. (iso.) = isolated yield







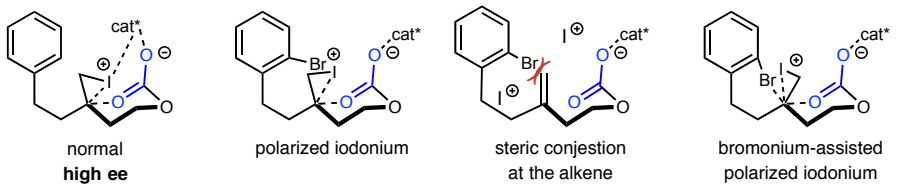
needs novel and innovative strategies to dramatically increase enantioselection. A simple screen of counterions for example would not suffice. The bromine atom in the *ortho* position obviously had an effect on ee as well and was another enigmatic factor to be cognizant of and overcome.

Predictably, cooling the reaction further to -50 °C resulted in an increase in ee up to 70% (as dictated by the Arrhenius equation) – this was the first and easiest modification to make in order to probe what temperatures would be tolerated (entry 1, Table 19). Notably, the solubility of NIS at this temperature was very low and the reaction proceeded at a prohibitively slow pace (6 days, 23% yield).

From here PBAM•$HNTf_2$ was examined and performed poorer at -20 °C than StilbPBAM•$HNTf_2$ (entry 3). Backbone modifications were then examined to investigate the sterics of the binding pocket(s). ^{5}MeStilbPBAM•$HNTf_2$ and ^{7}(MeO)StilbPBAM•$HNTf_2$ also performed poorly, yielding **263** in 25% and 20% ee, respectively. A newly developed achiral Brønsted acid FLAC (entry 7, Table 19) was examined, and StilbPBAM•FLAC acid salt was prepared, yet provided no benefit to the system. The strong carbon acid *bis*((trifluoromethyl)sulfonyl)methyl pentafluorobenzene (BTPF) developed by Yamamoto[192] was purchased and tested in the iodocarbonation reaction and also afforded the carbonate in low ee (40% ee, entry 9, Table 19).

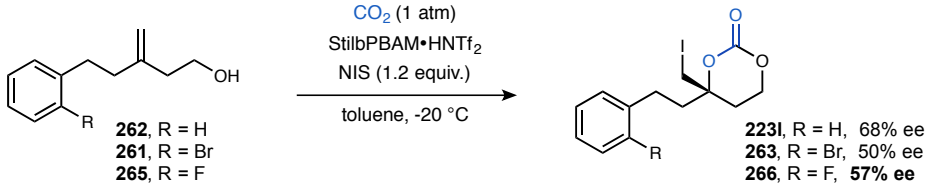
[192] Hasegawa, A.; Ishikawa, T.; Ishihara, K.; Yamamoto, H., *Bull. Chem. Soc. Jpn*. **2005**, *78*, 1401.

Figure 40. Proposed deleterious interactions of the *ortho*-bromoarene on the formation/stabilization of the iodonium.



These nominal studies suggest the bromine adversely affects this system, and perhaps interferes with the formation and/or stabilization of the iodonium intermediate. Conceptually, it possible that 1) the bromine disrupts the favorable energetic dynamics of the iodonium delivery or transition state, 2) polarizes the iodonium to more carbocation-like character at the benzylic position or 3) some combination of these factors through halogen-halogen-type interactions (Figure 40). Thus, facial selectivity of the incoming carbonic acid is more variable leading to the lower enantioselection observed. To disrupt this potential deleterious interaction, StilbPBAM•Br_3CCO_2H (entry 10, Table 19) was prepared and tested as a source of bromine that may disrupt Br–I intramolecular interactions or may assist in substrate catalyst/counterion Br–Br

Scheme 80. Comparisons of the various halogenated arene derivatives and resulting ee.



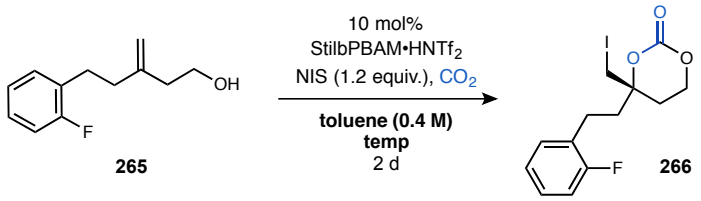
interactions. This catalyst system did not provide the carbonate in overall better ee (42% ee), but was in line with many of the best catalysts systems examined (i.e. entry 8, 40% ee, StilbPBAM•$C_3F_6NTf_2$; Table 19).

To further probe this notion of halogen-halogen interactions, a smaller, less electron-rich functional handle was installed in the *ortho*-position – the fluorine analogue **265** was prepared in

analogous fashion. In line with our hypothesis, **265** proved mildly better in the enantioselective iodocarbonation reaction than compared to the bromine alcohol **261**, yet still poorer than the saturated phenyl derivative **262** (Scheme 80). Fluorine could still be a competent functional handle through coupling reactions or S_NAr chemistry.

A reaction temperature of -50 °C could increase enantioselection to more synthetically

Table 20. Optimization attempts employing the fluorinated analogue **266**.[a]



entry	temp (ºC)	yield (%)	ee (%)	notes
1	-20	53	57	n/a
2	-50	12	84	4 d
3	-50	17	82	pulverized NIS
4	-50	12	85	3 equiv. NIS
5	-50	8	83	3 equiv. NIS+IPA (5 equiv.)
6	-50	14	85	1.3 equiv. NIS+IPA (5 equiv.)
7	-50	17	84	0.5 M
8	-50	21	80	0.7 M
9	-50	24	80	20 mol % cat.
10	-50	28	68	1.5 M
11	-50	35	62	2.0 M

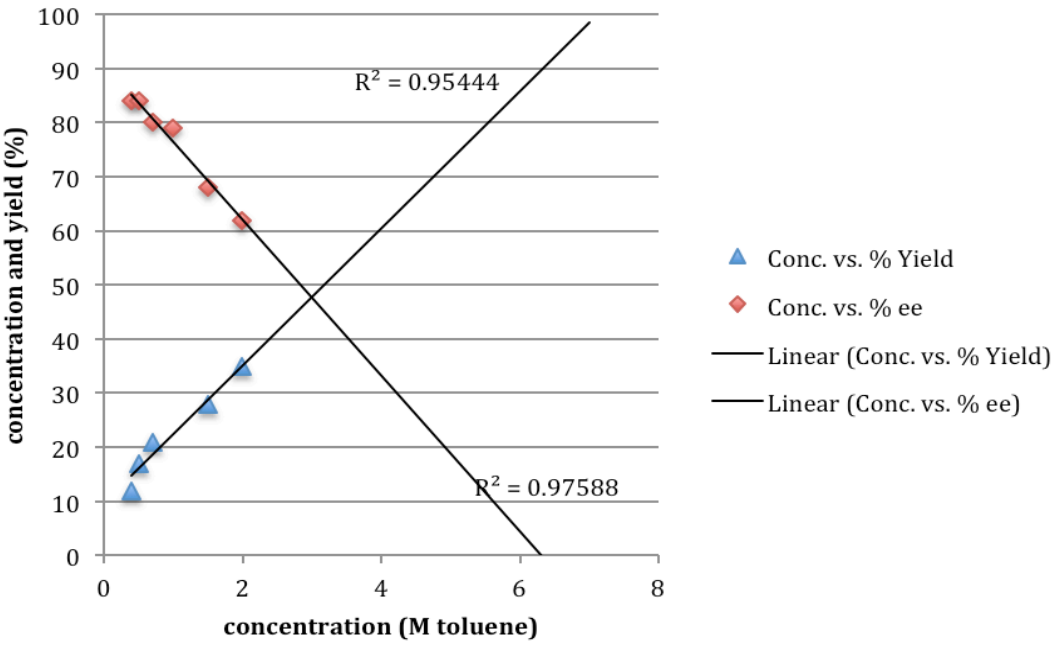
[a]Reaction conditions are outlined above and below the arrows unless stated otherwise. Isolated yields reported. ee determined by HPLC using a chiral stationary phase. 1 atm CO_2 employed.

useful levels, yet yield decreased. Employing alcohol **265** at -50 °C under the optimized iodocarbonation conditions afforded carbonate **266** in 84% ee – a significant improvement compared to all past aliphatic substrates, yet the yield was unfortunately low (12% yield) after 4 days (Table 20). Attempts to improve reaction yield was next pursued. It was evident that NIS was sparingly soluble in toluene at these temperatures and a number of tactics, such as

pulverizing the NIS, adding NIS in portions, and polar solvent additives, were employed to address this issue. These unfortunately resulted in only marginal improvements to chemical yield although enantioselection remained constant.

The concentration of the iodocarbonation reaction was next examined to explore 1) NIS solubility and 2) changes in enantioselection. Concentrating the reaction further to 0.5 M from 0.4 M in toluene at -50 °C resulted in slight improvement in yield (Table 20). This was pushed further and soon recognized an interesting inverse relationship between concentrations and enantioselection – as concentration was increased, yield improved (trendline R_2 = 0.997) yet

Chart 4. Relationship of concentration vs. enantioselection and yield in the iodocarbonation with fluorinated analogue **265**. Trendlines and R_2 values added for clarity.

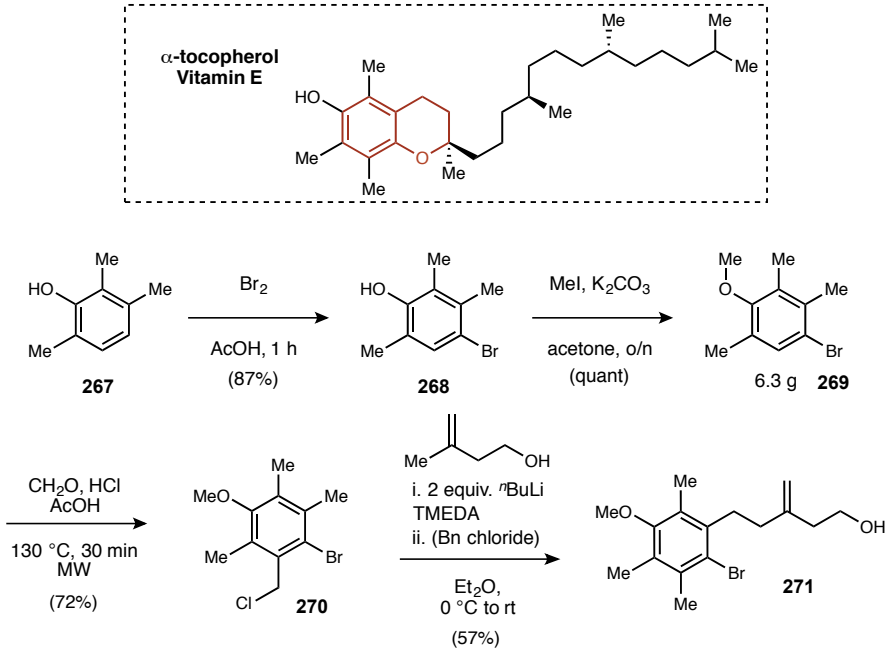


enantioselection decreased significantly (trendline R_2 = 0.976; Chart 4). This is analogous to what was observed in the iodocarbonation of styrene-derived homoallylic alcohols where higher concentrations generally improved the chemical yield. If we extrapolate these trendlines in order to reach desirable yields (100% yield) we arrive at very high concentrations (~7 M toluene) at

which point the ee would be near 0% or racemic. After this realization, this approach was no longer pursued.

As a final push to examine this carbon capture approach to enantioselective chroman formation, the steric effects of the brominated alcohol substrate was next explored. Perhaps if the pendant aryl halide (bromine) was more shielded from the forming iodonium during the halocyclization reaction, together with a favorable catalyst combination, enantioselection could improve. The decorated arylbromo alcohol **271** was prepared from a modified literature protocol on preparative scale (> 1g) – this iodocarbonate intermediate would be a direct oxygenated

Scheme 81. Decorated alcohol **271** was prepared and set the stage for the enantioselective iodocarbonation reaction.

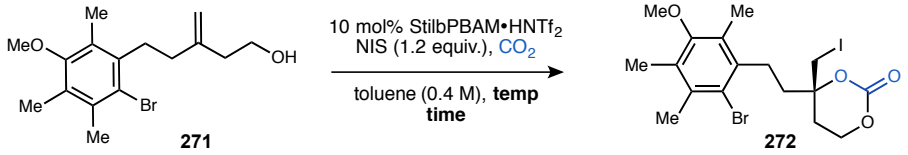


precursor to the vitamin E (α-tocopherol) chroman core (Scheme 81). After screening a host of catalysts and reaction modifications based on previous data (not all reaction data provided), only disappointing results were observed. Enantioselection for carbonate **272** topped out at 61% ee in

trace yield after 4 days (entry 3, Table 21). The insolubility of both NIS and alcohol **271** in this case was largely responsible for low yield.

At this stage it was apparent that simple catalyst, concentration, temperature, and additive adjustments to the enantioselective iodocarbonation reaction with aliphatic homoallylic alcohols were not effective in enhancing enantioselection. At present, the outlook is brightest if a new Brønsted basic ligand and/or achiral Brønsted acid combination is developed as an effective system for more challenging aliphatic homoallylic alcohols.

Table 21. Decorated arylbromo alcohol **271** tested under previously optimized conditions in the iodocarbonation reaction.



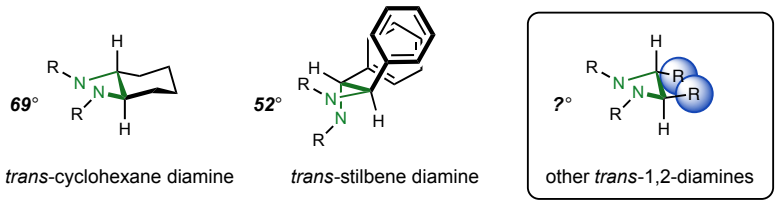
entry	temp (°C)	isolated yield	ee	notes
1	-20	61%	38%	2 d
2	-20	23%	41%	0.2 M, 4 d
3	-50	trace	61%	0.2 M, 4 d

3.4 AnthPBAM: Synthesis and Potential Applications of a New Chiral, C_2-Symmetric bis(Amidine) Organocatalyst

The ability to readily screen and examine a range of catalysts during reaction optimization and development has always been highly desired and is often necessary if projects are to be successful. Throughout the years, we have seen remarkable selectivity and specificity using the Brønsted basic *bis*(amidine) framework in the aza-Henry and iodocyclization reactions, yet it has been a longstanding goal to extend our knowledge of this catalyst substructure to

different systems. While examining various enantioselective reactions throughout my tenure in the group, it became evident that more diverse BAM ligands would be a nice addition to the catalyst library. Considering the dramatic stereoselectivity (and reactivity) effects observed when switching from *trans*-1,2-cyclohexandiamine to *trans*-stilbene diamine in the iodocyclization chemistry, it would be reasonable to explore additional chiral diamine backbones that present the

Figure 41. Common chiral 1,2-diamines employed in asymmetric catalysis and potential for different backbones



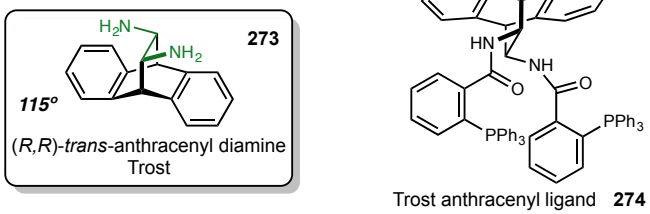
hydrogen-bonding BAM framework in a different orientation (Figure 41).

After investigating various potential chiral *trans*-1,2-dimaines, it was apparent that branching away from the two previously employed diamine backbones was going to be expensive. The enantiopure *trans*-diamine is derived from a mixture of *cis* and *trans* stereoisomers via a chiral resolution of this material using enantiomerically pure tartaric acid.

The chiral diamine **273**, derived from anthracene, has been used for some time as a chiral pool reagent. Seminal examples date back to the early 1990's when Barry Trost[193] used the diamine to assemble chiral phosphine ligands for palladium. The diamine has since been used in a number of asymmetric syntheses,[194] and is still used as an essential part of the chiral diamine ligands regularly screened in his group's chemistry (Trost anthracenyl ligand **274**, Figure 42).[195]

[193] Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int. Ed.* **1992**, *31*, 228.
[194] Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3492. Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2003**, *125*, 8744.
[195] Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092.

Figure 42. The anthracene-derived chiral 1,2-diamine **273** and its N-C-C-N dihedral angle. Also, the first application of this diamine to catalysis as the Trost ligand **274**.

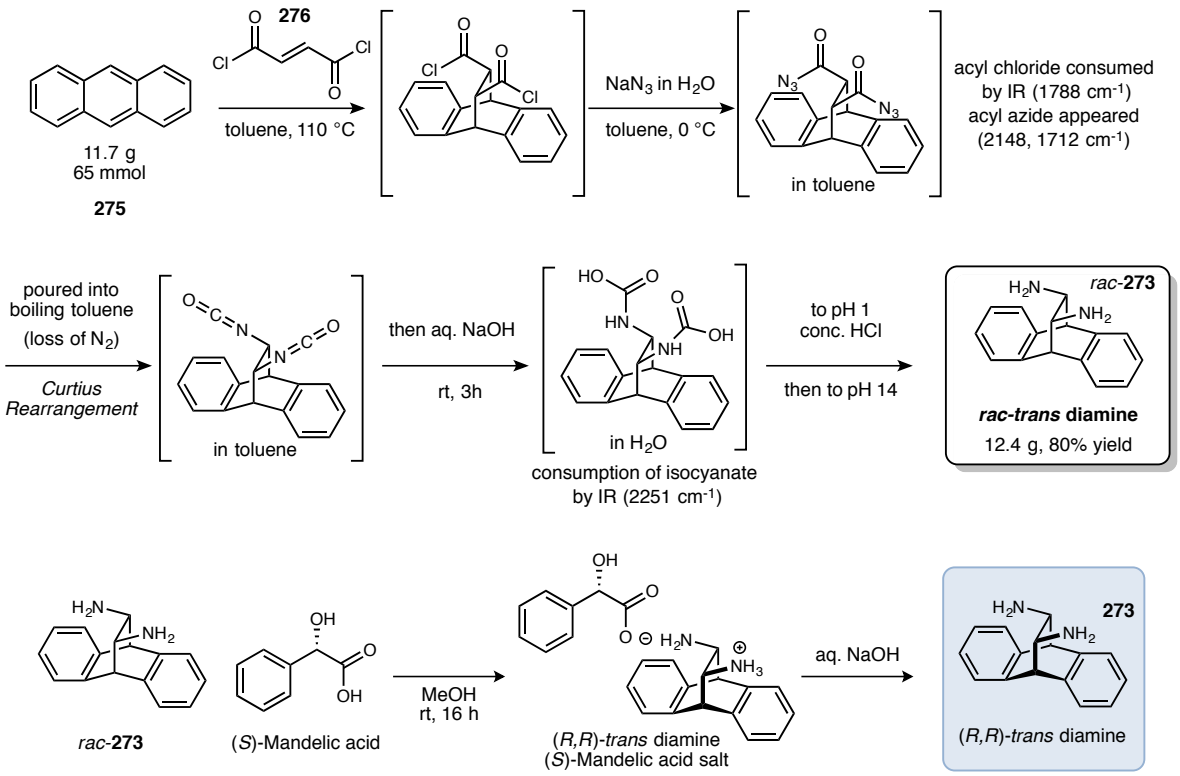


The diamine is commercially available from Sigma Aldrich yet is relatively expensive compared to other common diamines (Sigma, 1 gram for $538).[196]

This ligand presents one of the most rigid chiral diamine scaffolds available and essentially blocks an entire face of the catalyst (**273**, Figure 42). The N-C-C-N dihedral angle is, however, far larger than the other common chiral 1,2-diamines and these features collectively make for a very interesting chiral backbone. This ligand is reported to have an N-C-C-N dihedral angle of between 114.2-117.0º,[197] as compared to the *trans*-stilbene diamine and *trans*-cyclohexanediamine (52° and 69°, respectively, Figure 41). In the past we have thought it to be more worthwhile to use chiral diamines with smaller dihedral angles, yet in conjunction with the high rigidity and facial preference of this anthracenyl diamine, there is no clear way to predict selectivity and reactivity.

[196] Quote from Sigma Aldrich on November 14, 2015.
[197] Barrón-Jaime, A.; Aguirre, G.; Parra-Hake, M.; Chávez, D.; Madrigal, D.; Sanders, B.; Cooksy, A. L.; Somanathan, R. *J. Mex. Chem. Soc.* **2013**, *57*, 54.

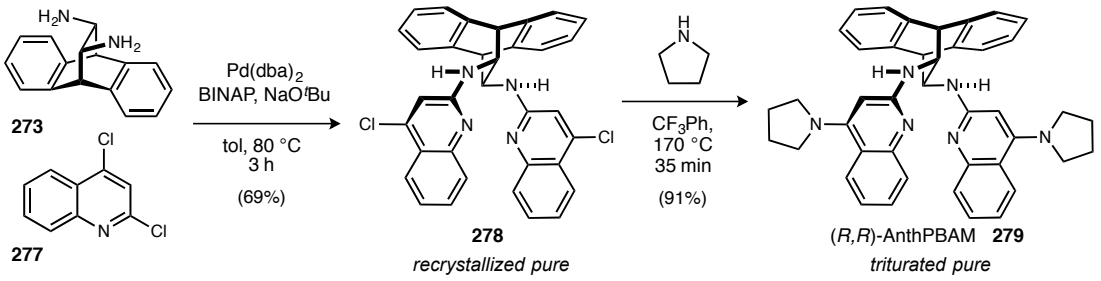
Scheme 82. The preparation of *rac*-**273** following known protocol and the chiral resolution to afford (*R,R*)-**273**. Non-isolable intermediates were followed by IR.



Fortunately, chemists at Chirotech (now a subsidiary of Dow Chemical) developed an improved protocol on preparative scale to access diamine **273** from cheap and readily available starting materials.[198] Anthracene **275** and fumaroyl chloride **276** are the two primary reagents employed. This procedure proved fruitful and ultimately afforded *rac*-**273** in 80% yield over 5 steps (no intermediates isolated). The enriched (*R,R*) enantiomer of **273** was ultimately isolated in great recovery following a chiral resolution using (*S*)-mandelic acid (Scheme 82). Over 7 grams of (*R,R*)-**273** were isolated as the (*S*)-mandelic acid salt (>$3,000.00 market value).

[198] Fox, M. E.; Gerlach, A.; Lennon, I. C.; Meek, G.; Praquin, C. *Synthesis-Stuttgart* **2005**, 3196.

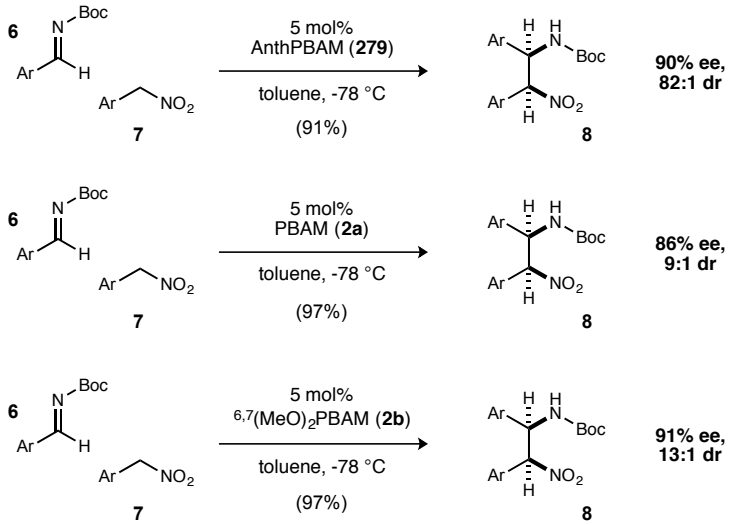
Scheme 83. Completion of (*R*,*R*)-AnthPBAM **279** from diamine **273**.



After breaking the salt, the enriched diamine **273** was subjected to standard Buchwald-Hartwig amination conditions with 2,4-dichloroquinoline to generate the desired amidine (4-Cl-AnthBAM **278**, Scheme 83). Due to the high rigidity and crystalline nature of this intermediate, **278** could be recrystallized to purity. Microwave-assisted S_NAr reaction with pyrrolidine went smoothly providing the final AnthPBAM free base catalyst **279** in 91% yield (no retro Diels-Alder adduct was observed). The free base subsequently was purified via trituration (see Experimental).

With this new chiral BAM ligand in hand, it was subjected to a variety of benchmark

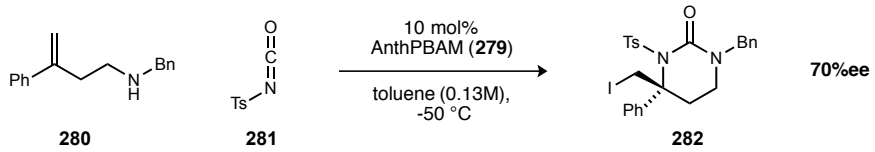
Scheme 84. Benchmarking AnthPBAM **279** in the aza-Henry reaction.[a] Ar = *p*-Cl-C_6H_4



[a]All reactions were 0.1 M in toluene for 24 h. The reaction mixtures were quickly filtered through silica gel and stereoselection was determined by chiral HPLC.

reactions developed in the group where BAM (or MAM) catalysts have previously shown efficacy. The catalyst was first examined in the aza-Henry reaction with *p*-Cl aryl Boc-imine and *p*-Cl aryl nitromethane (Scheme 84). As outlined, **279** performed remarkably well in this system when employed as the free base, affording the aza-Henry adduct **8** in very high levels of diastereoselection not seen with previous BAM catalysts (only MAM catalysts were more selective in this system). The other BAM catalyst results (**2a** and **2b**, previously optimized) are also included in Scheme 84.

Scheme 85. Moderate ee observed in the iodocyclization reaction using tosyl isocyanates (**281**).



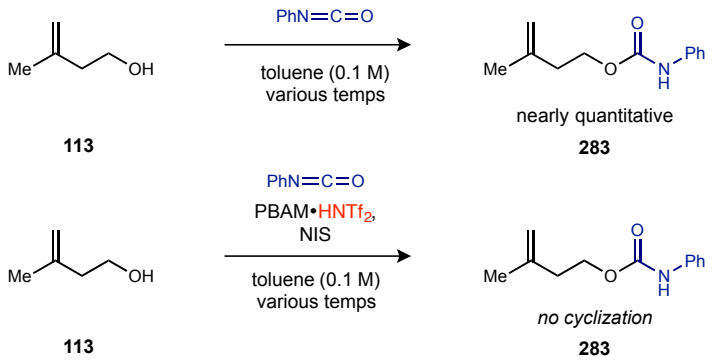
Testing **279** as the triflimide Brønsted acid salt in the iodolactonization and iodocarbonation chemistry, however, showed much lower efficacy compared to the stilbene-derived BAM catalysts. Reactivity was remarkably low (lower than PBAM free base) and for material that was isolated, stereoselection was also low (<15% ee). Interestingly, **279** (free base) was tested by a colleague in a reaction en route to the chiral iodourea **282**, and promising ee was observed (up to 70% ee, Scheme 85). These were perplexing results since the BAM free base catalysts have traditionally resulted in both low enantioselection and reactivity. Typically, the $HNTf_2$ catalyst salts are ideal and enantioselection is greatly improved. In this reaction however, **279**•$HNTf_2$ had no beneficial effect. This and other related projects are current ongoing.

3.5 Conclusion and Future Work

Having shown general success for an organocatalyzed, enantioselective CO_2-fixation reaction beginning from simple 1,1-disubstituted alkenes, one can imagine extending this work to include a wider breadth of preliminary electrophiles (and nucleophiles) other than CO_2 (i.e. using isocyanates as the preliminary electrophile, Scheme 85). There is a myriad of electrophile possibilities that could be employed for this chemistry, which is another attractive attribute of this 3-component, one pot approach to generate complexity via halocyclization chemistry. Mechanistically analogous to the CO_2-fixation strategy, upon initial nucleophilic attack to an electrophile, a nucleophilic anion (or protonated species, depending the Brønsted and electronic nature of the pronucleophile) is generated *in situ* and could suffice as a transient nucleophile primed for halocyclization. One could imagine various nucleophilic species to be amenable in this chemistry including nitrogen, sulfur, oxygen, or potentially carbon nucleophiles.

Prioir to the CO_2-fixation project in the Johnston group, isocyanates and imines were briefly explored in my hands – this data is however incomplete but may serve as a nice template for future projects. Following addition to the isocyanate (or imine) with a suitable nucleophile, a nucleophilic nitrogen species (and/or possibly oxygen in the case of isocyanates) is generated *in situ* and is now primed for halocyclization (Scheme 86).

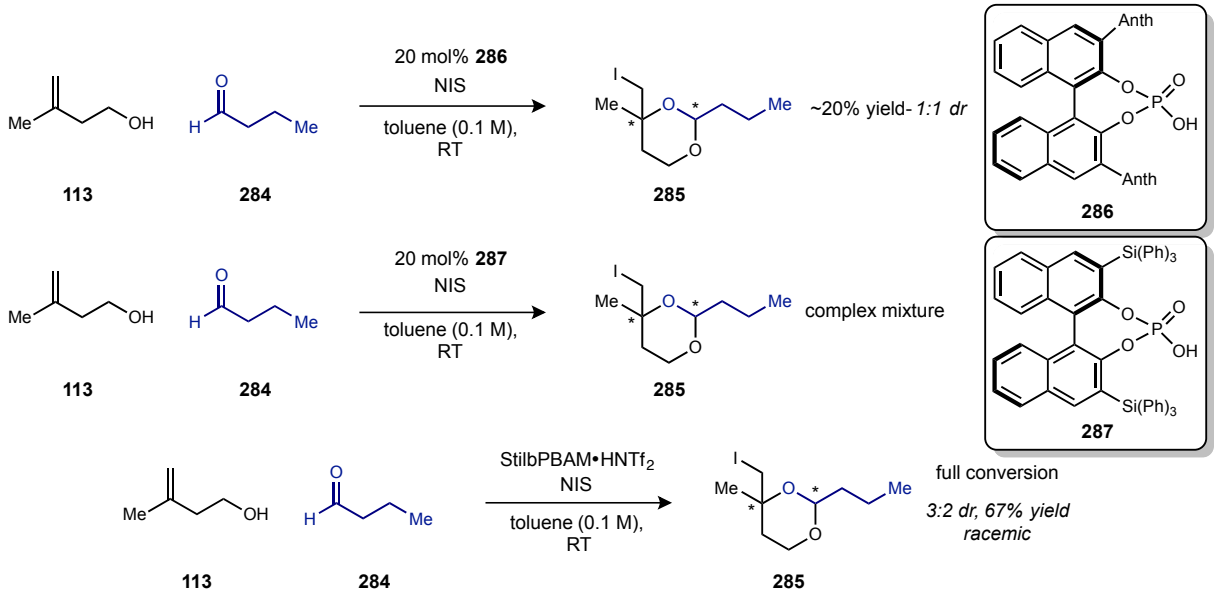
Scheme 86. Initial attempts at an asymmetric iodocyclization following capture of isocyanates



To date we had only seen success in the enantioselective halocyclization chemistry with carboxylate-derived groups and phophoramidates[199] bearing oxygen nucleophiles, but it could be posited that an imide, carbamate, or even aminal (–N–CR_2–OR) could be sterically and electronically similar to that of a carboxylic acid. Moreover, these groups could be readily tuned with the addition of electron donating or withdrawing groups to suit the reaction's needs. Not surprisingly, isocyanates proved to be viable electrophiles in the initial addition step but subsequent cyclization was never observed under these conditions. Aliphatic tosyl imines were also briefly explored (not pictured), but little desired product was seen after extensive reaction times. These imines upon cyclization would afford cyclic aminals and two non-contiguous stereocenters could be forged in the process.

Aldehydes were also subjected under analogous reaction conditions, the final product of which would yield acetals bearing two stereocenters (Scheme 87). Butyl aldehyde **284** was first examined, as this class of electrophiles compared to benzaldehyde derivatives are generally more

Scheme 87. Select reaction attempts to form iodoacetal **285**, although enantioselection could not ultimately be achieved.



[199] Toda, Y.; Pink, M.; Johnston, J. N. *J. Am. Chem. Soc.* **2014**, *136*, 14734.

reactive (at carbon, and do not require discrete Lewis/Brønsted acid activation) and would be better nucleophiles (at oxygen, pKa ~ 14-16, far less acidic than carboxylic acids) following the initial addition step. The reactivity profile for this reaction seemed to be suitable, for iodoacetal **285** was observed following *in situ* generation of the hemiaminal. A number of catalytic conditions were attempted – presumably the alcohol addition to the sp^2-hybridized aldehyde carbon would need to be stereoselectivity controlled as well, a challenging feat using a simple alcohol and the lack of facial differentiation of the aldehyde π-system (Scheme 87).

In this context, enantioselective acetalizations are rare, but a recent report from List is one of the few elegant examples using chiral Brønsted acids.[200] Modest levels of diastereoselection (4:1 dr at 0 °C) and yield (67%) were observed, however, the iodoacetal products were isolated as their racemates. The diastereoselection in this case is unlikely to come from catalyst control, but rather a favorable, lower energy 6-membered transition state that may exist before hemiacetal ring-opening of the iodonium. The ability to readily tune nucleophile acidity may be the most critical aspect critical to improving catalyst recognition and enantioselection in future reactions.

[200] Coric, I.; List, B. *Nature* **2012**, *483*, 315.

IV. Experimental

Experimental Section

All reagents and solvents were commercial grade and purified prior to use when necessary. Toluene (tol) and dichloromethane (CH_2Cl_2) were dried by passage through a column of activated alumina as described by Grubbs.[201] Aldimines not included were prepared as reported in the literature.[202] 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. IRA-900-NO_2 resin was prepared by washing IRA900-Cl resin with aq $NaNO_2$ until the wash no longer tested positive for chloride by a $AgNO_3$ test.

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 as neat films on a NaCl plate (transmission). Mass spectra were recorded on a Waters LCT spectrometer by use of the ionization method noted. Melting points were measured on a Meltemp melting point apparatus and are not corrected. Optical rotations were measured on a Perkin Elmer-341 polarimeter.

Absolute and relative configuration of the aza-Henry adducts were assigned by analogy to previously synthesized adducts, for which a crystal structure was obtained.[203]

PBAM (**2a**) and PBAM derivatives were prepared from previously detailed reports.[204] The purification of StilbPBAM (**133**), which was prepared according to the previously published procedure,[205] was carried out as follows: The resulting crude solid from the reaction was dissolved in dichloromethane and transferred to a 125 mL separatory funnel, washed with 6 M NaOH (50 mL) and water (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to provide a light brown solid (1.1 g, >95%). This solid was dissolved in benzene (70 mL) and precipitated by the slow addition of hexanes (80 mL) over 5 min to the

[201] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Organometallics **1996**, *15*, 1518.
[202] Kanazawa, A. M.; Denis, J.; Greene, A. E. *J. Org. Chem*. **1994**, *59*, 1238.
[203] Davis, T.A.; Johnston, J.N. *Chem. Sci.* **2011**, *2*, 1076.
[204] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076. Davis, T.A.; Dobish, M.C.; Schwieter, K.E.; Chun, A.C.; Johnston, J.N. *Org. Synth.* **2012,** *89,* 380.
[205] Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068.

stirring slurry at rt. The solid was filtered with hexanes to provide a light tan solid (700 mg, 62%). Analytical data matches that previously reported in the literature.[205]

General Procedure for Preparation of Aldoximes[206]

Aldehyde (1.00 mmol), hydroxyl amine hydrochloride (1.20 mmol), pyridine (1.80 mmol), and ethanol (333 μL) were combined in a flask at room temperature. The mixture was stirred for 1-20 h and ethanol was evaporated under reduced pressure. The mixture was diluted with EtOAc, washed twice with 1 M aq HCl, once with satd aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a white crystalline solid. Flash column chromatography was carried out if needed.

General Procedure for Preparation of Aryl Nitroalkanes

The aldoxime (1.00 mmol), MCPBA (2.0-3.0 mmol), and CH_2Cl_2 (1.0 mL) were combined in a flask at room temperature. The reaction was monitored by TLC or ^1H NMR and after 1-3 d the mixture was quenched with satd aq $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, MeOH/dichloromethane) of the residue provided the title compound.

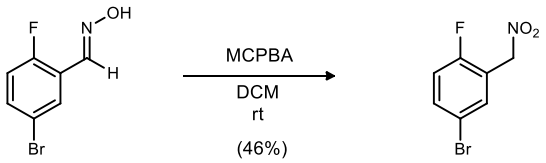
General Procedure for Enantioselective aza-Henry Additions

Imine (100 μmol) and $^{3,5}(CF_3)_2$BenzMAM (**68**) (2.8 mg, 5.0 μmol) were dispensed into a flame-dried vial with a stir bar. Toluene (1.0 mL) was added, and the reaction was stirred at room temperature until homogeneous. The reaction mixture was chilled to -78 °C before the nitroalkane (110 μmol) was added. The reaction mixture was warmed to -20 °C and stirred for 18-60 h. The chilled mixture was either diluted with CH_2Cl_2 to dissolve precipitate and quickly flushed through a pad of silica gel or diluted with cold hexanes and filtered through a Buchner funnel with filter paper. Vacuum filtration with cold hexanes resulted in analytically pure material. If added to silica, the pad was flushed with CH_2Cl_2, and the filtrate was concentrated and the residue purified by column chromatography (SiO_2, ethyl acetate in hexanes), if needed.

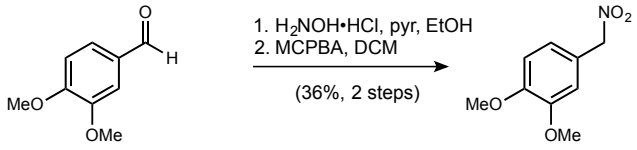
General procedure for preparing racemic aza-Henry addition product for chiral HPLC assay development.

[206] Goverdhan, K.L. *Green Chemistry* **2001**, 3, 275.

Imine (100 μmol) and the nitroalkane (110 μmol) were dispensed into a flame-dried vial with a stir bar. CH_2Cl_2 (1.0 mL) and DMAP (~20 μmol) were added, and the reaction was stirred at room temperature until the reaction was complete by TLC (0.5-5 h). The solvent was evaporated and the residue was purified by column chromatography (SiO_2, ethyl acetate in hexanes).

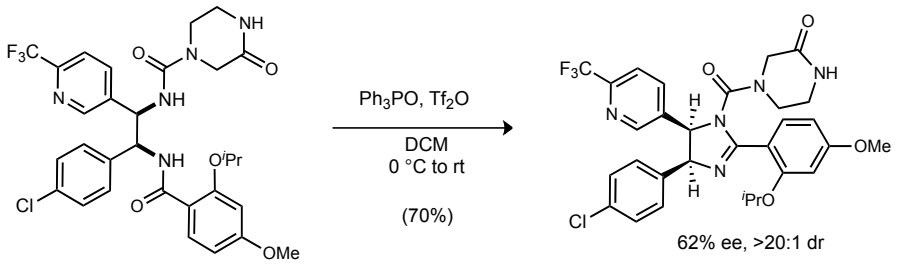


5-Bromo-2-fluoro-(nitromethyl)benzene (7d). Aldoxime (1.01 g, 4.63 mmol), MCPBA (1.60 g, 9.27 mmol), and dichloromethane were combined in a flask at room temperature. After 48 h, the mixture was quenched with satd aq $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0-2% methanol in dichloromethane) of the residue provided the compound as a bronze oil (502 mg, 46%). R_f = 0.85 (CH_2Cl_2); IR (film) 3074, 2915, 2369, 1761, 1560, 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.06 (t, J = 8.8 Hz, 1H), 5.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.6 (d, $^1J_{CF}$ = 251 Hz), 135.2, 134.8 (d, $^3J_{CF}$ = 3 Hz), 119.0 (d, $^2J_{CF}$ = 16 Hz), 117.7 (d, $^2J_{CF}$ = 23 Hz), 116.9 (d, $^3J_{CF}$ = 4 Hz), 72.2 (d, $^3J_{CF}$ = 3 Hz); HRMS (APCI): Exact mass calcd for $C_7H_5BrFNO_2$ $[M]^+$ 232.9482, found 232.9476.



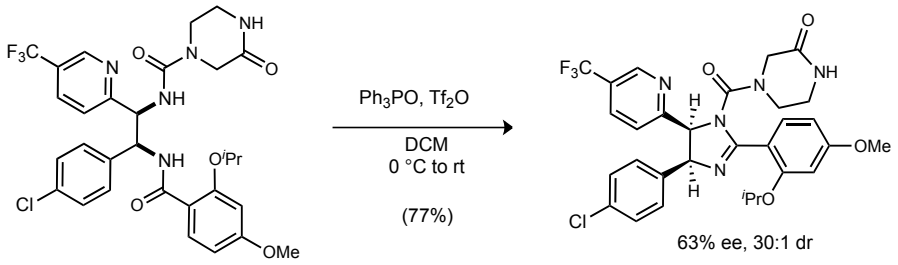
1,2-Dimethoxy-4-(nitromethyl)benzene (7h). Aldehyde (3.0 g, 18.0 mmol), hydroxyl amine hydrochloride (1.50 g, 21.7 mmol), pyridine (2.62 mL, 32.5 mmol), and ethanol (6.0 mL) were combined in a flask at room temperature. The mixture was stirred for 15 h and ethanol was evaporated under reduced pressure. The mixture was diluted with EtOAc, washed twice with 1 M aq HCl, once with satd aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a white crystalline solid. This material was carried on without further

purification. The aldoxime (3.30 g, 18.2 mmol), MCPBA (6.29 g, 36.4 mmol), and CH_2Cl_2 (18 mL) were combined in a flask at room temperature. After 18 h, the mixture was quenched with satd aq $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, dichloromethane) of the residue provided the compound as a yellow solid (1.26 g, 36%). Mp = 66-67 ºC; R_f = 0.9 (CH_2Cl_2); IR (film) 3016, 2948, 2838, 1554, 1506, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 2.0, 1.6 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.36 (s, 2H), 3.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 150.3, 149.2, 123.0, 122.1, 112.6, 111.1, 79.9, 55.9 (2C); HRMS (CI): Exact mass calcd for $C_9H_{11}NO_4$ [M]+ 197.0604, found 197.0602.

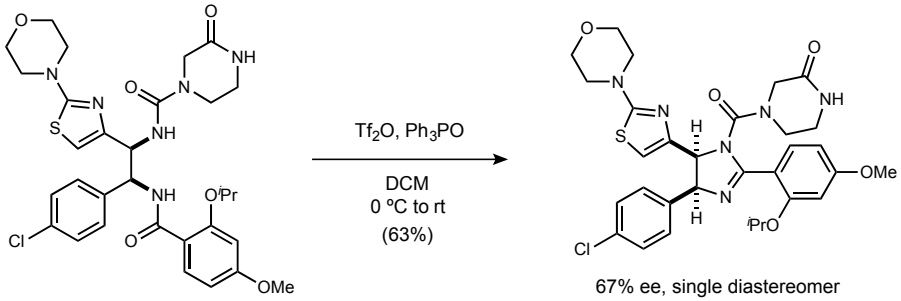


2-Trifluoromethyl pyridine-*cis*-imidazoline (22). Tf_2O (23 µL, 140 µmol) was added to a stirring solution of Ph_3PO (79 mg, 284 µmol) in CH_2Cl_2 (510 µL) at 0 °C. The mixture was stirred for 10 min before the urea (45.0 mg, 71.0 µmol) was added as a solution in CH_2Cl_2 (1.7 mL) and the mixture was stirred at 0 °C and slowly warmed to rt over 2 h. Tf_2O (23 µL, 140 µmol) was then added and stirred for an additional 90 min. The reaction mixture was quenched with satd aq $NaHCO_3$ at room temperature, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 2-5% methanol in dichloromethane) of the residue provided the title compound as a white solid (30.0 mg, 70%). $[\alpha]_D^{20}$ -19 (*c* 0.25, $CHCl_3$); mp 124-125 °C; R_f = 0.54 (10% MeOH in CH_2Cl_2); IR (film) 3250 (br), 2938, 2848, 2356, 2092, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 6.60 (s, 1H), 6.55 (dd, *J* = 8.8, 1.0 Hz, 1H), 6.46 (d, *J* = 1.0 Hz, 1H), 5.69 (dd, *J* = 9.6, 9.6 Hz, 2H), 4.60 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.84 (s, 3H), 3.74 (d, *J* = 18.4 Hz, 1H), 3.50-3.47 (m, 2H), 3.13-3.10 (m, 1H), 3.02-2.96 (m, 2H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.29 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.7, 163.4, 160.0, 157.1, 154.5, 148.7, 146.9 (q, $^2J_{CF}$ = 35 Hz), 136.0, 135.8, 135.1, 133.4, 132.6,

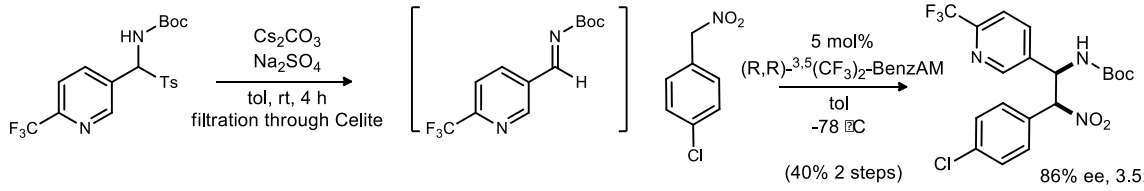
132.1, 131.9 (q, $^{3}J_{CF}$ = 17 Hz), 129.1, 128.4, 121.3 (q, $^{1}J_{CF}$ = 272 Hz),119.3, 112.7, 104.7, 100.0, 71.5, 71.1, 67.5, 55.6, 49.7, 42.1, 40.0, 22.0; HRMS (ESI): Exact mass calcd for $C_{30}H_{30}ClF_3N_5O_4$ $[M+H]^+$ 616.1938, found 616.1927.



5-Trifluoromethyl pyridine-*cis*-imidazoline (23). Tf_2O (38 µL, 227 µmol) was added to a stirring solution of Ph_3PO (127 mg, 454 µmol) in CH_2Cl_2 (500 µL) at 0 °C. The mixture was stirred for 10 m before the urea (72.0 mg, 114 µmol) was added as a solution in CH_2Cl_2 (811 µL) and the mixture was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature before addition of satd aq $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (0-6% methanol in dichloromethane) of the residue provided the compound as a white solid (54 mg, 77%). Mp 136-137 ^{o}C; R_f = 0.67 (10% MeOH in CH_2Cl_2); IR (film) 3250 (br), 2938, 2848, 2356, 2092, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.60 (m, *J* = 8.0, 1.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.56 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.48 (d, *J* = 2.0 Hz, 1H), 6.40 (br s, 1H), 5.90 (d, *J* = 10.4 Hz, 1H), 5.65 (d, *J* = 10.4 Hz, 1H), 4.58 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.84 (s, 3H), 3.83-3.67 (m, 2H), 3.34 (d, *J* = 3.6 Hz, 2H), 3.07 (m, 2H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.33 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.1, 159.7, 157.1, 154.8, 145.6, 135.7, 133.1, 132.2, 132.0, 129.1, 128.5, 127.9, 121.7, 113.2, 104.6, 100.3, 71.2, 69.9, 68.0, 55.5, 49.0, 42.0, 40.3, 22.1, 22.0; HRMS (CI): Exact mass calcd for $C_{30}H_{30}ClF_3N_5O_4$ $[M+H]^+$ 616.1938, found 616.1964.

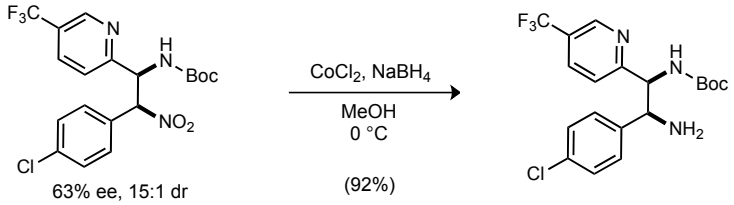


2-Morpholinothiazole (–)-*cis*-imidazoline (24). Tf_2O (10 µL, 60 µmol) was added to a stirring solution of Ph_3PO (33.0 mg, 120 µmol) in CH_2Cl_2 (100 µL) at 0 °C. The mixture was stirred for 10 min before the urea (20.1 mg, 30.6 µmol) was added as a solution in CH_2Cl_2 (300 µL) and the mixture was stirred at 0 °C and warmed to room temperature over 19 hours. Tf_2O (23 µL, 140 µmol) was then added and stirred for an additional 2 hours. The reaction mixture was quenched with $NaHCO_3$ at rt, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 2-5% methanol in dichloromethane) of the residue provided the product as a yellow oil (12.0 mg, 63%). $[\alpha]_D^{20}$ -42 (*c* 0.50, $CHCl_3$); R_f = 0.57 (10% MeOH/CH_2Cl_2); IR (film) 3212 (br), 3100, 2976, 2920, 2846, 2363, 2332, 1681, 1613, 1520, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.32 (s, 1H), 6.00 (s, 1H), 5.60 (d, *J* = 10.0 Hz, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 4.56 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.93 (d, *J* = 18.0 Hz, 1H), 3.84 (s, 3H), 3.66 (d, *J* = 18.0 Hz, 1H), 3.65 (t, 4.8 Hz, 4H), 3.48-3.42 (m, 1H), 3.26-319 (m, 1H), 3.10 (t, *J* = 4.8 Hz, 4H), 3.10-2.05 (m, 2H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 170.6, 166.9, 162.8, 159.9, 157.0, 154.8, 148,3, 137.1, 132.5, 131.9, 129.2, 127.4, 113.9, 104.6, 104.5, 100.5, 71.2, 71.1, 66.0, 65.5, 55.5, 49.7, 48.3, 41.5, 40.6, 22.1 (2C); HRMS (ESI): Exact mass calcd for $C_{31}H_{36}ClN_6O_5S$ $[M+H]^+$ 639.16, found 639.2151. BAV-I-281



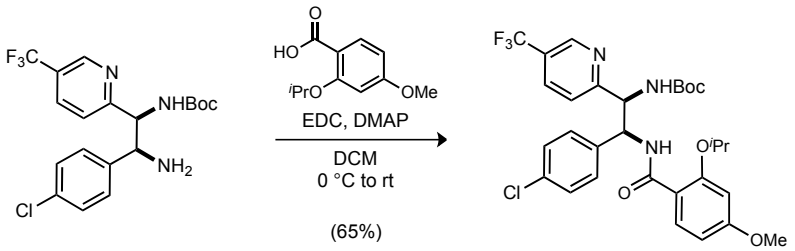
***tert*-Butyl ((1*S*,2*S*)-2-(4-chlorophenyl)-2-nitro-1-(5-(trifluoromethyl)pyridin-2-yl)ethyl)carbamate (35)**. To a flame dried flask was added the sulfone (50.0 mg, 116 µmol),

Na_2SO_4 (131 mg, 928 μmol), Cs_2CO_3 (189 mg, 581 μmol), and toluene (1.5 mL) at rt. The mixture was vigorously stirred for 4 h. The solution was filtered through a Celite plug with excess CH_2Cl_2 and concentrated down to toluene (1.5 mL) with a stream of air. (*R,R*)-$^{3,5}(CF_3)_2$-BenzMAM (3.3 mg, 6.0 μmol) was stirred into solution until solvated. The solution was chilled to -78 °C before the addition of the nitroalkane (10.2 mg, 60.0 μmol). After stirring at -78 °C for 24 hours, the mixture was immediately filtered through a plug of silica and concentrated. Column chromatography (SiO_2, 5-10% ethyl acetate in hexanes) afforded a white solid (10 mg, 40% over 2 steps). The major diastereomer was determined to be 86% ee and the minor to be 85% ee, with 3.5:1 dr determined by chiral HPLC (Chiralcel AD-H: 8% ^{i}PrOH/hexanes, 1.0 mL/min; at 20 min ramped to 25% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1,$ major/major) = 9.2 min, $t_r(d_1e_2,$ major/minor) = 10.0 min, $t_r(d_2e_1,$ minor/major) = 14.5 min, $t_r(d_1e_2,$ major/minor) = 61.0 min). Mp 128-129 °C; R_f = 0.74 (25% ethyl acetate/hexanes); IR (film) 3357 (br), 2979, 2928, 1700, 1569, 1487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.58-7.53 (m, 3H), 7.40 (d, *J* = 8.0 Hz, 2H), 5.94-5.92 (m, 2H), 5.18 (dd, *J* = 8.8, 8.8 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) ppm 159.9, 154.2, 146.8 (q, $^3J_{CF}$ = 4 Hz), 136.5, 134.5, 130.3, 129.9, 129.3 (q, $^3J_{CF}$ = 5 Hz), 129.1, 126.7 (q, $^2J_{CF}$ = 33 Hz), 124.5, 123.2 (q, $^1J_{CF}$ = 271 Hz), 92.2, 80.7, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{19}ClF_3N_3NaO_4$ $[M+Na]^+$ 468.0914; found 468.0899.

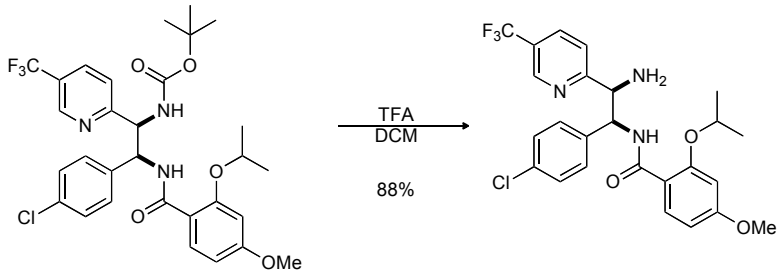


***tert*-Butyl ((1*S*,2*S*)-2-amino-2-(4-chlorophenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)ethyl)carbamate (39)**. The nitroalkane (150 mg, 337 μmol) was dissolved in MeOH (1.4 mL) at room temperature. $CoCl_2$ (44.0 mg, 337 μmol) was added and the reaction mixture was chilled to 0 °C before $NaBH_4$ (63.0 mg, 1.68 mmol) was added in three portions over 40 m. The reaction mixture was stirred at 0 °C for an additional 30 m before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc. aq NH_4OH. The mixture was filtered through a glass frit, washed with water, then excess CH_2Cl_2, dried with $MgSO_4$ and concentrated to white solid (129 mg, 92%). Mp 139-140 °C; R_f = 0.50 (50% ethyl

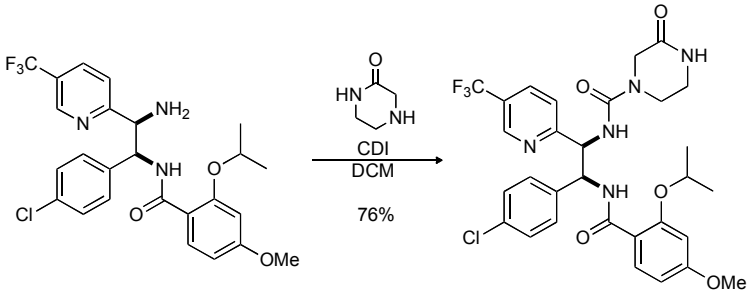
acetate/hexanes); IR (film) 3376, 3306, 2973, 2924, 1704, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.97 (br d, 1H), 5.01 (br dd, 1H), 4.51 (br d, 1H), 1.92-1.90 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.1, 155.2, 146.0, 145.9, 140.2, 133.3, 133.2, 128.5, 128.4, 128.3, 123.3, 79.9, 60.6, 59.0, 53.4, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}ClF_3N_3O_2$ $[M+H]^+$ 416.1353, found 416.1361.



***tert*-Butyl ((1*S*,2*S*)-2-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(5-(trifluoromethyl)pyridin-2-yl)ethyl) carbamate (40).** The amine (119 mg, 286 μmol) and carboxylic acid (60.1 mg, 286 μmol) were dissolved in CH_2Cl_2 (1.5 mL) at room temperature. The solution was chilled to 0 °C and EDC (71.3 mg, 372 μmol) and DMAP (4 mg, 29 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 ($MgSO_4$), and concentrated. The resulting white solid was washed with a 1:6 mixture CH_2Cl_2/hexanes, leaving behind a white solid (112.0 mg, 65%) that was pure by ^1H NMR. Mp 152-153 °C (dec.); R_f = 0.80 (50% EtOAc/hexanes); IR (film) 3347, 3061, 2980, 2924, 2336, 2332, 1697, 1634, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 5.83-5.82 (m, 1H), 5.29-5.27 (m, 1H), 4.75 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.84 (s, 3H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.4, 163.4, 161.5, 157.1, 155.1, 145.9 (q, $^4J_{CF}$ = 3 Hz), 137.2, 134.2, 133.5 (q, $^3J_{CF}$ = 12 Hz), 128.8 (q, $^4J_{CF}$ = 5 Hz), 128.5, 128.3, 125.7 (q, $^2J_{CF}$ = 34 Hz), 123.4 (q, $^1J_{CF}$ = 270 Hz), 123.2, 115.4, 105.1, 100.3, 80.12, 71.8, 71.6, 58.8, 57.0, 55.5, 28.3 28.1, 22.1; HRMS (ESI): Exact mass calcd for $C_{30}H_{33}ClF_3N_3NaO_5$ $[M+Na]^+$ 608.2139, found 608.2123.

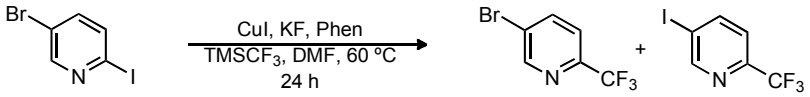


***N*-((1*S*,2*S*)-2-Amino-1-(4-chlorophenyl)-2-(5-(trifluoromethyl)pyridin-2-yl)ethyl)-2-isopropoxy-4-methoxybenzamide (41)**. The amide (110.0 mg, 181.0 μmol) was dissolved in CH_2Cl_2 (1.80 mL) and TFA (554 μL, 7.24 mmol) was added and the mixture and was stirred at room temperature for 16 h. The 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 (80.0 mg, 88%). R_f = 0.21 (15% ethyl acetate in hexanes); IR (film) 3353, 3060, 2912, 2842, 1636, 1598, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 8.0 Hz, 1H), 8.74 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.82 (dd, *J* = 1.0, 8.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 8.8, 2.4Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 5.57 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.77 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.55 (d, *J* = 5.2 Hz, 1H), 3.84 (s, 3H), 1.59 (br, 2H), 1.50 (d, *J* = 6.0 Hz, 3H), 1.49 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.8, 163.3, 157, 2, 134.0, 133.2, 128.8, 128.3, 106.7, 105.1, 105.0, 100.7, 100.3, 100.2, 73.9, 71.5, 55.7, 55.5, 29.7, 22.2, 22.1; HRMS (ESI): Exact mass calcd for $C_{25}H_{26}ClF_3N_3O_3$ $[M+H]^+$ 508.1615, found 508.1612.



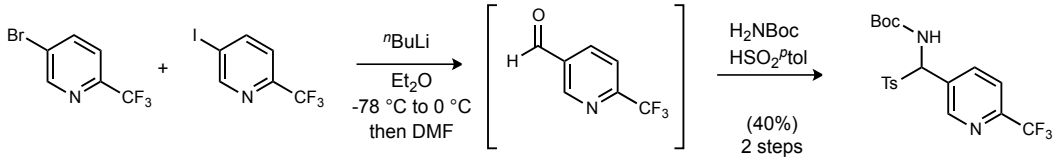
***N*-((1*S*,2*S*)-2-(4-Chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(5-(trifluoromethyl)pyridin -2-yl)ethyl)-3-oxopiperazine-1-carboxamide (42).** The amine (76.0 mg, 149 μmol) was dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature. CDI (28.9 mg, 179 μmol) was added and the reaction was stirred for 1 h. 2-Oxo-piperazine (30.0 mg, 300 μmol) was added, and the reaction mixture was stirred for an additional 4 h. The reaction mixture

was concentrated and purified by column chromatography (0-5% methanol in dichloromethane) to provide a white solid (72.0 mg, 76%). Mp 163-165 °C (dec.); R_f = 0.39 (10% MeOH/CH_2Cl_2); IR (film) 3351 (br), 3240, 2930, 1642, 1605, 1538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.51 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.77 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.12-7.08 (m, 3H), 6.78 (br s, 1H), 6.57-6.54 (m, 2H), 6.46 (d, *J* = 2.0 Hz, 1H), 5.91 (dd, *J* = 4.0, 4.8 Hz, 1H), 5.52 (dd, *J* = 4.0, 3.2 Hz, 1H), 4.69 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.05 (d, *J* = 3.6 Hz, 2H), 3.83 (s, 3H), 3.64-3.63 (m, 2H), 3.38-3.36 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.4, 165.8, 163.6, 161.2, 157.1, 156.0, 145.8, 144.3, 137.0, 134.3, 133.5, 128.6, 128.3, 123.2, 114.6, 105.2, 100.3, 93.4, 71.4, 59.3, 57.1, 55.5, 53.4, 47.5, 40.9, 40.0, 22.0, 21.8; HRMS (CI): Exact mass calcd for $C_{30}H_{32}ClF_3N_5O_5$ $[M+H]^+$ 634.2044, found 634.2069.

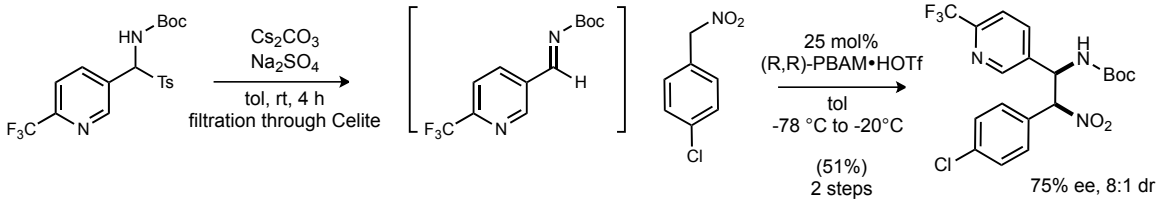


5-Bromo-2-(trifluoromethyl)pyridine (47, 48). CuI (141 mg, 742 μmol), 1,10-phenanthroline (133 mg, 742 μmol), and potassium fluoride (862 mg, 14.8 mmol) were combined under an inert atmosphere. This mixture was treated with 5-bromo-2-iodo-pyridine (2.10 g, 7.42 mmol) and DMF (14.8 mL) and subjected to two freeze-pump-thaw cycles (40 min each) using N_2. To the stirred solution was added trimethyl(trifluoromethyl)silane (2.18 mL, 14.8 mmol) at room temperature, and the mixture was heated to 60 °C under argon for 24 h. The reaction mixture was cooled to room temperature and quenched with water. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed twice with ice water, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (0-2% diethyl ether in hexanes) of the brown solid provided a 3:1 mixture of compounds as white crystals (1.215 g, 72% yield). Mp 57-58 °C; R_f = 0.43 (10% Et_2O/hexanes); IR (film) 3109, 3042, 1977, 1555 cm^{-1}; 5-Bromo-2-(trifuoromethyl)pyridine: ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.59 (d, *J* = 8.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 151.4, 146.6, 140.0, 121.9, 121.7; LRMS (APCI): Exact mass calcd for $C_6H_4BrF_3N$ $[M+H]^+$ 225.99, found 226.0. 5-Iodo-2-(trifuoromethyl)pyridine: ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, *J* = 2.0 Hz, 1H), 8.21 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.47 (d, *J* = 8.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 151.2,

145.8, 129.4, 124.0; LRMS (APCI): Exact mass calcd for $C_6H_4F_3IN$ $[M+H]^+$ 272.99, found 273.0.

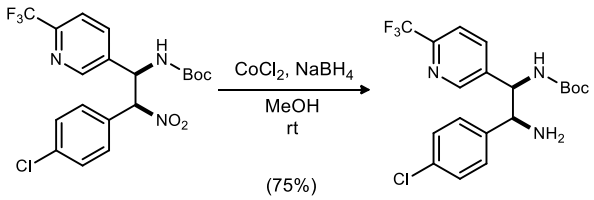


***tert*-Butyl (tosyl(6-(trifluoromethyl)pyridin-3-yl)methyl)carbamate (49).** To a flame-dried flask was added the halo trifluoromethylpyridine (825 mg, 3.31 mmol) as a 3:1 mixture dissolved in diethyl ether (12 mL) at room temperature. The solution was chilled to -78 °C before the slow addition of *n*-butyllithium (1.55 mL, 3.97 mmol, 2.56 M in hexanes). After 40 min, DMF (380 µL, 4.97 mmol) was added to the solution at -78 °C and stirred for 20 m. The mixture was gradually warmed to 0 °C, before quenching with satd aq $NaHCO_3$ at 0 °C. The aqueous layer was extracted with diethyl ether and the organic layers were combined, washed twice with ice water, dried ($MgSO_4$), and concentrated to diethyl ether (35 mL). The carbamate (387 mg, 3.31 mmol) and *p*-toluene sulfinic acid (620 mg, 3.97 mmol) were added to the solution, followed by dichloromethane (6 mL) and stirred for 2 d at room temperature or until an appreciable amount of precipitate had formed. The reaction mixture was cooled to 0 °C and filtered to recover the precipitate as a white solid (587 mg, 40% yield over 2 steps). Mp 175-176 °C; R_f = 0.4 (50% EtOAc/hex); IR (film) 3357, 3067, 2980, 2957, 1715, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.01 (d, *J* = 10.8 Hz, 1H), 5.79 (d, *J* = 10.8 Hz, 1H), 2.45 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 153.4, 150.1, 149.0 (q, $^2J_{CF}$ = 36 Hz), 146.0, 137.8, 132.8, 130.0, 129.7, 129.5, 121.2 (q, $^1J_{CF}$ = 273 Hz), 120.3, 81.9, 71.4, 27.9, 21.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}F_3N_2O_4S$ $[M+H]^+$ 431.1251, found 431.1261.



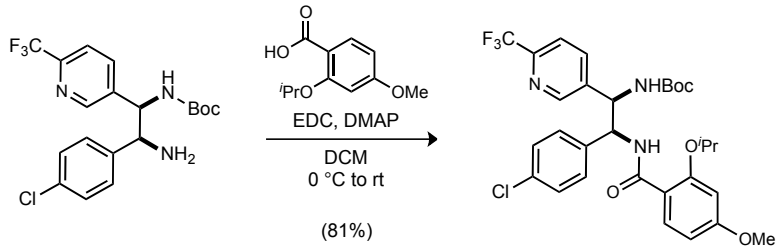
***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-2-nitro-1-(6-(trifluoromethyl)pyridin-3-yl)ethyl)carbamate (50).** To a flame dried flask was added the sulfone (40 mg, 93 µmol),

Na_2SO_4 (106 mg, 744 μmol), Cs_2CO_3 (241 mg, 744 μmol), and toluene (1.0 mL) at rt. The mixture was vigorously stirred for 4 h and then filtered through a plug of Celite with excess DCM and concentrated to a toluene (1 mL) solution with a stream of air. PBAM•HOTf (15.3 mg, 23.3 μmol) was stirred in solution until solvated, chilled to -78 °C, and reacted with the nitroalkane (17.5 mg, 102 μmol). After stirring at -78 °C for 24 h, the mixture was warmed to -20 °C and stirred for 2 h. The solution was then filtered through a plug of silica and concentrated. Column chromatography (SiO_2, 10% ethyl acetate in hexanes) of the residue afforded a white solid (21 mg, 51% over 2 steps). The major diastereomer was determined to be 75% ee and the minor to be 65% ee, 8:1 dr determined by chiral HPLC (Chiralcel IA: 10% ^{i}PrOH/hexanes, 0.8 mL/min: $t_r(d_1e_1$ major/minor) = 12.7 min, $t_r(d_1e_2$ major/major) = 13.7 min, $t_r(d_2e_1$ minor/major) = 23.2 min, $t_r(d_1e_2$ minor/minor) = 38.8 min). Mp 160-161°C; R_f = 0.50 (25% EtOAc/hexanes); IR (film) 3385 (br), 2984, 2922, 2362, 1685, 1553 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 5.97 (br d, 1H), 5.61 (dd, J = 9.6, 9.2 Hz, 1H), 5.00 (br d, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 149.3, 148.4 (q, $^2J_{CF}$ = 36 Hz), 137.0, 136.6 (q, $^3J_{CF}$ = 3 Hz), 129.8, 129.7, 129.5, 129.3, 121.0, (q, $^1J_{CF}$ = 273 Hz), 120.6, 92.0, 81.6, 54.7, 28.1, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClF_3N_3O_4$ $[M+H]^+$ 446.1094, found 446.1108.



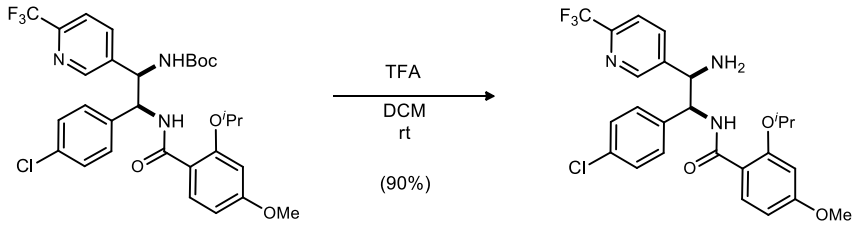
***tert*-Butyl ((1*R*,2*S*)-2-amino-2-(4-chlorophenyl)-1-(6-(trifluoromethyl)pyridin-3-yl)ethyl)carbamate (51).** The nitroalkane (168 mg, 378 μmol) was dissolved in MeOH (4.2 mL) at room temperature. $CoCl_2$ (49.0 mg, 337 μmol) was added and the reaction mixture was chilled to 0 °C before $NaBH_4$ (71.4 mg, 1.88 mmol) was added in three portions over 30 min. The reaction mixture was stirred at 0 °C for an additional 30 min before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc. aq NH_4OH. The

mixture was filtered through a glass frit, washed with water, and the aqueous layer was collected. The remaining solid was thoroughly washed with CH_2Cl_2 and collected in a separate flask. The organic solution was dried ($MgSO_4$) and concentrated to a white solid that was pure by ^{1}H NMR (118 mg, 75%). Column chromatography (SiO_2, 40-60% ethyl acetate in hexanes) of the residue yielded the desired diastereomer (80 mg, >30:1 dr by ^{1}H NMR). $[\alpha]_D^{20}$ -15 (*c* 0.35, $CHCl_3$); Mp 139-140 °C; R_f = 0.55 (50% EtOAc/hexanes); IR (film) 3341 (br), 2980, 2924, 2356, 1697, 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 5.65 (br s, 1H), 4.92 (br s, 1H), 4.34 (s, 1H), 1.60 (br s, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 149.1, 147.3 (q, $^2J_{CF}$ = 35 Hz), 139.5, 136.5, 133.8, 128.8, 128.0, 127.9, 121.5 (q, $^1J_{CF}$ = 273 Hz), 120.1, 119.7, 80.4, 58.7, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}ClF_3N_3O_2$ $[M+H]^+$ 416.1353, found 416.1350.

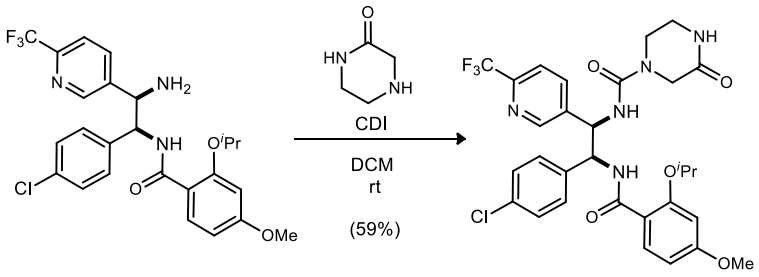


***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(6-(trifluoromethyl)-pyridin-3-yl)ethyl)carbamate (52).** The amine (80.0 mg, 192 μmol) and carboxylic acid (40.4 mg, 192 μmol) were dissolved in CH_2Cl_2 (1.0 mL) at room temperature. The solution was chilled to 0 °C and EDC (44.1 mg, 230 μmol) and DMAP (2.35 mg, 19.2 μmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature over 2 h. After 17 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water, satd aq $NaHCO_3$, and again with water. The organic layer was dried ($MgSO_4$) and concentrated to a white solid (93 mg, 81%). $[\alpha]_D^{20}$ -0.85 (*c* 0.39, $CHCl_3$); Mp 232-233 °C (dec.); R_f = 0.83 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 6.8 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.60 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.51 (s, 1H), 6.46 (s, 1H), 5.90 (d, *J* = 6.0 Hz, 1H), 5.14 (br, 2H), 4.67 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.85 (s, 3H), 1.40 (s, 9H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.4, 164.4, 161.5, 158.1, 155.1, 146.2 (q, $^4J_{CF}$ = 3 Hz), 137.2, 134.8, 133.5

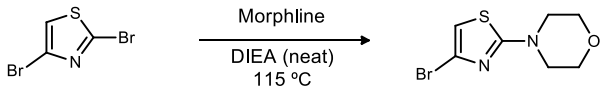
(q, $^{3}J_{CF}$ = 12 Hz), 128.8 (q, $^{4}J_{CF}$ = 5 Hz), 128.5, 128.9, 123.5 (q, $^{2}J_{CF}$ = 33 Hz), 123.4 (q, $^{1}J_{CF}$ = 270 Hz), 123.2, 115.6, 105.1, 100.1, 80.3, 71.8, 71.1, 58.8, 57.0, 55.5, 28.3, 22.1; HRMS (ESI): Exact mass calcd for $C_{30}H_{33}ClF_3N_3NaO_5$ $[M+Na]^+$ 630.1959, found 630.1952.



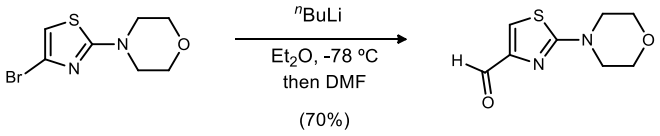
***N*-((1*S*,2*R*)-2-Amino-1-(4-chlorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-2-isopropoxy-4-methoxybenzamide (53)**. The amide (71.0 mg, 120 μmol) was dissolved in CH_2Cl_2 (3.0 mL). TFA (357 μL, 4.67 mmol) was added and the mixture was stirred at room temperature for 22 h. The reaction mixture was diluted with CH_2Cl_2, poured into satd aq $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a golden oil of 76% purity (65 mg, 90% mass recovery) by ^{1}H NMR. R_f = 0.57 (25% EtOAc/hexanes); IR (film) 3365 (br), 2981, 2921, 2847, 2361, 2334, 1647, 1607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.47 (s, 1H), 8.09 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 1.2 Hz, 1H), 5.59 (br s, 2H), 4.71 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.82 (s, 3H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.22 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.2, 157.2, 149.3 (q, $^{3}J_{CF}$ = 3 Hz), 147.4 (q, $^{2}J_{CF}$ = 35 Hz), 136.3, 136.2, 128.9, 121.4 (q, $^{1}J_{CF}$ = 272 Hz), 120.0, 106.7, 105.3, 100.3, 73.9, 71.6, 60.3, 55.7, 55.5, 29.7, 22.0, 21.9; HRMS (ESI): Exact mass calcd for $C_{25}H_{26}ClF_3N_3O_3$ $[M+H]^+$ 508.1615, found 508.1596.



***N*-((1*R*,2*S*)-2-(4-Chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-3-oxopiperazine-1-carboxamide (54).** The amine (65 mg, 128 μmol) was dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature. CDI (24.9 mg, 154 μmol) was added and the reaction was stirred for 3 h. 2-Oxo-piperazine (25.6 mg, 256 μmol) was added, and the reaction mixture was stirred for an additional 12 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, 2-4% methanol in dichloromethane) to provide a white solid (48 mg, 59%). $[\alpha]_D^{20}$ -150 (*c* 0.82, $CHCl_3$); mp 189-190 °C (dec); R_f = 0.35 (10% MeOH/CH_2Cl_2); IR (film) 3350, 3242, 2978, 2930, 2849, 2247, 1645, 1605, 1537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.0 Hz, 1H), 8.40 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 4.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0, 1H), 7.31 (d, *J* = 8.0, 2H), 7.01 (br d, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 1H), 6.44 (s, 1H), 5.86 (dd, *J* = 7.6, 2.4 Hz, 1H), 5.20 (m, 1H), 4.64 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.13 (s, 2H), 3.84 (s, 3H), 3.66-3.64 (m, 1H), 3.60 (m, 1H), 3.38-3.36 (m, 2H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.8, 167.6, 164.2, 157.3, 155.9, 149.5, 147.3 (q, $^3J_{CF}$ = 34 Hz), 137.2, 135.9, 134.4 (2C), 129.0, 128.1, 121.4 (q, $^1J_{CF}$ = 273 Hz) 119.6, 113.0, 105.6, 100.3, 71.6, 60.7, 57.3, 53.4, 47.4, 41.0, 40.0, 21.9, 21.5; HRMS (ESI): Exact mass calcd for $C_{30}H_{31}ClF_3N_5NaO_5$ $[M+Na]^+$ 656.1864, found 656.1833.



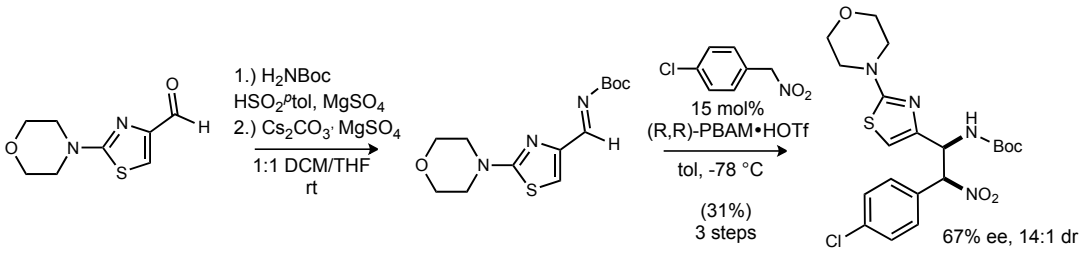
4-(4-Bromothiazol-2-yl)morpholine (56). General procedure adapted from patent precedence by Kan *et al.*[207] 2,4-Dibromothiazole (1.00 g, 4.12 mmol), morpholine (356 µL, 4.12 mmol), and diisopropyl ethylamine (3.17 mL) were combined in a reaction flask at room temperature under an argon. The reaction mixture was vigorously stirred at 115 °C (conventional heating) for 5 h, cooled to room temperature, diluted with H_2O, and extracted with ethyl acetate. The organic layers were combined, washed with ice water, dried ($MgSO_4$), filtered, and concentrated to a brown oil. Column chromatography (SiO_2, 10-40% ethyl acetate in hexanes) of the residue yielded a white powder (753 mg, 73%). Mp 61-62 °C; R_f = 0.11 (10% Et_2O/hexanes); IR (film) 3115, 2963, 2893, 2849, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 1H), 3.80 (t, *J* = 4.8 Hz, 4H), 3.46 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.0, 121.8, 104.0, 66.0, 48.0; LRMS (APCI): Exact mass calcd for $C_7H_{10}BrN_2OS$ $[M+H]^+$ 247.9624, found 247.9620. BAV-I-214



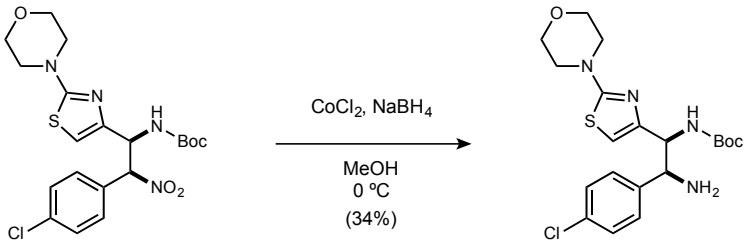
2-Morpholinothiazole-4-carbaldehyde (57). General procedure adapted from Reider *et al.*[208] To a flame-dried flask was added the substrate (750 mg, 3.01 mmol) dissolved in diethyl ether (15 mL) at room temperature. The solution was chilled to -78 °C before slowly adding of *n*-butyllithium (2.56 M in hexanes, 1.41 mL, 3.61 mmol). After stirring for 50 min, DMF (466 µL, 6.02 mmol) was added to the solution at -78 °C and gradually warmed to 0 °C after 20 min. The reaction mixture was quenched with $NaHCO_3$ at 0 °C and the aqueous layer was extracted with diethyl ether. The organic layers were combined and washed twice with ice water, dried ($MgSO_4$), and concentrated. Column chromatography (SiO_2, 60% ethyl acetate in hexanes) of the residue yielded a light yellow oil (416 mg, 70% yield). R_f = 0.13 (50% Et_2O/hexanes); IR (film) 3458, 3084, 2959, 2917, 2855, 2369, 1683, 1551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.50 (s, 1H), 3.82 (t, *J* = 4.8 Hz, 4H), 3.54 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$)

[207] Kan, J.; Coate, H.; Chen, X. U.S. *Patent 2009197862*, **2009**.
[208] Reider, P.; Wang, X. *Tet. Lett.* **2000**, *41*, 4335.

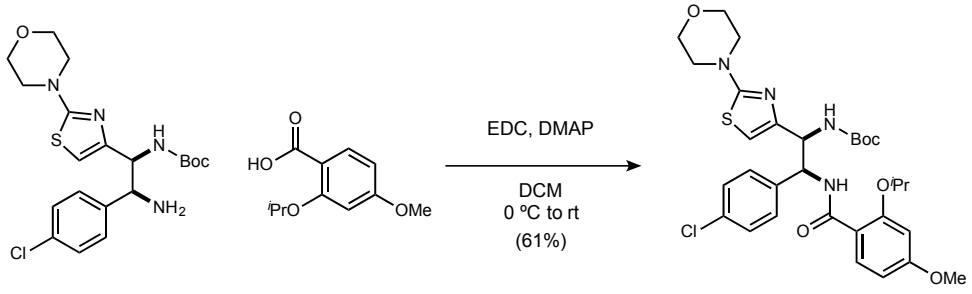
ppm 184.0, 171.6, 152.5, 120.8, 66.0, 48.5; LRMS (APCI): Exact mass calcd for $C_8H_{11}N_2O_2S$ $[M+H]^+$ 197.0390, found 197.0396.



***tert*-Butyl ((1*S*,2*S*)-2-(4-chlorophenyl)-1-(2-morpholinothiazol-4-yl)-2-nitroethyl)carbamate (60).** To a flame dried flask was added the aldehyde (75.0 mg, 379 μmol), $MgSO_4$ (41.0 mg, 341 μmol), $HSO_2{}^pTol$ (65.0 mg, 417 μmol), H_2NBoc (48.8 mg, 417 μmol), and 1:1 CH_2Cl_2/THF (3.8 mL) at rt. The mixture was stirred and monitored by ^1H NMR. After 24 h, Cs_2CO_3 (256 mg, 758 μmol) and $MgSO_4$ (45 mg, 379 μmol) were added and the mixture was vigorously stirred for 150 min. The reaction mixture was filtered through a plug of Celite with excess CH_2Cl_2 and concentrated to a brown oil containing a mixture of the carbamate, aldehyde, and imine (majority % comp. by ^1H NMR). The flask was backfilled with argon, diluted with toluene (2.8 mL), and PBAM•HOTf (25.0 mg, 42.0 μmol) was added to the stirring solution at rt. The solution was chilled to -78 °C before the addition of the nitroalkane (48.0 mg, 280 μmol). After stirring at -78 °C for 24 h, the mixture was warmed to -20 °C and stirred for 2 h. The solution was filtered directly through a plug of silica with DCM and concentrated. Column chromatography (SiO_2, 25-30% ethyl acetate in hexanes) of the residue afforded the product as an off-white foam (54 mg, 31% over 3 steps). The major diastereomer was determined to be 67% ee and the minor to be 65% ee, with 14:1 dr determined by chiral HPLC (Chiralcel IC: 7% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$ major/major) = 16.6 min, $t_r(d_1e_2$ major/minor) = 21.7 min, $t_r(d_2e_1$ minor/major) = 22.8 min, $t_r(d_1e_2$ minor/minor) = 24.7 min). R_f = 0.73 (50% EtOAc/hexanes); IR (film) 3420 (br), 2972, 2917, 2855, 2351, 1710, 1551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 6.51 (s, 1H), 5.75 (d, J = 10.0 Hz, 1H), 5.62 (t, J = 10.0 Hz, 1H), 5.06 (d, J = 9.2 Hz, 1H), 3.81-3.76 (m, 4H), 3.46-3.42 (m, 4H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.1, 154.1, 147.6, 135.9, 130.3, 130.1, 128.8, 128.7, 105.5, 92.7, 80.0, 65.9, 48.3, 28.1, 27.9; HRMS (ESI): Exact mass calcd for $C_{20}H_{26}ClN_4O_5S$ $[M+H]^+$ 469.1313, found 469.1317.

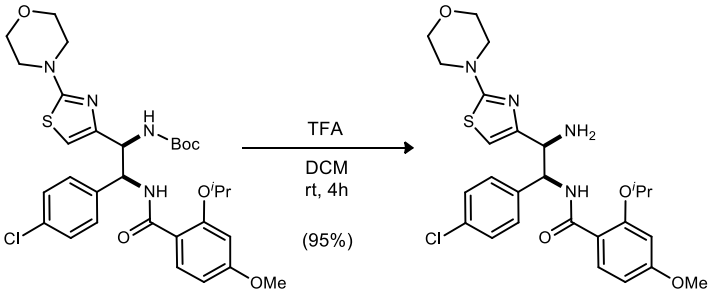


***tert*-Butyl ((1*S*,2*S*)-2-amino-2-(4-chlorophenyl)-1-(2-morpholinothiazol-4-yl)ethyl)carbamate (61).** The nitroalkane (125 mg, 267 μmol) was dissolved in MeOH (1.5 mL) at room temperature. $CoCl_2$ (34.6 mg, 267 μmol) was added and the reaction mixture was chilled to 0 °C before $NaBH_4$ (50.5 mg, 1.34 mmol) was added in three portions over 30 min. The reaction mixture was stirred at 0 °C for an additional 30 m before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc. aq NH_4OH. The mixture was filtered through a glass frit and washed with water. The remaining solid was thoroughly washed with CH_2Cl_2 and collected in a separate flask. The organic solution was dried ($MgSO_4$) and concentrated to a foam. Column chromatography (SiO_2, 60-100% ethyl acetate in hexanes) of the residue afforded the product as a tan oil (40 mg, 34%). R_f = 0.53 (100% EtOAc); IR (film) 3363 (br), 2973, 2925, 2850, 2357, 1707, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.14 (m, 4H), 6.08 (s, 1H), 5.44 (br d, 1H), 4.69 (br d, 2H), 4.30 (s, 1H), 4.10 (d, *J* = 3.6 Hz, 1H), 3.85-3.70 (m, 4H), 3.49-3.35 (m, 4H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.8, 154.9, 141.0, 132.6, 129.1, 128.5 (2C), 128.0, 104.6, 66.1, 58.9, 48.5, 28.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{28}ClN_4O_3S$ $[M+H]^+$ 439.1571, found 439.1593.



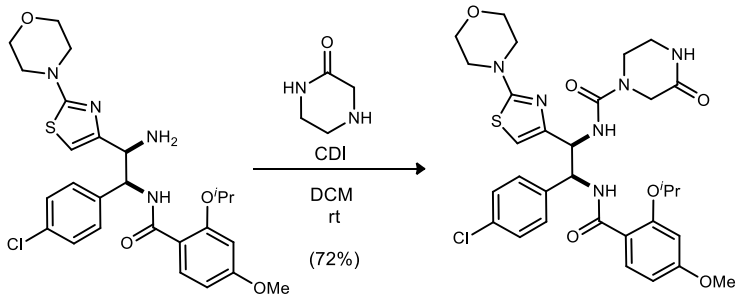
***tert*-Butyl ((1*S*,2*S*)-2-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(2-morpholinothiazol-4-yl)ethyl)carbamate (62).** The amine (35.0 mg, 79.7 μmol) and carboxylic acid (16.8 mg, 79.7 μmol) were dissolved in CH_2Cl_2 (0.5 mL) at room temperature. The solution was chilled to 0 °C and EDC (20.0 mg, 104 μmol) and DMAP (1 mg, 8 μmol) were added. The reaction mixture was stirred and allowed to warm to room temperature. After 17 h, the reaction

mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated to a yellow oil. Column chromatography (SiO_2, 50% ethyl acetate in hexanes) of the residue afforded the desired compound as a white solid (30 mg, 61%). Mp 164-165 °C; R_f = 0.32 (50% EtOAc/hexanes); IR (film) 3389 (br), 2973, 2917, 2841, 2349, 1717, 1655, 1606, 1516, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 1H), 6.07 (s, 1H), 5.72 (dd, *J* = 4.4, 3.2 Hz, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 5.00 (dd, *J* = 4.4, 3.2 Hz, 1H), 4.69 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.76 (t, *J* = 4.4 Hz, 4H), 3.38 (t, *J* = 4.4 Hz, 4H), 1.42 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.6, 165.3, 163.1, 156.9, 155.1, 149.6, 137.9, 133.8, 128.8, 128.5, 128.3, 128.2, 116.6, 105.3, 104.3, 101.0, 79.9, 71.9, 66.0, 56.6, 55.5, 48.4, 28.3, 22.2, 22.0; HRMS (ESI): Exact mass calcd for $C_{31}H_{40}ClN_4O_6S$ $[M+H]^+$ 631.2357, found 631.2338.

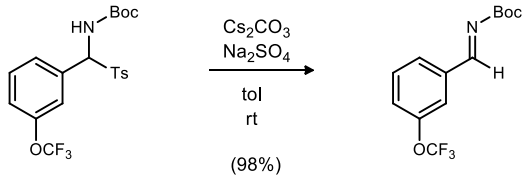


***N*-((1*S*,2*S*)-2-Amino-1-(4-chlorophenyl)-2-(2-morpholinothiazol- 4-yl)ethyl)-2-isopropoxy-4-methoxybenzamide (63)**. The Boc-amide (29 mg, 46 μmol) was dissolved in CH_2Cl_2 (0.5 mL). TFA (106 μL, 1.37 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2, poured into satd aq $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a golden oil. Column chromatography (SiO_2, 50-100% ethyl acetate in hexanes) of the residue provided the title compound as a golden oil and as a single diastereomer (23 mg, 95%). $[\alpha]_D^{20}$ -61 (*c* 0.29, $CHCl_3$); R_f = 0.44 (10% MeOH/CH_2Cl_2); IR (film) 3382, 2966, 2924, 2848, 2238, 1655, 1606, 1523, 1499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 6.0 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.12 (s, 1H), 5.63 (br s, 1H), 4.75 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.36 (br d, 1H), 3.83 (s, 3H), 3.78 (t, *J* = 4.8 Hz, 4H), 3.39 (t, *J* = 4.4 Hz, 4H), 2.15 (m, 2H),

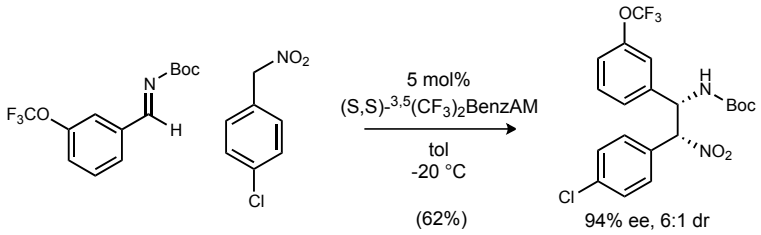
1.48 (d, J = 6.0 Hz, 3H), 1.45 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.6, 164.8, 163.2, 157.2, 137.7, 134.0, 132.7, 128.9, 127.9, 115.8, 105.1, 103.0, 100.6, 77.1, 76.9, 71.6, 66.1, 55.5, 48.5, 29.7, 22.2, 22.1; HRMS (ESI): Exact mass calcd for $C_{26}H_{32}ClN_4O_4S$ $[M+H]^+$ 532.0780, found 532.0761.



***N*-((1*S*,2*S*)-2-(4-Chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(2-morpholinothiazol-4-yl)ethyl)-3-oxopiperazine-1-carboxamide (64).** The free amine (23 mg, 43 μmol) was dissolved in CH_2Cl_2 (1.0 mL) and stirred at room temperature. CDI (8.4 mg, 52 μmol) was added and the reaction was stirred for 3 h. 2-Oxo-piperazine (8.6 mg, 86 μmol) was added, and the reaction mixture was stirred for an additional 18 hours. The reaction mixture was washed with water, and the organic layer was concentrated and purified by column chromatography (SiO_2, 1-4% methanol in dichloromethane) to afford the product as a yellow foam (25 mg, 72%). $[\alpha]_D^{20}$ -38 (*c* 0.21, $CHCl_3$); R_f = 0.42 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 6.56 (dd, J = 8.8, 2.0 Hz, 1H), 6.53 (br s, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.08 (s, 1H), 6.04 (d, J = 7.6 Hz, 1H), 5.75 (dd, J = 7.6, 3.6 Hz, 1H), 5.25 (dd, J = 7.6, 3.6 Hz, 1H), 4.67 (qq, J = 6.0, 6.0 Hz, 1H), 3.99 (s, 2H), 3.83 (s, 3H), 3.72 (t, J = 4.4 Hz, 4H), 3.64 (br d, J = 1.6 Hz, 2H), 3.38 (br d, J = 2.0 Hz, 2H), 3.29 (t, J = 4.4 Hz, 4H), 1.33 (d, J = 6.0 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.3, 167.3, 165.9, 163.4, 157.0, 155.9, 149.0, 137.8, 134.0, 133.1, 128.5, 128.3, 115.4, 105.4, 104.3, 100.7, 71.6, 66.0, 57.3, 56.2, 55.5, 48.3, 47.5, 41.0, 39.9, 29.6, 22.0, 21.9.

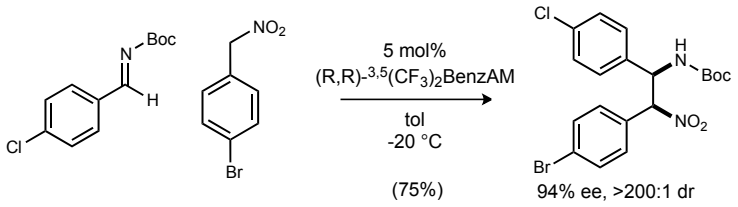


(*E*)-*tert*-Butyl 3-(trifluoromethoxy)benzylidenecarbamate (65). To a flame dried flask was added the sulfone (200 mg, 449 μmol), Na_2SO_4 (384 mg, 2.69 mmol), Cs_2CO_3 (293 mg, 8.98 μmol), and THF (2.2 mL) at rt. The mixture was monitored by ^{1}H NMR and vigorously stirred for 75 m. The solution was filtered through a plug of Celite with excess CH_2Cl_2 and concentrated to a colorless oil which was 90% pure by ^{1}H NMR (128 mg, about 98%). This material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.80 (d, J = 6.8 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.40 (m, 1H), 1.58 (s, 9H). The extent to which this compound was prone to decomposition precluded acquisition of the remaining analytical data.

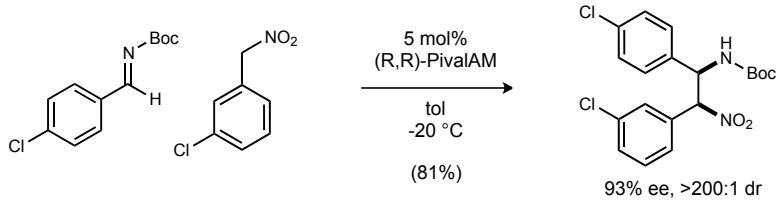


***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-2-nitro-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (66).** Imine (163 mg, 564 μmol) and (*S,S*)-**68** (15.4 mg, 28 μmol) were added to a flask in toluene (5.6 mL) under argon. The mixture was cooled to -20 °C and nitroalkane (106 mg, 620 μmol) was added. After 48 h the reaction was filtered through a plug of silica gel and concentrated. Column chromatography (SiO_2, 0-15% ethyl acetate in hexanes) afforded the product as a white crystalline solid (160 mg, 62%). The major diastereomer was determined to be 94% ee and the minor to be 92% ee, with 6:1 dr determined by chiral HPLC (Chiralcel AD: 6% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_2e_2 minor/minor) = 11.5 min, t_r(d_1e_1 major/major) = 13.4 min, t_r(d_1e_2 major/minor) = 15.4 min, t_r(d_2e_1 minor/major) = 20.3 min); mp = 145 °C; R_f = 0.58 (20% EtOAc/hexanes); IR (film) 3372, 2981, 2927, 1686, 1558, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 1H), 7.39 (m, 4H), 7.29 (m, 2H), 7.20 (m, 1H), 5.78 (br dd, 1H), 5.61 (br d, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.7, 154.3, 139.5, 136.6, 130.5, 130.0, 129.6, 129.3, 129.2 (2C), 125.7, 125.4, 124.7,

121.2, 120.4 (q, $^1J_{CF}$ = 249 Hz), 119.9, 93.0, 28.3, 28.0; HRMS (APCI): Exact mass calcd for $C_{20}H_{20}ClF_3N_2NaO_5$ $[M+Na]^+$ 483.0911, found 483.0907.

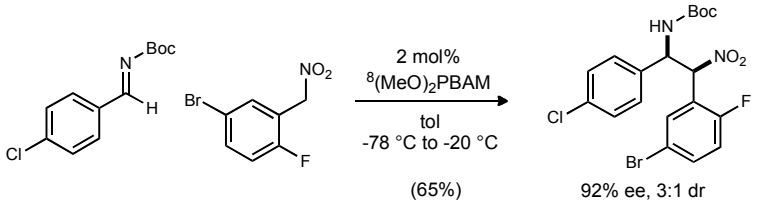


***tert*-Butyl ((1*R*,2*S*)-2-(4-bromophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (69a).** The imine (348 mg, 1.45 mmol) and catalyst **68** (40.0 mg, 73.0 μmol) were added to a flask in toluene (14.5 mL) under argon. The mixture was cooled to -78 °C and the nitroalkane (377 mg, 1.61 mmol) added. After 36 h the white precipitate was vacuum filtered and washed with hexanes to afford the title compound as a white crystalline solid (493 mg, 75%). The major diastereomer was determined to be 94% ee with >200:1 dr determined by chiral HPLC (Chiralcel IA: 15% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 10.2 min, $t_r(d_2e_1$ minor/major) = 11.8 min, $t_r(d_1e_1$ major/major) = 24.2 min, $t_r(d_2e_2$ minor/minor) = 33.4 min). $[\alpha]_D^{20}$ -23 (*c* 0.27, $CHCl_3$); Mp = 183-184 ºC; R_f = 0.40 (20% EtOAc/hexanes); IR (film) 3375, 2980, 1683, 1544, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.74 (d, *J* = 8.8 Hz, 1H), 5.57 (dd, *J* = 9.2, 8.8 Hz, 1H), 4.82 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 134.8, 132.1, 130.3, 129.3, 129.0, 128.6, 128.2, 124.8, 93.2, 30.9, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M+Na]^+$ 477.0193, found 477.0211.

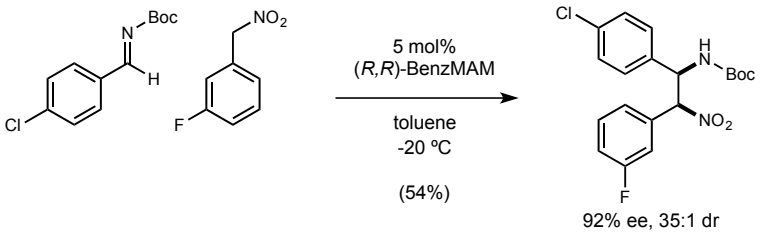


***tert*-Butyl ((1*R*,2*S*)-2-(3-chlorophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (69b).** Prepared according to the general procedure with a 48 h reaction time using catalyst **67**. The reaction precipitate was added to the filter paper a Buchner funnel and washed with cold hexanes to afford the product as a white crystalline solid (35 mg, 81%) that was found to be 93% ee and >200:1 dr by chiral HPLC (Chiralcel IA: 9% ^{i}PrOH/hexanes, 0.6 mL/min: $t_r(d_1e_1$ major/major) =

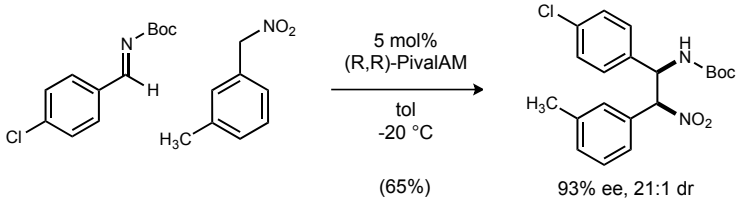
12.6 min, $t_r(d_2e_1$ minor/major) = 15.0 min, $t_r(d_1e_2$ major/minor) = 17.1 min, $t_r(d_2e_2$ minor/minor) = 18.6 min). $[\alpha]_D^{20}$ -37 (*c* 0.44, $CHCl_3$); mp = 182-183 ºC; R_f = 0.55 (25% EtOAc/hexanes); IR (film) 3389, 3056, 2980, 1683, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 1H), 7.44 (m, 2H), 7.37-7.28 (m, 5H), 5.76 (br d, 1H), 5.56 (br dd, 1H), 4.86 (br d, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz. $CDCl_3$) ppm 154.2, 134.9, 134.8, 133.1, 130.5, 130.3, 130.2, 130.1, 129.3, 129.1, 128.9, 128.6, 128.3, 128.0, 126.8, 93.2, 28.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}N_2NaO_4$ $[M+H]^+$ 433.0698; found 433.0715.



***tert*-Butyl ((1*R*,2*S*)-2-(5-bromo-2-fluorophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (69c).** The reaction was run with 2 mol% $^8(MeO)_2$ -PBAM at -78 °C for 20 h then moved to -20 °C for an additional 24 hr. Following silica plug removal of the catalyst, column chromatography (SiO_2, 0-10% ethyl acetate in hexanes) afforded the product as a white crystalline solid (422 mg, 65%). The major diastereomer was determined to be 92% ee and the minor to be 90% ee, with 3:1 dr determined by chiral HPLC (Chiralcel IA: 10% ^{i}PrOH/hexanes, 0.8 mL/min: $t_r(d_1e_1$ minor/major) = 17.6 min, $t_r(d_1e_2$ minor/minor) = 18.6 min, $t_r(d_2e_1$ major/major) = 20.9 min, $t_r(d_1e_2$ major/minor) = 44.6 min). Mp = 184-185 ºC; R_f = 0.30 (25% EtOAc/hexanes); IR (film) 3505, 3374 (br), 2976, 2935, 1698, 1561, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 2.4, 2.4 Hz, 1H), 7.52 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 8.8 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 5.64 (br d, 1H), 4.84 (d, *J* = 9.6 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.0 (d, $^1J_{CF}$ = 259 Hz), 154.6, 135.3, 135.0, 134.9, 130.9, 129.4, 129.2, 128.5, 128.2 (d, $^3J_{CF}$ = 4 Hz), 127.9 (d, $^3J_{CF}$ = 4 Hz), 120.8 (d, $^2J_{CF}$ = 24 Hz), 117.3, 85.4, 28.0; HRMS (APCI): Exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ $[M+Na]^+$ 495.0098, found 495.0107.

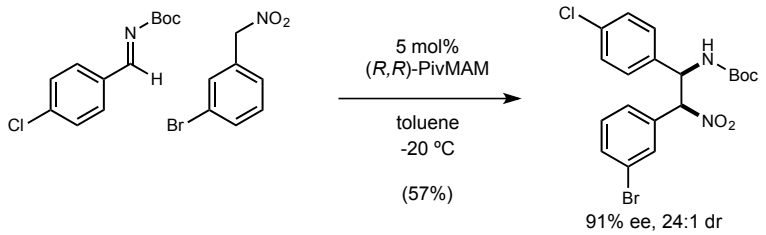


***tert*-Butyl ((1*S*,2*R*)-1-(4-chlorophenyl)-2-(3-fluorophenyl)-2-nitroethyl)carbamate (69d).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the adduct as a white crystalline solid (42 mg mg, 54%). that was found to be 35:1 dr and 92% ee by chiral HPLC analysis (Chiralpak AD-H, 8% *i*PrOH/hexanes, 1 mL/min, $t_r(d_1e_1$, major/major) = 21.6min, $t_r(d_2e_2$, minor/minor) = 23.8 min, $t_r(d_2e_2$, minor/minor) = 30.9 min, $t_r(d_1e_2$, major/minor) = 40.2 min). Mp = 162-164 °C; R_f = 0.53 (33% EtOAc/hexanes); IR (film) 3379, 2977, 1680, 1553, 1523, 1289, 1252, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 6 H), 7.18 (m, 2 H), 5.80 (s, 1 H), 5.59 (s, 1 H), 4.92 (s, 1 H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.8, 161.3, 154.2, 135.6, 134.8, 133.4, 133.3, 131.2, 130.5, 130.4, 129.2, 129.1, 129.0, 128.6, 128.3, 128.2, 125.2, 124.5, 117.5, 117.3, 115.9, 115.6, 93.2, 93.1, 80.8, 28.2, 28.1, 28.0, 27.8. Exact mass calcd for $C_{19}H_{20}ClFN_2NaO_4$ $[M+Na]^+$ 417.0093, found 417.1101.

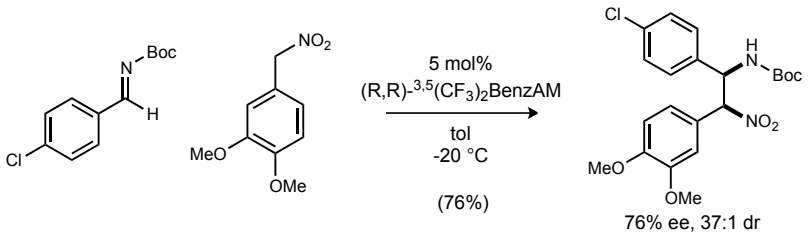


***tert*-Butyl ((1*R*,2*S*)-1-(4-chlorophenyl)-2-nitro-2-(m-tolyl)ethyl)carbamate (69e).** Prepared according to the general procedure with a 60 h reaction time using catalyst **67**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (22 mg, 65%) and found to be 21:1 dr and 93% ee by chiral HPLC analysis (Chiralpak AD-H, 10% ^{i}PrOH/hexanes, 1.0 ml/min: $t_r(d_2e_1$, minor/major) =17.9 min, $t_r(d_1e_2$,, major/minor) = 22.0 min, $t_r(d_2e_2$, minor/minor) = 26.3, $t_r(d_1e_1$, major/major) = 32.0 min). 79% ee and 34:1 dr material used for optical rotation: $[\alpha]_D^{20}$ -25.8 (*c* 1.13, $CHCl_3$); mp = 127-130 °C; R_f = 0.56 (33% EtOAc/hexanes); IR (film) 3385, 1681, 1548, 1521, 1365, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 8 H), 5.72 (d, *J* = 8.8 Hz, 1 H), 5.61 (dd, *J* = 8.8, 8.8 Hz, 1 H), 4.74 (d, *J*

= 7.6 Hz, 1 H), 2.39 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 138.8, 134.5, 131.4, 131.1, 130.8, 129.1, 128.8, 128.6, 125.6, 94.0, 68.1, 38.7, 28.9, 28.2, 28.0, 23.7, 22.9, 21.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}ClN_4NaO_4$ $[M+Na]^+$ 413.1244, found 413.1252.

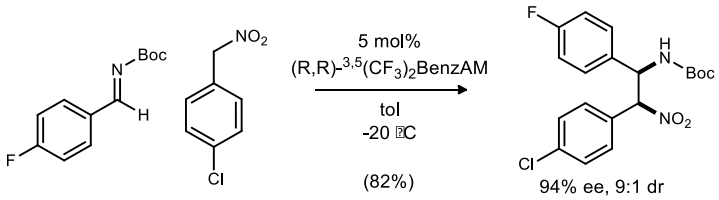


***tert*-Butyl ((1*R*,2*S*)-2-(3-bromophenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (69f).** Imine (50.0 mg, 2.086 mmol) and catalyst **67** (41.0 mg, 104 μmol)) in toluene (17 mL) were stirred at rt for 10 min then cooled to -78 °C and then nitroalkane (496 mg, 2.30 mmol) in cold toluene (3 mL) was added and stirred at -78 °C for 30 min then at -20 °C for 48 h. The crude product that precipates out was filtered and washed with cold hexanes to give a off-white crystalline solid (740 mg, 78%) that was found to be 92% ee and 25:1 dr by chiral HPLC (Chiralcel AD-H: 8% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 11.5 min, $t_r(d_2e_1$ minor/major) = 14.0 min, $t_r(d_1e_1$ minor/minor) = 18.6 min, $t_r(d_2e_2$ major/major) = 21.3 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, J = 1.8 Hz, 1H), 7.62-7.55 (m, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.38-7.33 (m, 2H), 7.33-7.27 (m, 3H), 5.75 (s, 1H), 5.56 (t, J = 9.7 Hz, 1H), 4.83 (s, 1H), 1.28 (s, 9H); LRMS (ESI) $C_{19}H_{21}BrClN_2O_4$ $[M+H]^+$ 455.73, found 455.44.

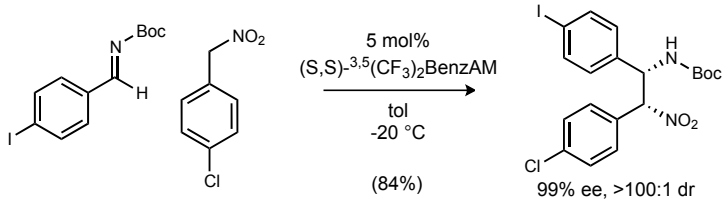


***tert*-Butyl ((1*R*,2*S*)-1-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69g).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 10-25% ethyl acetate in hexanes) afforded the adduct as an off-white solid (56.0 mg, 76%) that was found to be 76% ee and 37:1 dr by chiral HPLC (Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 16.9 min, $t_r(d_1e_1$ major/major) = 19.2 min, $t_r(d_1e_2$ major/minor) = 20.1 min, $t_r(d_2e_2$ minor/minor) = 25.5 min). $[\alpha]_D^{20}$ -4.5 (*c* 0.40,

$CHCl_3$); mp = 148-149 ºC; R_f = 0.25 (CH_2Cl_2); IR (film) 3367, 2975, 2837, 1703, 1557, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.29, (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 4.0 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.70 (d, *J* = 10.0 Hz, 1H), 5.64 (d, *J* = 8.4 Hz, 1H), 4.82 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 150.7, 149.2, 136.2, 134.6, 129.2, 128.6, 123.5, 122.1, 110.9, 93.9, 80.6, 56.0 (2C), 28.1; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ $[M+Na]^+$ 459.1299, found 459.1309.

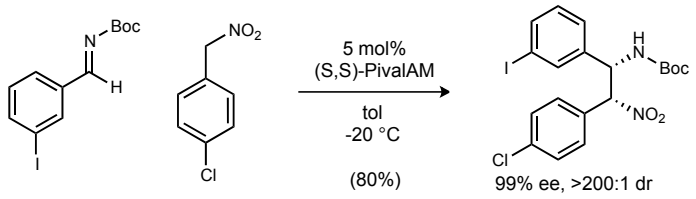


***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-1-(4-fluorophenyl)-2-nitroethyl)carbamate (69h).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 1-10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (21 mg, 82%) that was found to be 94% ee and 9:1 dr by chiral HPLC (Chiralcel AD-H: 8% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_1e_2 major/minor) = 11.7 min, t_r(d_2e_1 major/minor) = 19.6 min, t_r(d_1e_1 major/major) = 25.7 min, t_r(d_2e_2 minor/minor) = 40.2 min). Mp = 179-181 ºC; R_f = 0.49 (20% EtOAc/hexanes); IR (film) 3378, 2977, 2922, 1678, 1560, 1519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 8.4, 8.4 Hz, 2H), 7.05 (dd, *J* = 8.4, 8.4 Hz, 2H), 5.75 (br d, 1H), 5.59 (br dd, 1H), 4.80 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 162.4 (d, $^1J_{CF}$ = 249 Hz), 154.2, 136.5, 133.0, 130.1, 129.8, 129.1, 129.0 (d, $^4J_{CF}$ = 7.5 Hz), 116.1 (d, $^2J_{CF}$ = 23 Hz), 93.4, 80.8, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClFN_2NaO_4$ $[M+Na]^+$ 417.0095, found 417.1010.

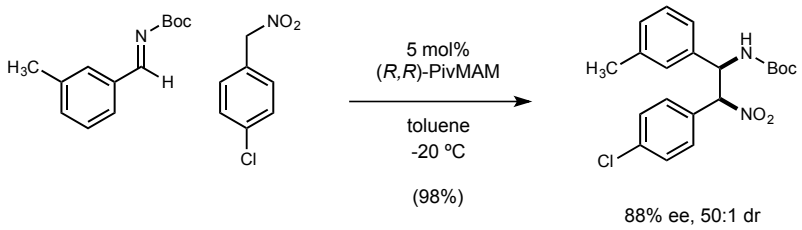


***tert*-Butyl ((1*S*,2*R*)-2-(4-chlorophenyl)-1-(4-iodophenyl)-2-nitroethyl)carbamate (69i).** Prepared according to the general procedure with a 24 h reaction time using catalyst **68**. Column

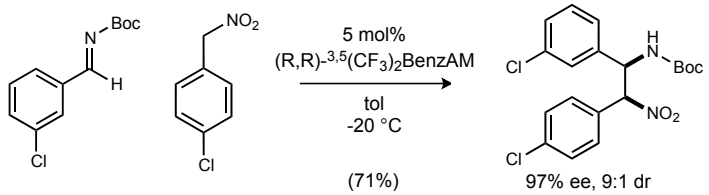
chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (27 mg, 84%) that was found to be a 99% ee and >100:1 dr by chiral HPLC; (ChiralPak AD-H, 15% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_1e_1, major/major) = 11.8 min, t_r (d_2e_1, minor/major) = 14.1 min, t_r (d_1e_1, major/major) = 22.8 min, t_r (d_2e_2, minor/minor = 42.4 min); $[\alpha]_D^{20}$ +22 (*c* 0.16, $CHCl_3$); Mp = 189 – 190 °C; R_f = 0.50 (20% EtOAc in hexanes); IR (film) 3380, 2979, 1679, 1548, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.75 (d, *J* = 8.8 Hz, 1H), 5.55 (dd, *J* = 9.4, 8.8 Hz, 1H), 4.76 (d, *J* = 9.2 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (100.6 MHz, $(CD_3)_2SO$) ppm 154.7, 138.4, 137.9, 135.4, 131.1, 130.9, 130.3, 129.2, 95.3, 92.9, 79.2, 55.9, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClIN_2NaO_4$ $[M+Na]^+$ 525.0050, found 525.0082.



***tert*-Butyl ((1*S*,2*R*)-2-(4-chlorophenyl)-1-(3-iodophenyl)-2-nitroethyl)carbamate (69j).** Prepared according to the general procedure with a 72 h reaction time using catalyst **67**. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the adduct as a white crystalline solid (360 mg, 80%). The major diastereomer was determined to be 99% ee with >200:1 dr determined by chiral HPLC (Chiralcel AD-H: 15% ^{i}PrOH/hexanes, 0.6 mL/min: t_r(d_1e_1 major/major) = 14.3 min, t_r(d_2e_2 minor/minor) = 15.2 min, t_r(d_1e_2 major/minor) = 29.5 min, t_r(d_2e_1 minor/minor) = 32.4 min). $[\alpha]_D^{20}$ +220 (*c* 0.20, $CHCl_3$); mp = 170-172 ºC; R_f = 0.45 (20% EtOAc/hexanes); IR (film) 3393, 2981, 2360, 1679, 1545, 1518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.09 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.72 (br d, *J* = 9.2 Hz, 1H), 5.55 (br dd, 1H), 4.82 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.1, 139.4, 138.0, 136.6, 136.1, 130.7, 130.1, 129.7, 129.4, 129.1, 126.6, 94.8, 93.1, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClIN_2NaO_4$ $[M+Na]^+$ 525.0054, found 525.0071.

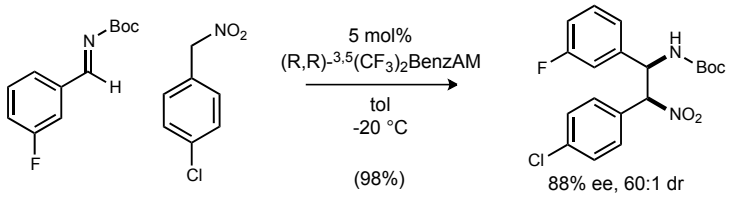


***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-2-nitro-1-(m-tolyl)ethyl)carbamate (69k).** Prepared according to the general procedure with a 48 h reaction time using catalyst **67**, and following silica gel filtration the product was isolated as a white crystalline solid (48 mg, 98% overall) that was found to be 88% ee and 50:1 dr by chiral HPLC (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(d_1e_1 major/major) = 9.6 min, t_r(d_2e_2 minor/minor) = 12.4 min, t_r(d_1e_2 minor/major) = 14.9, t_r(d_1e_2 major/minor) = 32.7 min). $[\alpha]_D^{20}$ -38 (*c* 0.11, $CHCl_3$, recrystalized material, 96% ee, 200:1 dr); mp = 186-188 °C; R_f = 0.56 (33% EtOAc/hexanes); IR (film) 3399, 2984, 2921, 2359, 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.28 (m, 2 H), 7.15 (m, 3 H), 5.76 (d, *J* = 10.0 Hz, 1 H), 5.64 (m, 1 H), 4.71 (d, *J* = 9.6 Hz, 1 H), 2.48 (s, 3 H), 1.3 (s, 9 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 138.9, 137.0, 136.3, 130.2, 130.0, 129.7, 129.0, 128.9, 127.9, 124.0, 94.6, 80.4, 56.5, 28.0, 21.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}ClN_4NaO_4$ $[M+Na]^+$ 413.1243, found 413.1262.

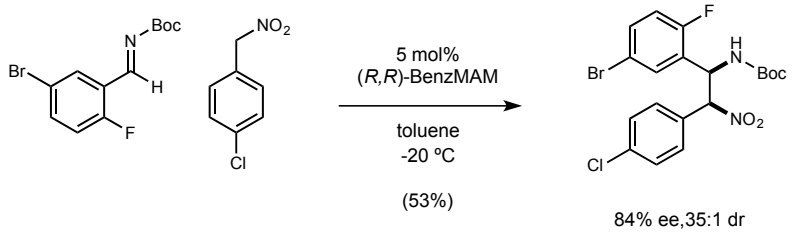


***tert*-Butyl ((1*R*,2*S*)-1-(3-chlorophenyl)-2-(4-chlorophenyl)-2-nitroethyl)carbamate (69l).** Prepared according to the general procedure with a 24 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (23 mg, 71%) that was found to be 97% ee and 9:1 dr determined by chiral HPLC (Chiralcel IA: 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_2e_2 minor/minor) = 18.4 min, t_r(d_2e_1 minor/major) = 21.3 min, t_r(d_1e_1 major/major) = 31.3 min, t_r(d_1e_1 major/minor) = 47.8 min). Mp = 174-175 ºC; R_f = 0.58 (20% EtOAc/hexanes); IR (film) 3385, 2977, 1685, 1553, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.34-7.22 (m, 4H), 5.73 (br d, 1H), 5.60 (br m, 1H), 4.71 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm

154.2, 139.2, 136.6, 135.0, 130.4, 130.1, 129.7, 129.1, 127.4, 125.5, 93.1, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}Cl_2N_2NaO_4$ $[M+Na]^+$ 433.0698, found 433.0713.

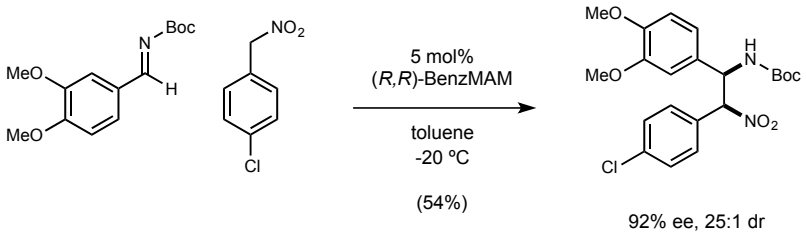


***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-1-(3-fluorophenyl)-2-nitroethyl)carbamate (69m).** Prepared according to the general procedure with a 18 h reaction time using catalyst **68**, and following silica gel filtration, the product was isolated as a white crystalline solid (37 mg, 98%), which was found to be 60:1 dr and 88% ee by chiral HPLC analysis (Chiralpak AD-H, 5% *i*PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$, minor/major) =28.7 min, $t_r(d_1e_2$, major/minor) = 34.8 min, $t_r(d_1e_1$, major/major) = 48.5, $t_r(d_2e_2$, minor/minor) = 70 min). $[\alpha]_D^{20}$ -11 (*c* 0.11, $CHCl_3$, 40% ee); mp = 169-171 °C; R_f = 0.58 (33% EtOAc/hexanes); IR (film) 3383, 2983, 1681, 1551, 1524, 1366, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.37 (m, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 7.08 (m, 2 H), 5.77 (br d, 1 H), 5.64 (br dd, 1 H), 4.86 (br d, 1 H), 1.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.1, 161.6, 136.6, 130.74, 130.66, 130.0, 129.6, 129.1, 122.8, 116.0, 115.8, 114.4, 114.2, 93.1, 27.9; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClFN_2NaO_4$ $[M+Na]^+$ 417.0093, found 417.1121.

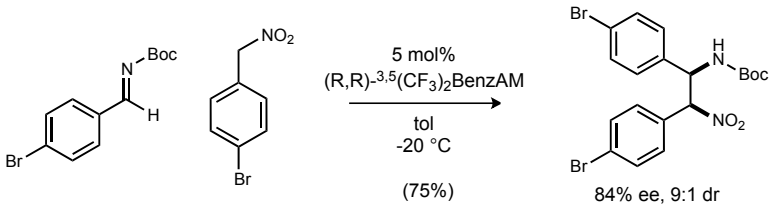


***tert*-Butyl ((1*R*,2*S*)-1-(5-bromo-2-fluorophenyl)-2-(4-chlorophenyl)-2-nitroethyl)carbamate (69n).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded an off-white crystalline solid (29.0 mg, 53%) that was found to be 84% ee and 25:1 dr by chiral HPLC (Chiralcel AD: 6% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ minor/major) = 12.9 min, $t_r(d_2e_1$ minor/major) = 14.6 min, $t_r(d_2e_2$ minor/minor) = 29.6 min, $t_r(d_1e_1$ major/major) = 32.8 min). $[\alpha]_D^{20}$ -11 (*c* 0.40,

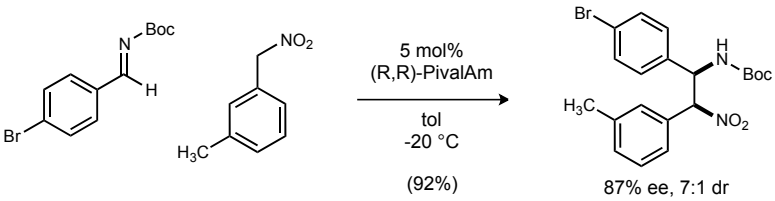
$CHCl_3$); mp = 165 ºC (dec.); R_f = 0.60 (20% EtOAc/hexanes); IR (film) 3327, 2980, 2924, 1704, 1565, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.44 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.28 (m, 1H), 7.00 (dd, *J* = 8.8, 8.8 Hz, 1H), 5.80 (br d, 1H), 5.64 (br d, 1H), 5.07 (br d, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.0 (d, $^1J_{CF}$ = 246 Hz), 154.1, 136.6, 133.7 (d, $^3J_{CF}$ = 8.0 Hz), 132.5, 130.1, 129.5, 129.3, 129.1, 126.0 (d, $^3J_{CF}$ = 13 Hz), 117.9 (d, $^2J_{CF}$ = 23 Hz), 117.3, 92.1, 28.1, 27.9; HRMS (ESI): Exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ $[M+Na]^+$ 495.0109, found 495.0098.



***tert*-Butyl ((1*S*,2*R*)-2-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69o).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the product as a tan crystalline solid (28.3 mg, 54%) that was found to be 92% ee and 25:1 dr by chiral HPLC (ChiralPak AD-H, 10% EtOH/hexanes, 1.0 mL/min: t_r (*anti*, minor) = 13.2 min, t_r (*syn*, major) = 15.8 min, t_r (*anti*, major) = 17.2 min, t_r (*syn*, minor) = 36.8 min). $[\alpha]_D^{20}$ -21 (c 0.36, $CHCl_3$); mp = 150-151 °C; R_f = 0.11 (20% EtOAc in hexanes); IR (film) 3383, 2989, 1676, 1595, 1519, 1463, 1423, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 6.82-6.89 (m, 3H), 5.77 (d, *J* = 9.2 Hz, 1H), 5.54 (dd, *J* = 9.4, 9.2 Hz, 1H), 3.87 (br d, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 149.3, 149.2, 136.3, 130.2, 130.0, 129.5, 128.9, 119.1, 111.3, 110.5, 93.4, 80.5, 55.9, 55.8, 29.6, 28.0; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ $[M+Na]^+$ 459.1299; found 459.1305.

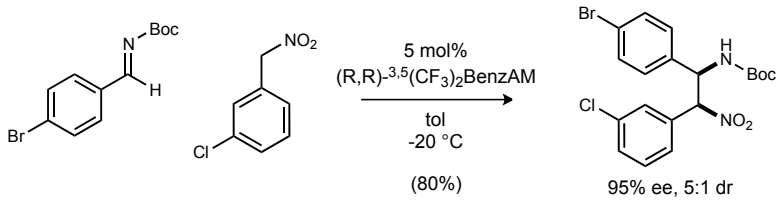


***tert*-Butyl ((1*R*,2*S*)-1,2-bis(4-bromophenyl)-2-nitroethyl)carbamate (69b2).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-10% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (19 mg, 75%) that was found to be 84% ee and 9:1 dr by chiral HPLC (Chiralcel IA: 6% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$ major/major) = 15.9 min, $t_r(d_1e_2$ major/minor) = 17.4 min, $t_r(d_2e_1$ minor/major) = 20.1 min, $t_r(d_2e_2$ minor/minor) = 50.5 min). Mp = 178-179 ºC (dec.); R_f = 0.54 (20% EtOAc/hexanes); IR (film) 3370, 2980, 2918, 1679, 1549, 1529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 5.73 (d, *J* = 6.8 Hz, 1H), 5.56 (dd, *J* = 9.6, 8.8 Hz, 1H), 4.85 (br d, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.1, 132.3, 132.1, 130.3, 128.9, 128.6, 124.8, 123.0, 93.2, 28.2, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}Br_2N_2NaO_4$ $[M+Na]^+$ 520.9687, found 520.9703.

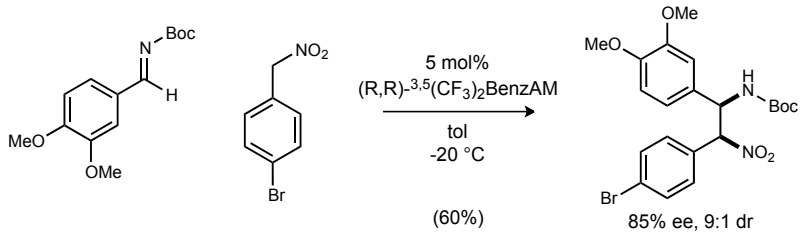


***tert*-Butyl ((1*R*,2*S*)-1-(4-bromophenyl)-2-nitro-2-(meta-tolyl)ethyl)carbamate (69b3).** Prepared according to the general procedure with a 48 h reaction time using catalyst **67**. Column chromatography (SiO_2, 0-10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (29 mg, 92%) that was found to be 87% ee and 7:1 dr by chiral HPLC (Chiralcel AD-H: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 25.9 min, $t_r(d_2e_2$ minor/minor) = 30.8 min, $t_r(d_1e_2$ major/minor) = 38.3 min, $t_r(d_1e_1$ major/major) = 43.8 min). mp = 165-166 ºC; R_f = 0.53 (25% EtOAc/hexanes); IR (film) 3379, 2965, 2924, 2848, 1689, 1551, 1517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 (m, 1H), 7.35 (s, 1H), 7.31 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.71 (br d, 1H), 5.58 (br dd, 1H), 5.44 (br d, 1H), 2.37 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 138.8, 136.8, 131.1, 129.2, 129.0, 128.8, 128.7,

127.5, 125.6, 122.7, 93.9, 29.7, 28.2, 28.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}BrN_2NaO_4$ $[M+Na]^+$ 457.0689, found 457.0696.

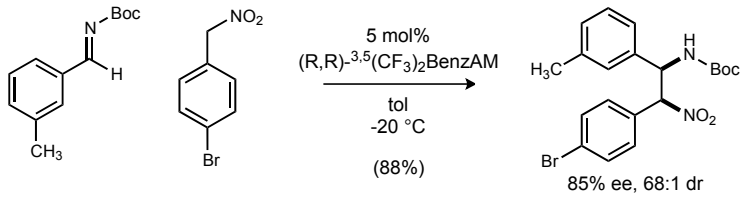


***tert*-Butyl ((1*R*,2*S*)-1-(4-bromophenyl)-2-(3-chlorophenyl)-2-nitroethyl)carbamate (69b4).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (23 mg, 80%) that was found to be 95% ee and 5:1 dr by chiral HPLC (Chiralcel IA: 10% ^{i}PrOH/hexanes, 0.6 mL/min: $t_r(d_1e_1$ major/major) = 21.0 min, $t_r(d_1e_2$ major/minor) = 25.1 min, $t_r(d_2e_1$ minor/major) = 29.6 min, $t_r(d_2e_2$ major/major) = 30.8 min). Mp = 184 ºC; R_f = 0.49 (25% EtOAc/hexanes); IR (film) 3368, 2976, 2914, 1677, 1554, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.42 (m, 2H), 7.35 (m, 1H), 7.23 (d, J = 8.4 Hz, 2H), 5.76 (br d, 1H), 5.56 (br dd, J = 8.0 Hz, 1H), 4.85 (br d, 1H) 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 136.1, 134.8, 133.1, 132.2, 130.5, 130.2, 128.9, 128.6, 126.8, 123.0, 93.1, 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M+Na]^+$ 477.0193, found 477.0208.

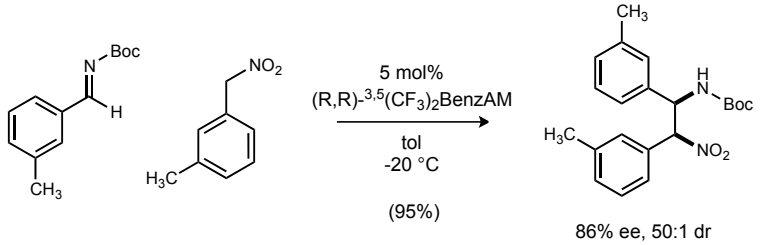


***tert*-Butyl ((1*R*,2*S*)-2-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69b6)**. Prepared according to the general procedure with a 44 h reaction time using catalyst **68**. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the product as an off-white crystalline solid (33 mg, 60%) that was found to be 85% ee and 9:1 dr by chiral HPLC (Chiralcel AD-H: 9% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 16.3 min, $t_r(d_2e_1$ minor/major) = 19.5 min, $t_r(d_1e_1$ major/major) = 22.4 min,

t_r(d_2e_2 major/major) = 53.5 min). Mp = 153-154 ºC; R_f = 0.19 (25% EtOAc/hexanes); IR (film) 3368, 2973, 2938, 1697, 1551, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 6.86 (m, 3H), 5.76 (d, *J* = 9.2 Hz, 1H), 5.54 (dd, *J* = 9.6, 9.2 Hz, 1H), 4.83 (br d, 1H), 3.87 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 149.4, 149.2, 131.9, 130.6, 130.5, 129.5, 124.6, 119.2, 111.3, 110.6, 93.5, 56.0, 55.9, 28.0; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}BrN_2NaO_6$ $[M+Na]^+$, 503.0790, found 503.0794.

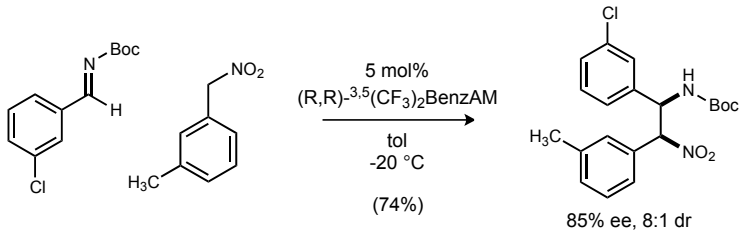


***tert*-Butyl ((1*R*,2*S*)-2-(4-bromophenyl)-2-nitro-1-(meta-tolyl)ethyl)carbamate (69c2).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Following silica plug filtration, the adduct was isoalted as an off-white solid (35 mg, 88%) that was found to be 85% ee and 68:1 dr by chiral HPLC (Chiralcel IA: 7% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_2e_1 minor/major) = 15.6 min, t_r(d_1e_2 major/minor) = 17.5 min, t_r(d_1e_1 major/major) = 21.1 min, t_r(d_2e_2 minor/minor) = 49.1 min). $[\alpha]_D^{20}$ -33 (*c* 0.54, $CHCl_3$); mp = 184-185 ºC; R_f = 0.57 (25% EtOAc/hexanes); IR (film) 3379, 2972, 2917, 1696, 1551, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.46 (*J* = 8.0 Hz, 2H), 7.25 (m, 1H), 7.13 (m, 3H), 5.73 (d, *J* = 9.6 Hz, 1H), 5.6 (br dd, 1H), 4.82 (br d, 1H), 2.35 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 138.9, 137.0, 132.3, 131.9, 131.6, 130.5, 129.7, 129.0, 127.9, 124.6, 124.0, 93.6, 28.0, 21.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}BrN_2NaO_4$ $[M+Na]^+$, 457.0739, found 457.0720.

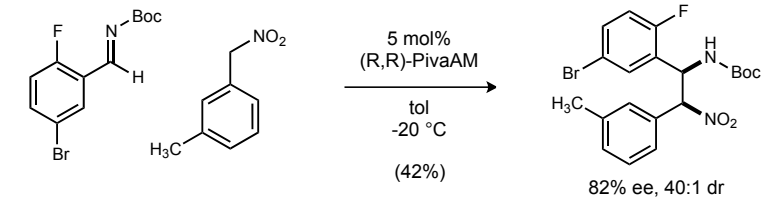


***tert*-Butyl ((1*R*,2*S*)-2-nitro-1,2-di-meta-tolylethyl)carbamate (69c3).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. The filtrate was analytically pure and was the adduct was isolated as a white crystalline solid (40.0 mg, 95%) that was found

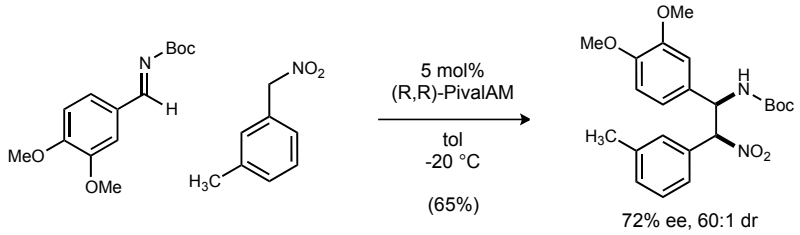
to be 86% ee and 50:1 dr by chiral HPLC (Chiralcel AD-H: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 9.8 min, $t_r(d_2e_2$ minor/minor) = 15.2 min, $t_r(d_1e_1$ major/major) = 16.4 min, $t_r(d_1e_2$ major/minor) = 18.1 min). $[\alpha]_D^{20}$ -35 (*c* 0.29, $CHCl_3$); mp = 179-180 ºC; R_f = 0.38 (25% EtOAc/hexanes); IR (film) 3384, 2911, 2857, 1686, 1549, 1529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 2H), 7.29 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.16-7.23 (m, 2H), 7.15-7.13 (m, 3H), 5.72 (d, *J* = 9.6 Hz, 1H), 5.64 (br dd, 1H), 4.82 (d, *J* = 8.0 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 138.7, 138.6, 137.6, 131.5, 130.9, 129.4, 129.3, 128.9, 128.7, 127.9, 125.8, 124.0, 94.4, 80.2, 28.0, 21.4, 21.3; HRMS (ESI): Exact mass calcd for $C_{21}H_{26}N_2NaO_4$ $[M+Na]^+$ 393.1790, found 393.1794.



***tert*-Butyl ((1*R*,2*S*)-1-(3-chlorophenyl)-2-nitro-2-(m-tolyl)ethyl)carbamate (69c4).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (25 mg, 74%) that was found to be 85% ee and 8:1 dr by chiral HPLC (Chiralcel AD: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 9.1 min, $t_r(d_1e_2$ major/minor) = 12.8 min, $t_r(d_2e_2$ minor/minor) = 14.8 min, $t_r(d_1e_1$ major/major) = 15.9 min). Mp = 153-154 ºC; R_f = 0.50 (20% EtOAc/hexanes); IR (film) 3390, 2980, 1687, 1548, 1515, 1365 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 8H), 5.71 (d, *J* = 9.6 Hz, 1H), 5.62 (dd, *J* = 9.6, 8.0 Hz, 1H), 4.79 (d, *J* = 8.8 Hz, 1H), 2.38 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (150 MHz. $CDCl_3$) ppm 154.2, 139.7, 138.8, 134.8, 131.2, 131.1, 130.2, 129.2, 128.9 (2C), 127.4, 125.7, 125.5, 94.0, 28.0, 21.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}ClN_2NaO_4$ $[M+Na]^+$ 413.1241; found 413.1245.

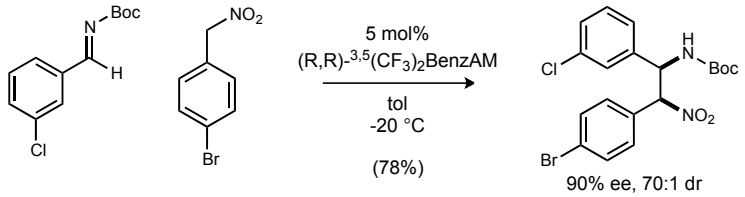


***tert*-Butyl ((1*R*,2*S*)-1-(5-bromo-2-fluorophenyl)-2-nitro-2-(m-tolyl)ethyl)carbamate (69c5).** Prepared according to the general procedure with a 48 h reaction time using catalyst **67**. Column chromatography (SiO_2, 5-10% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (23 mg, 42%) that was found to be 82% ee and 40:1 dr by chiral HPLC (Chiralcel IA: 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 7.4 min, $t_r(d_1e_1$ major/major) = 14.9 min, $t_r(d_1e_2$ major/minor) = 6.6 min, $t_r(d_2e_2$ minor/minor) = 9.2 min). $[\alpha]_D^{20}$ -13 (*c* 0.31, $CHCl_3$, 76% ee, 20:1 dr); mp = 159-165 ºC; R_f = 0.48 (20% EtOAc in hexanes); IR (film) 3450, 3000, 2950, 2410, 1710, 1590, 1490, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1H), 7.44 (ddd, *J* = 8.8, 4.8, 2.8 Hz, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 7.31 (t , *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 7.00 (dd, *J* = 10.8, 9.2 Hz, 1H), 5.80 (m, 2H), 4.98 (br d, 1H), 2.38 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.4 (d, $^1J_{CF}$ = 249 Hz), 154.5, 138.7, 133.4, 131.1 (d, $^3J_{CF}$ = 8 Hz), 130.9, 129.1, 128.8, 125.6, 118.0, 117.5 (d, $^2J_{CF}$ = 23 Hz), 92.8, 27.9, 21.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}BrFN_2NaO_4$ $[M+Na]^+$ 477.0645, found 477.0660.

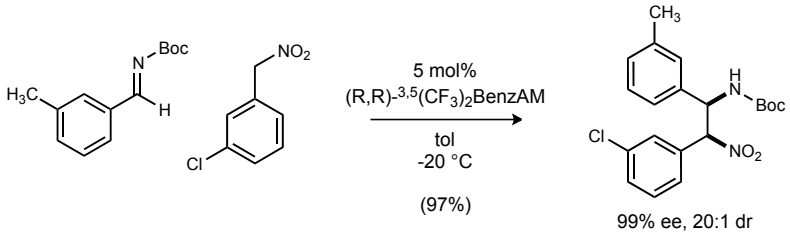


***tert*-Butyl ((1*R*,2*S*)-1-(3,4-dimethoxyphenyl)-2-nitro-2-(meta-tolyl)ethyl)carbamate (69c6).** Prepared according to the general procedure with a 36 h reaction time using catalyst **67**. Column chromatography (SiO_2, 0-20% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (18 mg, 65%) that was found to be 72% ee and 60:1 dr by chiral HPLC (Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 13.4 min, $t_r(d_1e_2$ major/minor) = 18.3 min, $t_r(d_1e_1$ major/major) = 22.2 min, $t_r(d_2e_2$ minor/minor) = 28.8 min). $[\alpha]_D^{20}$ -16 (*c* 0.25, $CHCl_3$); mp = 146-148 ºC; R_f = 0.31 (25% EtOAc/hexanes); IR (film) 3377, 2987, 2925, 1686, 1549, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.31-7.22 (m,

2H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.83 (m, 2H), 5.74 (d, *J* = 9.2 Hz, 1H), 5.58 (dd, *J* = 9.2, 8.8 Hz, 1H), 4.78 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 6H), 2.37 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 149.2, 149.1, 138.6, 131.5, 130.9, 130.2, 129.3, 128.7, 125.8, 119.2, 111.3, 110.6, 94.3, 55.9 (2C), 29.7, 28.0, 21.3; HRMS (ESI): Exact mass calcd for $C_{22}H_{28}N_2O_6$ $[M+Na]^+$, 439.1845, found 439.1862.

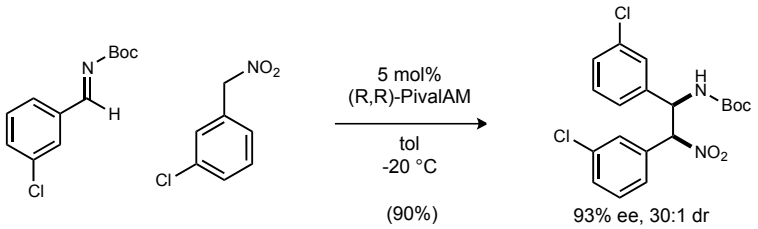


***tert*-Butyl ((1*R*,2*S*)-2-(4-bromophenyl)-1-(3-chlorophenyl)-2-nitroethyl)carbamate (69d2)**. Prepared according to the general procedure with a 20 h reaction time using catalyst **68**. Following silica plug filtration, the product was isolated as an an off-white crystalline solid (27 mg, 78%) that was found to be 90% ee and 70:1 dr by chiral HPLC (Chiralcel AD-H: 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_2e_1 minor/major) = 13.4 min, t_r(d_1e_2 major/minor) = 14.9 min, t_r(d_1e_1 major/major) = 20.9 min, t_r(d_2e_2 minor/minor) = 35.9 min). $[\alpha]_D^{20}$ -30 (*c* 0.25, $CHCl_3$); mp = 175-176 ºC; R_f = 0.54 (25% EtOAc/hexanes); IR (film) 3391 (s), 2991, 2928, 1692, 1560, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.43 (*J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29-7.22 (m, 2H), 5.73 (br d, *J* = 10.0 Hz, 1H), 5.95 (br d, 1H), 4.85 (br d, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 139.1, 135.0, 132.1, 130.4, 130.3, 130.2, 129.1, 127.4, 125.5, 124.8, 93.2, 28.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrClN_2NaO_4$ $[M+Na]^+$, 477.0193, found 477.0190.

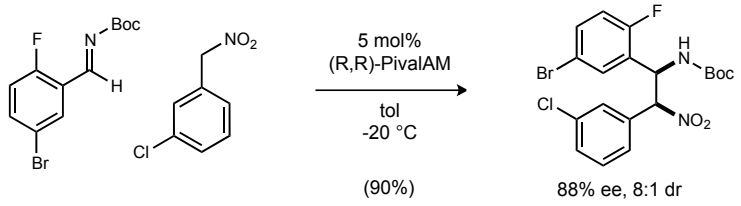


***tert*-Butyl ((1*R*,2*S*)-2-(3-chlorophenyl)-2-nitro-1-(m-tolyl)ethyl)carbamate (69d3).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Following silica plug filtration, the adduct was isolated as an off-white crystalline solid (22 mg, 97%) that was

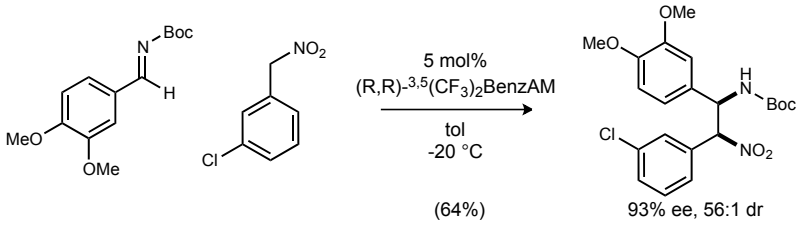
found to be 99% ee and 20:1 dr by chiral HPLC (Chiralcel IA: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_2$ minor/minor) = 10.5 min, $t_r(d_1e_1$ major/major) = 14.1 min, $t_r(d_1e_2$ major/minor) = 15.5 min, $t_r(d_2e_1$ minor/major) = 23.7 min). Mp = 151-152 ºC; R_f = 0.45 (25% EtOAc/hexanes); IR (film) 3391, 2977, 2922, 1692, 1553, 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28-7.24 (m, 1H), 7.14 (m, 3H), 5.73 (d, J = 9.2 Hz, 1H), 5.60 (br d, 1H), 4.77 (d, J = 9.2 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 154.1, 139.0, 136.9, 133.4, 130.3, 130.0, 129.7, 129.0, 127.9, 126.9, 124.0, 93.6, 28.0, 21.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}ClN_2NaO_4$ $[M+Na]^+$, 413.1244, found 413.1247.



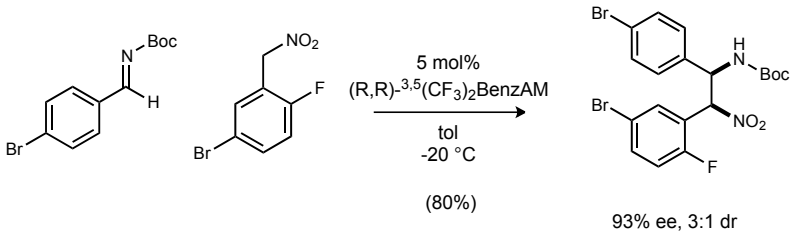
***tert*-Butyl ((1*R*,2*S*)-1,2-bis(3-chlorophenyl)-2-nitroethyl)carbamate (69d4).** Prepared according to the general procedure with a 48 h reaction time using catalyst **67**. Column chromatography (SiO_2, 5-10% ethyl acetate in hexanes) afforded the adduct as a white crystalline solid (27.0 mg, 90%) that was found to be 93% ee and 30:1 dr by chiral HPLC; (Chiralcel IA: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 10.6 min, $t_r(d_1e_2$ major/minor) = 12.9 min, $t_r(d_1e_1$ major/major) = 14.3 min, $t_r(d_2e_2$ minor/minor) = 17.5 min). $[\alpha]_D^{20}$ -44 (c 0.29, $CHCl_3$); mp = 170-171 ºC; R_f = 0.63 (20% EtOAc/hexanes); IR (film) 3372, 2986, 2924, 1682, 1558, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.47-7.43 (m, 2H), 7.38-7.31 (m, 3H), 7.30-7.24 (m, 2H), 5.75 (br d, 1H), 5.59 (br dd, 1H), 4.98 (br d, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 139.1, 135.0, 134.8, 133.0, 130.5, 130.4, 130.2, 129.2, 128.9, 127.4, 126.8, 125.5, 93.1, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}Cl_2N_2NaO_4$ $[M+Na]^+$ 433.0698, found 433.0715.



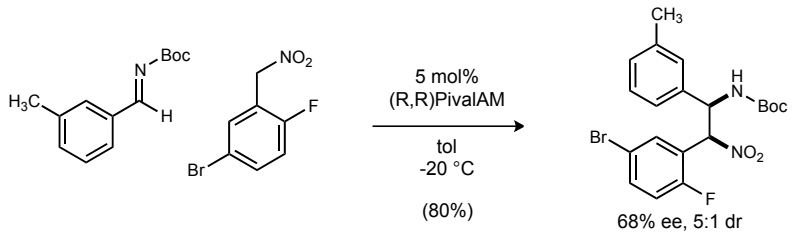
***tert*-Butyl ((1*S*,2*R*)-1-(4-bromophenyl)-2-(4-chlorophenyl)-2-nitroethyl)carbamate (69d5).** Prepared according to the general procedure with a 48 h reaction time using catalyst **67**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the adduct as a white solid (28 mg, 90%) that was found to be 88% ee and 8:1 dr determined by chiral HPLC (Chiralcel AD-H: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 10.6 min, $t_r(d_2e_1$ minor/major) = 13.8 min, $t_r(d_2e_2$ minor/minor) = 19.1 min, $t_r(d_1e_1$ major/major) = 22.2 min). Mp = 185-186 ºC; R_f = 0.45 (20% EtOAc/hexanes); IR (film) 3361, 2973, 2924, 1710, 1565, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.54-7.51 (m, 2H), 7.48-7.42 (m, 2H), 7.40-7.33 (m, 1H), 7.01 (dd, J = 8.8, 8.8 Hz, 1H), 5.80 (m, 2H), 5.03 (d, J = 9.6 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 160.2 (d, $^1J_{CF}$ = 244 Hz), 133.8, 133.7, 132.8, 130.9 (2C), 130.6, 130.2, 129.1, 128.8 (2C), 126.7, 125.9, 118.0 (d, $^2J_{CF}$ = 23 Hz), 117.4, 92.2, 28.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ $[M+Na]^+$ 495.0095, found 495.0100.



***tert*-Butyl ((1*R*,2*S*)-2-(3-chlorophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69d6).** Prepared according to the general procedure with a 60 h reaction time using catalyst **68**. Following the silica plug filtration, the resulting white solid was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the pure compound as an off-white solid (15.3 mg, 64%) that was found to be 93% ee and 56:1 dr by chiral HPLC (Chiralcel AD-H: 6% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 19.9 min, $t_r(d_2e_1$ minor/major) = 23.3 min, $t_r(d_1e_1$ major/major) = 25.5 min, $t_r(d_2e_2$ minor/minor) = 35.2 min). $[\alpha]_D^{20}$ -8.8 (c 0.25, $CHCl_3$); mp = 185 ºC (dec.); R_f = 0.17 (25% EtOAc/hexanes); IR (film) 3351, 2979, 2937, 1703, 1565, 1517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.35 (m, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 2H), 5.77 (d, J = 9.2 1H), 5.54 (dd, J = 9.6, 9.2 Hz, 1H), 4.80 (d, J = 9.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 149.4, 149.3, 134.6, 133.4, 130.3, 130.0, 129.5, 129.1, 126.9, 119.2, 111.4, 110.6, 93.5, 56.0, 55.9, 28.0; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ $[M+Na]^+$ 459.1299, found 459.1322.

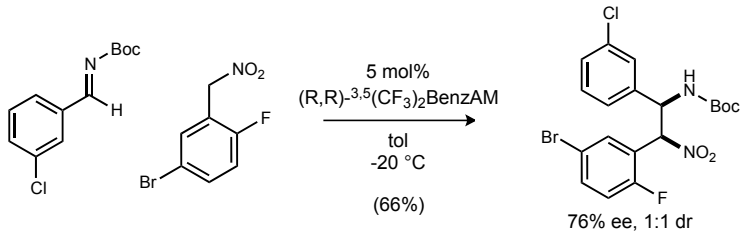


***tert*-Butyl ((1*R*,2*S*)-2-(5-bromo-2-fluorophenyl)-1-(4-bromophenyl)-2-nitroethyl)carbamate (69e2).** Prepared according to the general procedure with a 36 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-30% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (15.0 mg, 80%) that was found to be 93% ee and 3:1 dr by chiral HPLC (Chiralcel AD-H: 3% EtOH/hexanes, 0.8 mL/min: t_r(d_2e_2 minor/minor) = 22.8 min, t_r(d_2e_1 minor/major) = 25.6 min, t_r(d_1e_1 major/major) = 31.0 min, t_r(d_1e_2 major/minor) = 43.5 min). mp = 170-171 ºC; R_f = 0.6 (20% EtOAc/hexanes); IR (film) 3335, 2975, 2926, 1708, 1563, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.48 (m, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.94 (dd, *J* = 9.2, 8.4 Hz, 1H), 6.22 (d, *J* = 6.0 Hz, 1H), 5.58 (d, *J* = 6.0 Hz, 1H), 5.52 (d, *J* = 7.6 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.6 (d, $^1J_{CF}$ = 249 Hz), 154.6, 147.9, 135.3, 134.8 (d, $^3J_{CF}$ = 7.5 Hz), 132.2 (2C), 131.0, 128.4 (2C), 122.7, 120.9 (d, $^3J_{CF}$ = 13.5 Hz), 117.7, 117.6, 85.5 (d, $^3J_{CF}$ = 3 Hz), 28.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{19}Br_2FN_2NaO_4$ $[M+Na]^+$ 538.9593, found 538.9606.

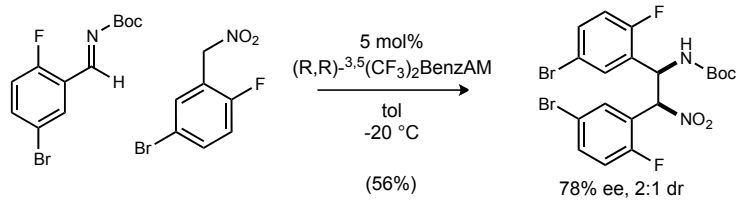


***tert*-Butyl ((1*R*,2*S*)-2-(5-bromo-2-fluorophenyl)-2-nitro-1-(meta-tolyl)ethyl)carbamate (69e3).** Prepared according to the general procedure with a 42 h reaction time using catalyst **67**. Column chromatography (SiO_2, 0-10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (34 mg, 80%) that was found to be 68% ee and 5:1 dr by chiral HPLC (Chiralcel AD: 7% EtOH/hexanes, 1.0 mL/min: t_r(d_2e_1 minor/major) = 9.5 min, t_r(d_1e_1 major/major) = 10.5 min, t_r(d_2e_2 minor/minor) = 12.2 min, t_r(d_1e_2 major/minor) = 34.6 min). Mp = 150-151 ºC; R_f = 0.60 (25% EtOAc/hexanes); IR (film) 3297, 2974, 2919, 1707, 1563, 1487

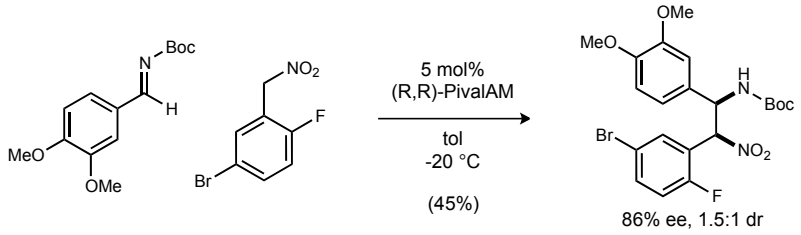
cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 4.0 Hz, 1H), 7.51 (m, 1H), 7.25 (m, 1H), 7.16 (m, 2H), 7.00 (m, 2H), 6.12 (d, J = 10.4 Hz, 1H), 5.61 (d, J = 10.0 Hz, 1H), 4.88 (br d, 1H), 2.36 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.9 (d, $^1J_{CF}$ = 248 Hz), 154.1, 139.0, 136.7, 134.7 (d, $^3J_{CF}$ = 8 Hz), 129.8, 129.1, 127.8, 127.3, 124.0, 121.2 (d, $^3J_{CF}$ = 13 Hz), 117.4 (d, $^2J_{CF}$ = 23 Hz), 117.1 (d, $^4J_{CF}$ = 3 Hz), 85.9 (d, $^3J_{CF}$ = 13 Hz), 28.1, 21.4; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}BrFN_2NaO_4$ $[M+Na]^+$, 475.0645, found 475.0663.



***tert*-Butyl ((1*R*,2*S*)-2-(5-bromo-2-fluorophenyl)-1-(3-chlorophenyl)-2-nitroethyl)carbamate (69e4).** Prepared according to the general procedure with a 24 h reaction time using catalyst **68**. Following silica plug filtration, ^{1}H NMR showed 3:1 dr. Column chromatography (SiO_2, 0-10% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (24 mg, 66%) that was found to be 76% ee and 1:1 dr (racemized on silica) by chiral HPLC (Chiralcel OJ-H: 3% EtOH/hexanes, 1.0 mL/min: t_r(d_1e_2 major/minor) = 20.2 min, t_r(d_1e_1 major/major) = 22.8 min, t_r(d_2e_2 minor/minor) = 25.3 min, t_r(d_2e_2 minor/minor) = 27.5 min). Mp = 158-159 ºC; R_f = 0.55 (20% EtOAc/hexanes); IR (film) 3372, 2986, 2924, 1682, 1558, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 6.0, 2.4, 1H), 7.54 (m, 1H), 7.34 (m, 2H), 7.25 (m, 2H), 7.04 (dd, J = 9.2, 9.2 Hz, 1H), 6.10 (d, J = 9.6 Hz, 1H), 5.66 (br d, J = 9.4 Hz, 1H), 4.90 (br d, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.9 (d, $^1J_{CF}$ = 249 Hz), 154.0, 138.3, 134.9 (d, $^2J_{CF}$ = 23 Hz), 134.8 (d, $^3J_{CF}$ = 8 Hz), 130.5, 129.3, 127.4, 124.9, 120.8 (d, $^3J_{CF}$ = 12 Hz), 117.6 (d, $^2J_{CF}$ = 24 Hz), 117.3 (d, $^4J_{CF}$ = 3 Hz), 85.6 (d, $^4J_{CF}$ = 4 Hz), 28.0; HRMS (ESI): Exact mass calcd for $C_{19}H_{19}BrClFN_2NaO_4$ $[M+Na]^+$, 495.0098, found 495.0115.

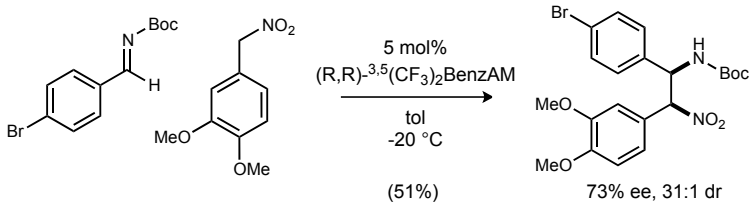


***tert*-Butyl ((1*R*,2*S*)-1,2-bis(5-bromo-2-fluorophenyl)-2-nitroethyl)carbamate (69e5).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the product as a white crystalline solid (22 mg, 56%) that was found to be 78% ee and 2:1 dr by chiral HPLC; (ChiralPak IA, 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$ major/major) = 5.9 min, $t_r(d_2e_1$ minor/major) = 6.5 min, $t_r(d_2e_2$ minor/minor) = 7.1 min, $t_r(d_1e_2$ major/minor) = 8.9 min). Mp = 156-157 °C; R_f = 0.78 (20% EtOAc in hexanes); IR (film) 3324, 2965, 2924, 1710, 1565, 1489 cm^{-1}; ^{1}H NMR for both diastereomers reported (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.72 (dd, *J* = 4.8 Hz, 1H), 7.53-7.37 (m, 4H), 7.03 (m, 2H), 6.94 (m, 2H), 6.28 (br d, 1H), 6.21 (d, *J* = 10.8 Hz, 1H), 5.79-5.71 (m, 2H), 5.10 (d, *J* = 9.6 Hz, 1H), 1.39 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.8 (d, $^1J_{CF}$ = 249 Hz), 159.4 (d, $^1J_{CF}$ = 249 Hz), 154.5, 154.1, 135.0 (2C), 133.9 (2C), 133.7, 133.5, 133.4, 132.1, 131.9, 130.1, 125.6, 120.7, 118.2, 118.0, 117.8, 117.6, 117.4 (2C), 117.2, 84.7, 84.4, 81.2, 81.0, 29.7, 28.3, 28.1; HRMS (ESI): Exact mass calcd for $C_{19}H_{18}Br_2F_2N_2NaO_4$ $[M+Na]^+$ 556.9499; found 556.9482.

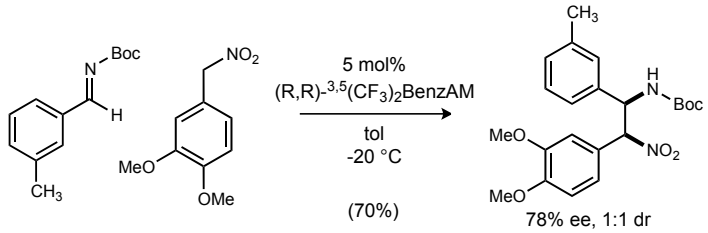


***tert*-Butyl ((1*R*,2*S*)-2-(5-bromo-2-fluorophenyl)-1-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69e6).** Prepared according to the general procedure with a 46 h reaction time using catalyst **67**. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the adduct as a white crystalline solid (22 mg, 45%) that was found to be 86% ee and 1.5:1 dr by chiral HPLC (Chiralcel IC: 8% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$ minor/major) = 15.1 min, $t_r(d_1e_1$ major/major) = 16.8 min, $t_r(d_2e_2$ minor/minor) = 20.0 min, $t_r(d_1e_2$ major/minor) = 38.3 min). Mp = 135-136 ºC; R_f = 0.27 (25% EtOAc/hexanes); IR (film) 3391, 2991, 2928, 1692, 1560, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.51 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.85 (m, 2H), 6.12 (d, *J* = 10.0 Hz, 1H), 5.60 (br d, 1H), 4.82 (d, *J* = 9.6 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.9 (d, $^1J_{CF}$ = 240 Hz), 149.5, 149.4,

134.7 (d, $^3J_{CF}$ =11 Hz), 132.4 (d, $^3J_{CF}$ = 9 Hz), 129.2, 126.9, 121.2, 121.1, 119.0, 117.2 (d, $^4J_{CF}$ = 3 Hz), 111.5, 85.5 (d, $^4J_{CF}$ = 2 Hz), 56.0, 55.9, 28.2, 28.0; HRMS (ESI): Exact mass calcd for $C_{21}H_{24}BrFN_2NaO_6$ $[M+Na]^+$, 521.0699, found 521.0684.

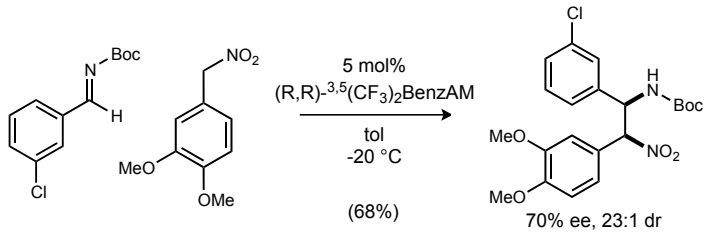


***tert*-Butyl ((1*R*,2*S*)-1-(4-bromophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69f2).** Prepared according to the general procedure with a 72 h reaction time using catalyst **68**. Column chromatography (SiO_2, 0-5% ethyl acetate in hexanes) afforded the adduct as a white solid (27 mg, 51%) that was found to be 73% ee and 31:1 dr by chiral HPLC; (ChiralPak IA, 7% EtOH/hexanes, 1.0 mL/min: t_r(d_1e_2 major/minor) = 16.1 min, t_r(d_1e_1 major/major) = 18.4 min, t_r(d_2e_2 minor/minor) = 21.0 min, t_r(d_2e_1 minor/major) = 28.8 min). $[\alpha]_D^{20}$ -5.4 (*c* 0.37, $CHCl_3$); mp = 183-184 °C; R_f = 0.24 (20% EtOAc in hexanes); IR (film) 3376, 2975, 2926, 1687, 1556, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.09-7.05 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.70 (d, *J* = 10.0 Hz, 1H), 5.62 (br dd, 1H), 4.86 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 143.3, 150.7, 149.2, 136.7, 132.1, 129.0 (2C), 128.2, 125.3, 123.5, 122.8, 122.1, 110.9, 93.8, 56.0, 28.1; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}BrN_2BrO_6$ $[M+Na]^+$ 503.0794; found 503.0777.

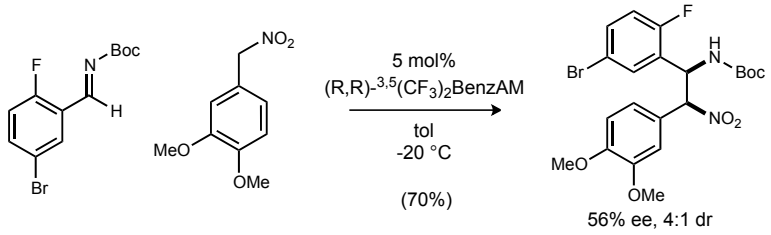


***tert*-Butyl ((1*R*,2*S*)-2-(3,4-dimethoxyphenyl)-2-nitro-1-(m-tolyl)ethyl)carbamate (69f3).** Prepared according to the general procedure with a 72 h reaction time using catalyst **68**. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold

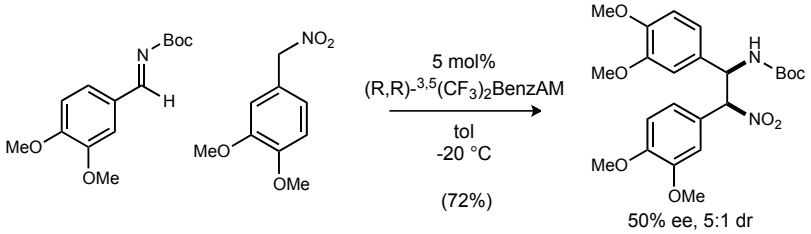
hexanes to afford the product as a light brown crystalline solid (30 mg, 70%) that was found to be 78% ee and 1:1 dr (racemized from 20:1 dr (^{1}H NMR) shortly after Buchner filtration) determined by chiral HPLC (Chiralcel AD: 10% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_1e_1 major/major) = 15.2 min, t_r(d_1e_2 major/minor) = 22.4 min, t_r(d_2e_1 minor/major) = 24.8 min, t_r(d_2e_2 minor/minor) = 39.0 min). Mp = 175-177 ºC; R_f = 0.31 (20% EtOAc/hexanes); IR (film) 3344, 2972, 2931, 1703, 1558, 1524, 1468 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.2 Hz, 1H), 7.15-7.08 (m, 5H), 6.85 (d, J = 8.4 Hz, 1H), 5.70 (m, 2H), 4.81 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.34 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.4, 150.5, 149.0, 138.7, 137.0, 129.5, 128.9, 127.7, 124.0, 122.2, 121.4, 111.1, 111.0, 94.3, 56.0, 28.2, 21.2; HRMS (ESI): Exact mass calcd for $C_{22}H_{28}N_2O_6$ [M+Na]$^+$, 439.1845, found 439.1862.



***tert*-Butyl ((1*R*,2*S*)-1-(3-chlorophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69f4).** Prepared according to the general procedure with a 72 h reaction time using catalyst **68**. The reaction precipitate was added to the filter paper of a Buchner funnel and washed with cold hexanes to afford the product as a light brown crystalline solid (38 mg, 68%) that was found to be 70% ee and 23:1 dr determined by chiral HPLC (Chiralcel IA: 7% EtOH/hexanes, 1.0 mL/min: t_r(d_1e_2 major/minor) = 8.5 min, t_r(d_1e_1 major/major) = 9.3 min, t_r(d_2e_1 minor/major) = 10.6 min, t_r(d_2e_2 minor/minor) = 12.8 min). Mp = 161-162 ºC; R_f = 0.4 (20% EtOAc/hexanes); IR (film) 3342, 2975, 2940, 1701, 1563, 1521, 1376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 1H), 7.30-7.28 (m, 2H), 7.25-7.22 (m, 1H), 7.09-7.05 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 5.70 (m, 2H), 4.88 (br d, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.3, 150.7, 149.2, 139.7, 134.8, 130.2, 128.9, 127.4, 125.5, 123.5, 122.1, 93.8, 56.0, 28.6; HRMS (ESI): Exact mass calcd for $C_{21}H_{25}ClN_2NaO_6$ [M+Na]$^+$ 459.1299, found 459.1301.

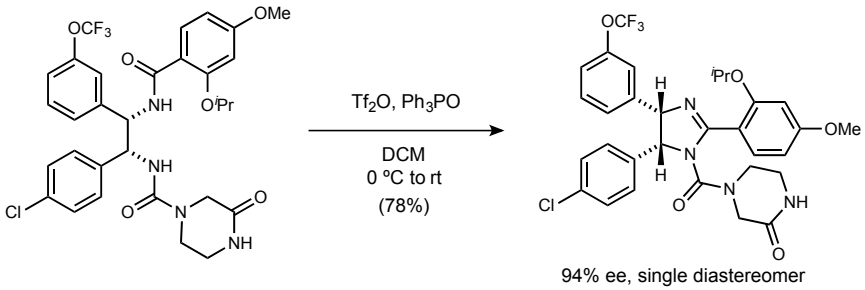


***tert*-Butyl ((1*R*,2*S*)-1-(5-bromo-2-fluorophenyl)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69f5).** Prepared according to the general procedure with a 72 h reaction time using catalyst **68**. Following silica plug filtration, ^{1}H NMR showed >20:1 dr. Column chromatography (SiO_2, 10-40% ethyl acetate in hexanes) afforded the adduct as an off-white solid (31.0 mg, 70%) that was found to be 56% ee and 4:1 dr (racemized on silica) by chiral HPLC (Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_2$ major/minor) = 9.5 min, $t_r(d_2e_1$ minor/major) = 10.3 min, $t_r(d_2e_2$ minor/minor) = 16.8 min, $t_r(d_1e_1$ major/major) = 23.4 min). Mp = 131-132 ºC; R_f = 0.66 (50% EtOAc/hexanes); IR (film) 3368, 2974, 2928, 1703, 1556, 1518, 1279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 4.8 Hz, 1H), 7.44 (m, 1H), 7.15 (br s, 1H), 7.09 (dd, J = 8.4, 2.0 Hz, 1H), 7.00 (dd, J = 8.8, 1.6 Hz, 1H), 6.88 (dd, J = 8.0, 8.0 Hz, 1H), 5.77 (m, 2H), 5.00 (d, J = 8.8 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 150.1 (d, $^{1}J_{CF}$ = 253 Hz), 133.5 (d, $^{3}J_{CF}$ = 9 Hz), 126.5 (d, $^{3}J_{CF}$ = 9 Hz), 123.2 (d, $^{2}J_{CF}$ = 27 Hz), 122.3, 122.1, 117.9 (d, $^{2}J_{CF}$ = 23 Hz), 117.3, 112.6, 111.1, 110.8, 110.7, 92.8 (d, $^{4}J_{CF}$ = 5 Hz), 80.5, 56.0 (2C), 28.1; HRMS (ESI): Exact mass calcd for $C_{21}H_{24}BrFN_2NaO_6$ $[M+Na]^+$ 521.0699, found 521.0701.



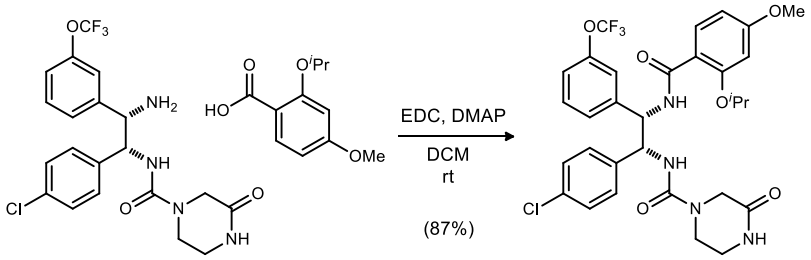
***tert*-Butyl ((1*R*,2*S*)-1,2-bis(3,4-dimethoxyphenyl)-2-nitroethyl)carbamate (69f6).** Prepared according to the general procedure with a 48 h reaction time using catalyst **68**. Following silica plug filtration, ^{1}H NMR showed >20:1 dr. Column chromatography (SiO_2, 10-40% ethyl acetate in hexanes) afforded the adduct as an off-white crystalline solid (23.0 mg, 72%) that was found

to be 50% ee and 5:1 dr (racemized on silica) by chiral HPLC (Chiralcel IA: 12% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_2e_2$ minor/minor) = 15.4 min, $t_r(d_1e_2$ major/minor) = 17.8 min, $t_r(d_1e_1$ major/major) = 24.8 min, $t_r(d_2e_2$ minor/minor) = 34.5 min). Mp = 171 ºC (dec); R_f = 0.75 (50% EtOAc/hexanes); IR (film) 3369, 2969, 2930, 2838, 1699, 1553, 1523, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.08 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.91-6.83 (m, 4H), 5.73 (d, *J* = 10.0 Hz, 1H), 5.63 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.78 (d, *J* = 9.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.4, 150.5, 149.2, 149.1 (2C), 130.1, 123.9, 122.2, 119.1, 111.3, 122.2, 119.1, 111.1, 111.0, 110.7, 110.6, 94.2, 80.3, 55.9 (4C), 28.1; HRMS (ESI): Exact mass calcd for $C_{23}H_{30}N_2NaO_8$ $[M+Na]^+$ 485.1900, found 485.1958.

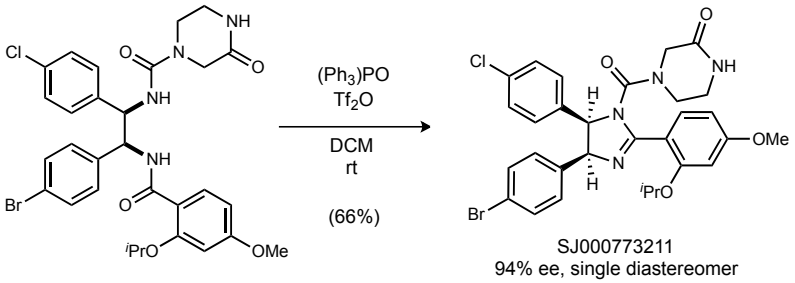


3-Trifluoromethoxy-*cis*-Imidazoline (74). Tf_2O (16 µL, 96 µmol) was added to a stirring solution of Ph_3PO (53 mg, 191 µmol) in dichloromethane (300 µL) at 0 °C, stirred for 10 min, then treated with *cis*-amide urea **19** (30.2 mg, 48.8 µmol) as a solution in dichloromethane (800 µL). The mixture was stirred at 0 °C for 1 h prior to stirring at room temperature for 4 hours. The reaction mixture was quenched with $NaHCO_3$, the aqueous layer was extracted with dichloromethane, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0-4% methanol in dichloromethane) of the residue provided the product as a white solid (21.0 mg, 73%). $[\alpha]_D^{20}$ -1.7 (*c* 0.21, $CHCl_3$); mp = 125-126 °C; R_f = 0.26 (5% MeOH/CH_2Cl_2); IR (film) 3216, 2980, 2932, 1683, 1614, 1440 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.56 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 6.40 (s, 1H), 5.59 (d. *J* = 10.0 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 4.61 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.83 (d, *J* = 18.0 Hz, 1H), 3.62 (d, *J* = 18.0 Hz, 1H), 3.42 (m, 1H), 3.18 (m, 1H), 3.00 (m, 2H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.33 (d, *J* = 6.0 Hz, 3H); ^{13}C

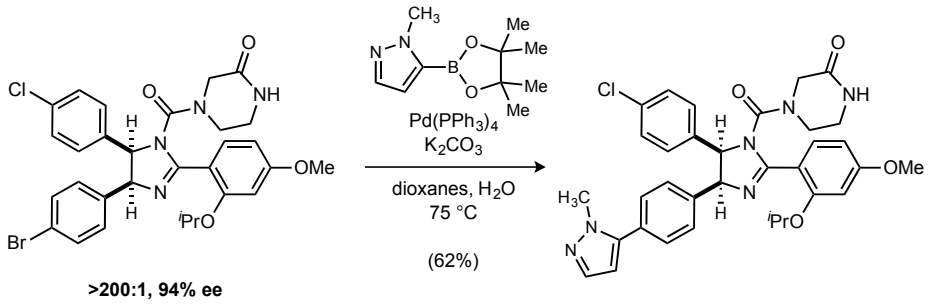
NMR (100 MHz, $CDCl_3$) ppm 166.8, 163.0, 160.6, 157.1, 154.7, 148.9, 134.8, 133.3, 132.1, 129.2, 128.2, 128.1, 126.4, 121.6, 120.6, 120.4 (q, $^1J_{CF}$ = 256 Hz), 119.9, 133.4, 104.6, 104.1, 100.2, 71.8, 71.1, 69.1, 63.9, 55.5, 49.3, 42.0, 40.5, 22.0 (2C), 18.0, 15.3; HRMS (ESI): Exact mass calcd for $C_{31}H_{31}ClF_3N_4O_5$ $[M+H]^+$ 631.1935, found 631.1917.



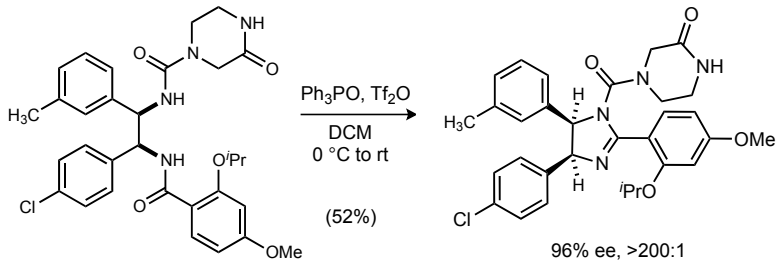
***N*-((1*S*,2*R*)-1-(4-Chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-2-(3-(trifluoromethoxy)phenyl) ethyl)-3-oxopiperazine-1-carboxamide (76).** The amine (35 mg, 76 μmol) and carboxylic acid (16 mg, 77 μmol) were dissolved in CH_2Cl_2 (385 μL), chilled to 0 °C, and treated with EDC•HCl (19 mg, 99 μmol) and DMAP (1.0 mg, 7.7 μmol). The reaction was stirred and allowed to gradually warm to room temperature over 2 h. After 17 h, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water, satd aq $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0-4% methanol in dichloromethane) afforded a single diastereomer of the amide as a yellow oil (42 mg, 87%). $[\alpha]_D^{20}$ +84 (*c* 1.01, $CHCl_3$); R_f = 0.2 (5% MeOH/CH_2Cl_2); IR (film) 3368, 3257, 2980, 2931, 1676, 1641, 1537, 1503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 5.2 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.17 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.87 (m, 1H), 6.83 (br d, 1H), 6.60 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.85 (dd, *J* = 8.0, 2.4 Hz, 1H), 5.14 (dd, *J* = 2.4, 2.4 Hz, 1H), (qq, *J* = 6.0, 6.0 Hz, 1H), 4.12 (br m, 2H), 3.85 (s, 3H), 3.70 (m, 1H), 3.58 (m, 1H), 3.38 (br m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.9, 167.2, 157.3, 155.9, 149.2, 140.5, 136.3, 134.5, 133.4, 130.0, 129.2, 128.1, 125.8, 121.0 (q, $^1J_{CF}$ = 254 Hz), 120.5, 119.8, 113.4, 105.4, 100.3, 71.6, 61.8, 57.7, 55.6, 47.5, 41.1, 40.0, 21.8, 21.4; HRMS (ESI): Exact mass calcd for $C_{31}H_{33}ClF_3N_4O_6$ $[M+H]^+$ 649.2041, found 649.2023.



4-Bromo-*cis*-Imidazoline (77). Tf_2O (143 µL, 845 µmol) was added to a stirring solution of $(Ph_3)PO$ (470 mg, 1.69 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C, stirred for 10 min, then treated with the *cis*-amide urea (272 mg, 422 µmol) as a solution in CH_2Cl_2 (2.0 mL). The mixture was stirred at 0 °C for 1 h prior to stirring at room temperature for 4 hours. The reaction mixture was quenched with $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0-2% methanol in dichloromethane) of the residue provided the product as a white solid (173 mg, 66%). $[\alpha]_D^{20}$ -69 (*c* 0.70, $CHCl_3$); mp = 118-120 °C; R_f = 0.39 (10% MeOH/CH_2Cl_2); IR (film) 3223, 3077, 2980, 2931, 1676, 1613, 1495, 1419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.00 (br s, 1H), 5.56 (d, *J* = 9.6 Hz, 1H), 5.46 (d, *J* = 9.6 Hz, 1H), 4.61 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.85 (s, 3H), 3.77 (d, *J* = 18.0 Hz, 1H), 3.65 (d, *J* = 18.0 Hz, 1H), 3.88 (m, 1H), 3.22 (m, 1H), 3.01 (m, 2H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.34 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.0, 160.2, 157.0, 154.7, 136.5, 135.0, 133.1, 132.1, 130.9, 129.6, 128.4,128.1, 121.0, 113.4, 104.6, 100.1, 71.8, 70.9, 69.1, 55.5, 49.4, 41.8, 40.3, 22.0 (2C); HRMS (ESI): Exact mass calcd for $C_{30}H_{31}BrClN_4O_4$ $[MH]^+$ 625.1217, found 625.1207.



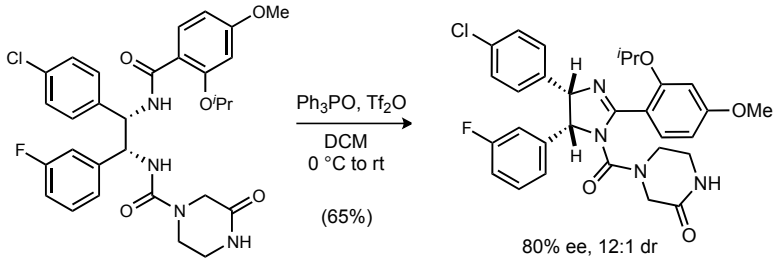
4-Pyrrol-*cis*-imidazoline (79).[209] To a microwave vial under an inert atmosphere was added $Pd(PPh_3)_4$ (4.7 mg, 4.1 μmol). The vial was charged with K_2CO_3 (13.3 mg, 96.0 μmol), the boronic ester (10.0 mg, 48.0 μmol), and the bromo arene (20.0 mg, 32.0 μmol). The vial was sealed, evacuated, and backfilled with argon. This process was repeated three times. A 5:1 mixture of dioxanes in water (865 μL) was then added via syringe under argon. The mixture was stirred for 20 h at 80 ºC (conventional heating) and the solvent was then evaporated after cooling. Column chromatography (SiO_2, 0-5% methanol in dichloromethane) of the residue afforded the adduct as an off-white foam (13 mg, 62%). $[\alpha]_D^{20}$ -37 (*c* 0.27, $CHCl_3$); R_f = 0.68 (10% $MeOH/CH_2Cl_2$); IR (film) 3259, 2923, 2852, 1674, 1607, 1423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 6.24 (d, *J* = 2.0 Hz, 1H), 5.86 (br s, 1H), 5.62 (d, *J* = 9.6 Hz, 1H), 5.58 (d, *J* = 9.6 Hz, 1H), 4.61 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.73 (m, 2H), 3.38 (m, 1H), 3.28 (m, 1H), 3.04 (m, 2H), 1.40 (d, *J* = 6.0 Hz, 3H), 1.62 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.5, 163.0, 160.3, 157.1, 154.9, 143.2, 138.4, 138.0, 135.3, 133.1, 132.2, 129.5, 128.4, 128.2 (2C), 127.9, 105.8, 104.6, 100.2, 72.2, 71.1, 69.3, 68.4, 63.7, 55.6, 49.8, 41.7, 40.5, 37.3, 29.7, 22.1; HRMS (ESI): Exact mass calcd for $C_{34}H_{36}ClN_6O_4$ $[M+H]^+$ 627.2487, found 627.2466.



3-Methyl-*cis*-imidazoline (80). The phosphine oxide (173 mg, 620 μmol) was dissolved in CH_2Cl_2 (2.2 mL) under an argon atmosphere before addition of triflic anhydride (52.0 μL, 310 μmol). This solution was stirred for 15 min before addition of the urea (82.0 mg, 140 μmol). The reaction was allowed to stir for 2 h before diluting with CH_2Cl_2 and quenching with satd aq

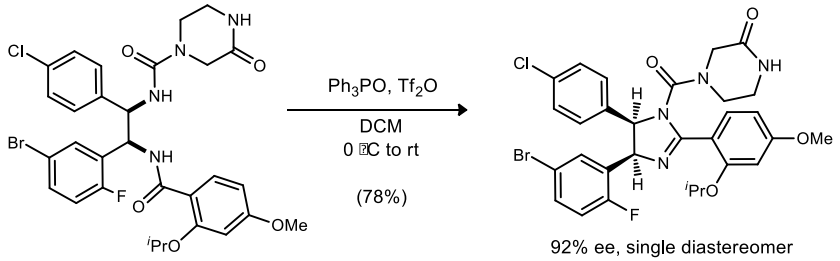
[209] Conditions adapted from patent precedence. WO2009/98104, A1, col. 173

$NaHCO_3$. The aqueous layer extracted with CH_2Cl_2 and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The product was then purified by column chromatography (0-5% MeOH in CH_2Cl_2) to afford the desired compound as a white solid (41 mg, 52%). $[\alpha]_D^{20}$ -125 (*c* 0.11, $CHCl_3$); mp = 113-115 °C; R_f = 0.40 (10% MeOH/CH_2Cl_2); IR (film) 3222, 2930, 1676, 1608, 1423, 1338, 1284, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.92-6.85 (m, 3 H), 6.85 (d, *J* = 7.5 Hz, 1 H), 6.69 (d, *J* = 7.5 Hz, 1 H), 6.64 (s, 1 H), 6.55 (dd, *J* = 6.3, 2.2 Hz, 1 H), 6.49 (d, *J* = 2.1 Hz, 1 H), 6.11 (s, 1 H), 5.59 (d, *J* = 9.9 Hz, 1 H), 5.47 (d, *J* = 9.9 Hz, 1 H), 4.60 (qq, 1 H), 3.84 (s, 3 H), 3.82 (d, *J* = 16 Hz, 1 H), 3.73 (d, *J* = 19 Hz, 1 H), 3.33-3.30 (m, 1 H), 3.27-3.19 (m, 1 H), 3.00 (br, 2 H), 2.12 (s, 3 H), 1.39 (d, *J* = 4.0 Hz, 3 H), 1.37 (d, *J* = 4.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.1, 162.7, 160.4, 156.9, 154.8, 137.4, 136.6, 136.0, 132.5, 131.8, 129.2, 128.1, 127.8, 127.7, 127.5, 123.9, 113.9, 104.5, 100.2, 71.9, 71.0, 69.5, 55.4, 53.4, 49.1, 41.7, 40.4, 29.6, 22.1, 22.0, 21.2; HRMS (ESI): Exact mass calcd for $C_{31}H_{34}ClN_4O_4$ $[M+H]^+$ 561.2263, found 561.2242.

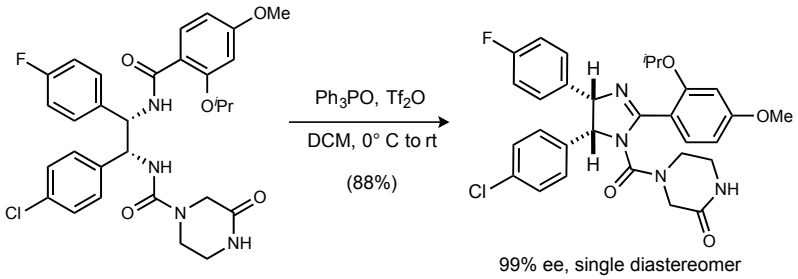


3-Fluoro-*cis*-imidazoline (81). Triphenyl phosphine oxide (92 mg, 0.330 mmol) was dissolved in dichloromethane (0.65 mL) at room temperature. Triflic anhydride (27.8 μL, 0.165 mmol) was delivered via syringe and the solution allowed to stir for 30 min. The urea (48 mg, 0.082 mmol) was delivered as a solution in dichloromethane (0.65 mL, 1.30 mL total) and the reaction stirred for 18 hours. The reaction was diluted with dichloromethane, quenched with saturated $NaHCO_3$, and extracted once. The aqueous layer was back extracted with dichloromethane and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to a yellow/orange foam. This material was redissolved in dichloromethane and purified by column chromatography (0-4% MeOH/CH_2Cl_2) to afford the desired Nutlin derivative as a light yellow solid (30 mg, 65%). Mp = 112-114 °C; R_f = 0.40 (10% MeOH/CH_2Cl_2); IR (film) 3223, 2979, 2929, 1676, 1607, 1424, 1340, 1280; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 1 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 6.99 (m, 1 H), 6.94 (d, *J* = 8.0 Hz), 6.76 (m, 2 H), 6.62 (d, *J* = 8.0 Hz), 6.58 (s, 1 H), 6.55 (dd, *J*

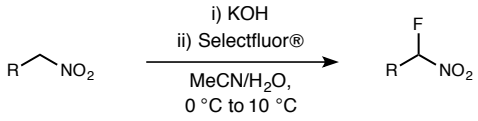
= 8.4, 2.0 Hz, 1 H), 6.48 (d, *J* = 2.0 Hz, 1 H), 5.55 (d, *J* = 9.6 Hz, 1 H), 5.49 (d, *J* = 9.6 Hz, 1 H), 4.61 (qq, *J* = 6.0, 6.0 Hz, 1 H), 3.84 (s, 3 H), 3.80 (d, *J* = 18.4 Hz, 1 H), 3.60 (d, *J* = 18.0 Hz, 1 H), 3.44 (m, 1 H), 3.15 (m, 1 H), 2.99 (m, 2 H), 1.39 (d, *J* = 6.0 Hz, 3 H), 1.33 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.0, 162.5 (d, $^1J_{CF}$ = 244 Hz), 160.2, 157.0, 154.8, 139.2, 139.1, 135.9, 132.8, 132.3, 129.5, 129.4, 129.1, 128.4, 127.8, 122.7, 114.4, 114.2, 114.1, 113.8, 113.3, 104.5, 100.0, 71.9, 70.9, 69.3, 55.5, 53.4, 49.5, 42.0, 40.4, 29.6, 22.0, 21.7; HRMS (ESI): Exact mass calcd for $C_{30}H_{31}ClFN_4O_4$ $[M+H]^+$ 565.2018, found 565.2023.



2-Fluoro-5-bromo-*cis*-Imidazoline (82). Tf_2O (35.8 µL, 212 µmol) was added to a stirring solution of Ph_3PO (118 mg, 424 µmol) in CH_2Cl_2 (300 µL) at 0 °C. The mixture was stirred for 10 min before the urea (70 mg, 106 µmol) was added as a solution in CH_2Cl_2 (800 µL) and the mixture was stirred at 0 °C and warmed to room temperature over 3 hours. The reaction mixture was quenched with $NaHCO_3$ at room temperature, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0-4% methanol in dichloromethane) of the residue provided the product as a white solid (52.0 mg, 78%). $[\alpha]_D^{20}$ -57 (*c* 0.71, $CHCl_3$); Mp = 123-124 °C; R_f = 0.57 (10% MeOH/CH_2Cl_2); IR (film) 3229, 2981, 2933, 2361, 1680, 1604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.16 (m, 1H), 7.02 (s, 4H), 6.64 (s, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.47 (s, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 5.55 (d, *J* = 10.0 Hz, 1H), 4.59 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.84 (s, 3H), 3.80 (d, *J* = 18.0 Hz, 1H), 3.58 (d, *J* = 18.0 Hz, 1H), 3.42 (m, 1H), 3.12 (m 1H), 3.02 (br m, 2H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.9, 163.1, 160.6, 158.7 (d, $^1J_{CF}$ = 244 Hz), 156.9, 154.9, 153.3, 133.4, 132.4, 132.1 (2C), 131.9, 131.7 (2C), 128.5, 128.4, 128.3, 128.1, 127.9, 116.5 (d, $^3J_{CF}$ = 4 Hz), 116.1 (d, $^2J_{CF}$ = 24 Hz), 113.4, 104.6, 100.0, 70.8, 68.1, 66.6, 55.5, 49.7, 42.1, 40.3, 22.1, 22.0; HRMS (ESI): Exact mass calcd for $C_{30}H_{30}BrClFN_4O_4$ $[M+H]^+$ 643.1123, found 643.1127.

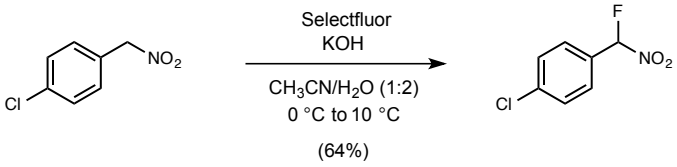


4-Fluoro-*cis*-Imidazoline (83). Triphenylphosphene oxide (136 mg, 488 μmol) and dichloromethane (200 μL) were added to a flame-dried flask. The solution was chilled to 0 °C and treated with triflic anhydride (41 μL, 244 μmol) and stirred for 10 min. The urea (71 mg, 122 μmol) was added as a solution in dichloromethane (800 μL) to the reaction flask and allowed to stir for 1 h at 0 °C. The mixture was allowed to warm to room temperature and stir for 3 more hours. The solution was diluted with dichloromethane and quenched with satd aq $NaHCO_3$. The mixture was extracted with dichloromethane and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification via column chromatography (0-5% methanol in dichloromethane) yielded an off white foam (60 mg, 88%). $[\alpha]_D^{20}$ +137 (*c* 0.28, $CHCl_3$); R_f = 0.33 (5% MeOH in CH_2Cl_2); IR (film) 3217, 1982, 1926, 1680, 1611, 1514, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.95-6.92 (m, 2H), 6.88-6.84 (m, 3H), 6.78 (dd, *J* = 8.8, 8.4 Hz, 2H), 6.53 (dd, *J* = 8.4, 8.4 Hz, 1H), 6.46 (dd, *J* = 2.0 Hz, 1H), 5.53 (d, *J* = 10.0 Hz, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 4.59 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.82 (s, 3H), 3.73 (d, *J* = 18.4 Hz, 1H), 3.62 (d, *J* = 18.4 Hz, 1H), 3.35 (m, 1H), 3.18 (m, 1H), 2.95 (br m, 2H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.0, 163.9, 161.9 (d, $^1J_{CF}$ = 244 Hz ppm), 160.0, 156.9, 154.8, 135.1, 133.1 (d, $^4J_{CF}$ = 3 Hz), 133.0, 132.2, 129.3 (d, $^3J_{CF}$ = 8 Hz), 128.3, 128.0, 114.6 (d, $^2J_{CF}$ = 21 Hz), 113.5, 104.5, 100.1, 71.7, 70.9, 69.2, 55.5, 49.4, 41.8, 40.3, 22.0 (2C); HRMS (ESI) Exact mass cald for $C_{30}H_{31}ClFN_4O_4$ $[M+H]^+$ 565.2018, found 565.1992.



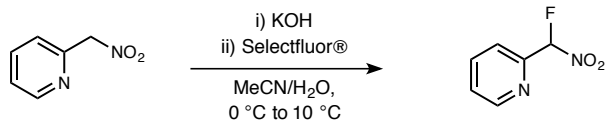
General Procedure to α-Fluoro Nitroalkanes.[210]

A round bottom flask was charged with the nitroalkane (3.50 mmol) and MeCN/H_2O (2.7 mL/5.4 mL). The solution was cooled to 0 °C, solid KOH (97%) (195 mg, 3.50 mmol) was added, and the reaction was vigorously stirred for 1 h at 0 °C. The reaction mixture was chilled to -20 °C to partially precipitate the nitronate salt and Selectfluor was added as a partially dissolved solution in CH_2Cl_2 which was chilled to -78 °C. This mixture was gradually warmed and vigorously stirred for 30 min or until the reaction exceeded 10 °C. The resulting biphasic mixture was diluted with diethyl ether and stirred for an additional 10 min. The water layer was extracted with diethyl ether, and the combined organics were dried ($MgSO_4$), filtered, and concentrated. The crude oil was purified by flash column chromatography (SiO_2) to give the title compound as a colorless oil.

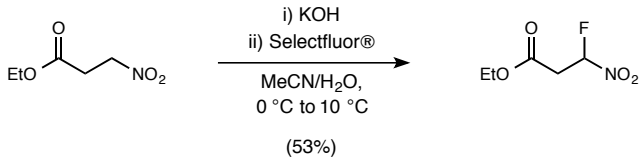


1-Chloro-4-(fluoro(nitro)methyl)benzene (131). This compound was prepared according to the general procedure employing 3.50 mmol of the nitroalkane. The crude oil was purified by flash column chromatography (SiO_2, 1-4% ethyl acetate in hexanes) to give the title compound as a colorless oil (420 mg, 64%). R_f = 0.8 (33% Et_2O/hexanes); IR (film) 3008, 2932, 1579, 1371, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 6.58 (d, $^2J_{HF}$ = 48.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 138.4, 129.5 (2C), 128.5 (d, $^2J_{CF}$ = 21.0 Hz), 127.9 (d, $^3J_{CF}$ = 6.0 Hz, 2C), 109.2 (d, $^1J_{CF}$ = 239 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) ppm –140.6 (d, J = 48.8 Hz); HRMS (CI GCMS): Exact mass calcd for $C_7H_6ClFNO_2$ $[M+H]^+$ 190.0066, found 190.0059.

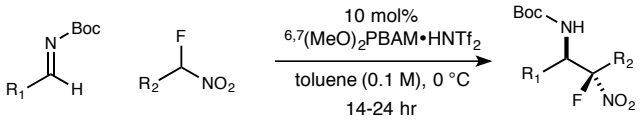
[210] *J. Fluor. Chem.* **2012**, *133*, 108-114.



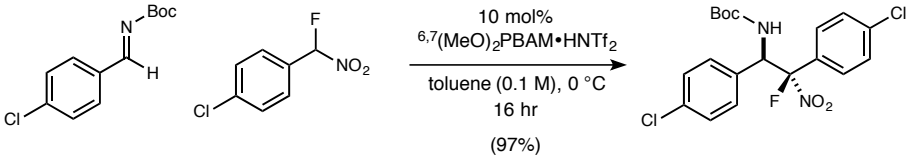
2-(Fluoro(nitro)methyl)pyridine (149). This compound was prepared according to the general procedure employing 753 μmol of the nitroalkane. The crude oil was purified by flash column chromatography (SiO_2, 30% ethyl acetate in hexanes) to give the title compound as a colorless oil (107 mg, 91%). R_f = 0.55 (33% Et_2O/hexanes); IR (film) 3069, 2934, 2988, 1586, 1377 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.69 (d, J = 4.2 Hz, 1H), 7.87 (m, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 7.8, 4.8 Hz, 1H), 6.72 (d, $^2J_{HF}$ = 49.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 150.1, 149.2 (d, $^2J_{CF}$ = 22.5 Hz), 137.7, 126.3, 121.5 (d, $^3J_{CF}$ = 4.5 Hz), 109.1 (d, $^1J_{CF}$ = 239 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) ppm –142.5; HRMS (CI GCMS): Exact mass calcd for $C_6H_5FN_2O_2$ $[M+]^+$ 157.0408, found 157.0406.



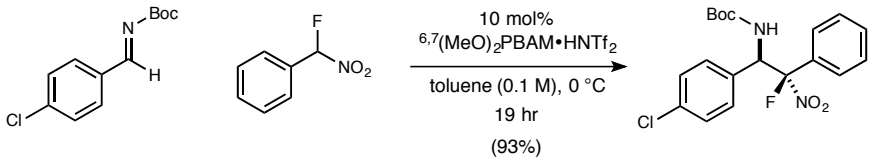
Ethyl 3-fluoro-3-nitropropanoate (152). This compound was prepared according to the general procedure employing 2.07 mmol of the nitroalkane. The crude oil was purified by flash column chromatography (SiO_2, 30% ethyl acetate in hexanes) to give the title compound as a colorless oil (180 mg, 53%). R_f = 0.65 (25% Et_2O/hexanes); IR (film) 2988, 2941, 1747, 1586, 1396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (ddd, J = 6.8, 4.0 Hz; $^2J_{HF}$ = 48.8 Hz, 1H), 4.23 (q, J = 6.8 Hz, 2H), 3.26-3.09 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 166.1 (d, $^3J_{CF}$ = 4.0 Hz), 106.9 (d, $^1J_{CF}$ = 239 Hz), 62.1, 38.2 (d, $^2J_{CF}$ = 22 Hz), 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) ppm –146.9.



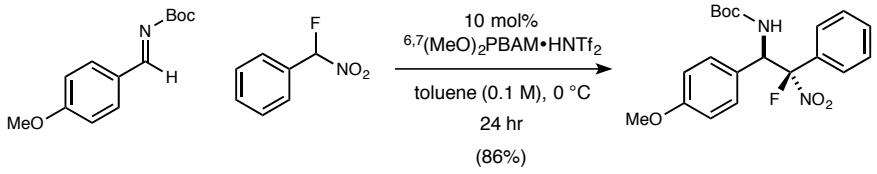
General Procedure to Enantioenriched α-Fluoro β-Amino Nitroalkanes (132-146).
A flame-dried reaction vial was charged with the nitroalkane (55 μmol), toluene (500 μL), and $^{6,7}(MeO)_2PBAM•HNTf_2$ (**2b**•$HNTf_2$) (4.54 mg, 5 μmol) at room temperature and stirred until homogeneous. The reaction was chilled to 0 °C before the imine (50 μmol) was added. The mixture was stirred at 0 °C for 14-24 h and monitored by TLC. The reaction mixture was quickly flushed through a pad of silica gel and washed through with CH_2Cl_2. The filtrate was concentrated, and the residue was purified by column chromatography (SiO_2, ethyl acetate in hexanes) to afford the title compound.



***tert*-Butyl ((1*R*,2*R*)-1,2-bis(4-chlorophenyl)-2-fluoro-2-nitroethyl)carbamate (132)**. This compound was prepared according to the general procedure employing 58 μmol of the nitroalkane with a 16 h reaction time. Column chromatography (SiO_2, 2-5% ethyl acetate in hexanes) afforded the adduct as a colorless oil (23 mg, 97%), which was found to be 4.8:1 dr and 91% ee for the major diastereomer and 86% ee for the minor diastereomer by chiral HPLC analysis (Chiralpak IA, 7% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 7.15 min, $t_r(d_1e_2$, major/minor) = 8.73 min, $t_r(d_2e_1$, minor/major) = 11.9 min, $t_r(d_2e_2$, minor/minor) = 45.8 min). R_f = 0.85 (25% EtOAc/hexanes); IR (film) 3410, 3313, 2987, 2932, 2869, 1711, 1580, 1502, 1371 cm^{-1}; Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.35-7.31 (m, 4H), 6.15 (dd, J = 28.2, 10.2 Hz, 1H), 5.13 (d, J = 9.6 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.1, 137.7, 135.4, 131.9, 129.9. 129.5 ($^2J_{CF}$ = 23 Hz), 129.1, 129.0, 127.5 ($^3J_{CF}$ = 9.2 Hz), 118.8 ($^1J_{CF}$ = 243 Hz), 81.1, 57.2 ($^2J_{CF}$ = 18 Hz), 27.9; ^{19}F NMR (376 Hz, $CDCl_3$) δ −139.7 (major), −139.8 (minor); HRMS (ESI): Exact mass calcd for $C_{19}H_{19}Cl_2FN_2NaO_4$ $[M+Na]^+$ 451.0604, found 451.0594.

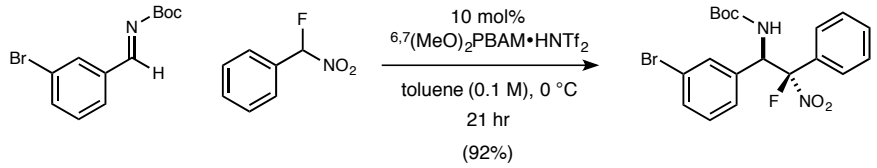


***tert*-Butyl ((1*R*,2*R*)-1-(4-chlorophenyl)-2-fluoro-2-nitro-2-phenylethyl)carbamate (136)**. This compound was prepared according to the general procedure employing 303 μmol of the nitroalkane with a 19 h reaction time. Column chromatography (SiO_2, 3-6% ethyl acetate in hexanes) afforded the adduct as a colorless oil (100 mg, 93%), which was found to be 5.2:1 dr and 95% ee for the major diastereomer by chiral HPLC analysis (Chiralpak IA, 4% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 9.3 min, $t_r(d_1e_2$, major/minor) = 10.3 min, $t_r(d_2e_1$, minor/major) = 12.5 min, $t_r(d_2e_2$, minor/minor) = 24.7 min). R_f = 0.82 (25% EtOAc/hexanes); IR (film) 3425, 3328, 3065, 2982, 2926, 1708, 1583, 1500, 1168 cm^{-1}; Major diastereomer: ^1H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 7.2 Hz, 2H), 7.50-7.46 (m, 3H), 7.36-7.32 (m, 4H), 6.20 (dd, J = 28.2, 9.6 Hz, 1H), 5.20 (d, J = 9.0 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.1, 135.2, 132.3, 131.2, 131.0 ($^2J_{CF}$ = 28 Hz), 130.0, 129.0, 128.8, 125.9 ($^3J_{CF}$ = 9.3 Hz), 119.0 ($^1J_{CF}$ = 243 Hz), 80.9, 57.3 ($^2J_{CF}$ = 18 Hz), 27.9; ^{19}F NMR (376 Hz, $CDCl_3$) δ −139.9; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}ClFN_2NaO_4$ $[M+Na]^+$ 417.0993, found 417.0976.

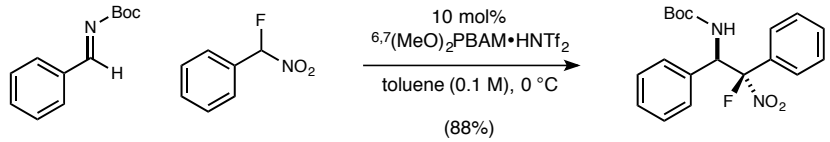


***tert*-Butyl ((1*R*,2*R*)-2-fluoro-1-(4-methoxyphenyl)-2-nitro-2-phenylethyl)carbamate (137)**. This compound was prepared according to the general procedure employing 181 μmol of the nitroalkane with a 24 h reaction time. Column chromatography (SiO_2, 4-7% ethyl acetate in hexanes) afforded the adduct as a colorless oil (60 mg, 86%), which was found to be 5.6:1 dr and 96% ee for the major diastereomer by chiral HPLC analysis (Chiralpak AD-H, 5% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 9.09 min, $t_r(d_2e_1$, minor/major) = 11.2 min, $t_r(d_1e_2$, major/minor) = 12.1 min, $t_r(d_2e_2$, minor/minor) = 18.4 min). R_f = 0.43 (15% EtOAc/hexanes); IR (film) 3416, 3334, 2970, 2935, 1698, 1568, 1513, 1170 cm^{-1}; Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 10.0 Hz, 2H), 7.50-7.43 (m, 3H), 7.36-

7.32 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.16 (dd, J = 27.6, 12.2 Hz, 1H), 5.15 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.0, 154.1. 131.4 ($^2J_{CF}$ = 23.0 Hz), 131.0, 129.8, 128.9 (2C), 126.0 ($^3J_{CF}$ = 10.0 Hz), 119.4 ($^1J_{CF}$ = 243 Hz), 114.2, 80.6, 58.8 ($^2J_{CF}$ = 17.0 Hz), 57.3, 28.0; ^{19}F NMR (376 Hz, $CDCl_3$) δ −140.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}FN_2NaO_5$ $[M+Na]^+$ 413.1489, found 413.1479.

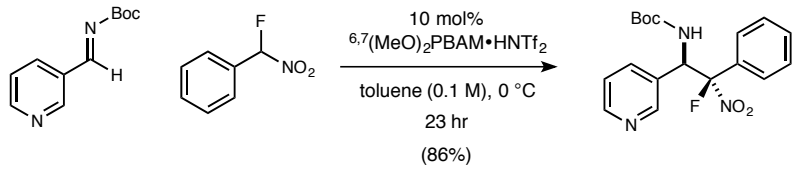


***tert*-Butyl ((1*R*,2*R*)-1-(3-bromophenyl)-2-fluoro-2-nitro-2-phenylethyl)carbamate (138)**. This compound was prepared according to the general procedure employing 119 μmol of the nitroalkane with a 21 h reaction time. Column chromatography (SiO_2, 3-7% ethyl acetate in hexanes) afforded the adduct as a colorless oil (48 mg, 92%), which was found to be 4.8:1 dr and 92% ee for the major diastereomer by chiral HPLC analysis (Chiralpak AD-H, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_1e_1, major/major) = 9.38 min, t_r(d_1e_2, major/minor) = 13.7 min, t_r(d_2e_1, minor/major) = 15.3 min, t_r(d_2e_2, minor/minor) = 22.8 min). R_f = 0.57 (15% EtOAc/hexanes); IR (film) 3421, 3324, 3069, 2972, 2924, 1710, 1579, 1372, 1165 cm^{-1}; Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 9.8 Hz, 2H), 7.49-7.37 (m, 4H), 7.29-7.22 (m, 2H), 7.12 (m, 1H), 6.20 (dd, J = 27.8, 9.2 Hz, 1H), 5.06 (d, J = 8.8 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.1, 135.9, 132.3, 131.6, 131.4 ($^2J_{CF}$ = 32.0 Hz), 131.1, 130.3, 128.7 (2C), 125.9 ($^3J_{CF}$ = 10.0 Hz), 122.8, 119.3 ($^1J_{CF}$ = 240 Hz), 81.0, 57.4 ($^2J_{CF}$ = 18.0 Hz), 28.0; ^{19}F NMR (376 Hz, $CDCl_3$) δ −139.8; HRMS (ESI): Exact mass calcd for $C_{19}H_{20}BrFN_2NaO_4$ $[M+Na]^+$ 461.0488, found 461.0479.

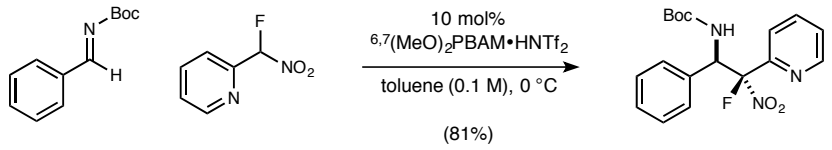


***tert*-Butyl ((1*R*,2*R*)-2-fluoro-2-nitro-1,2-diphenylethyl)carbamate (139)**. This compound was prepared according to the general procedure using the nitroalkane (65.0 mg, 418 μmol) and the imine (78.0 mg, 380 μmol) with a 20 h reaction time. Column chromatography (SiO_2, 15-20% ethyl acetate in hexanes) afforded the product as a colorless oil (120 mg, 88%), which was found

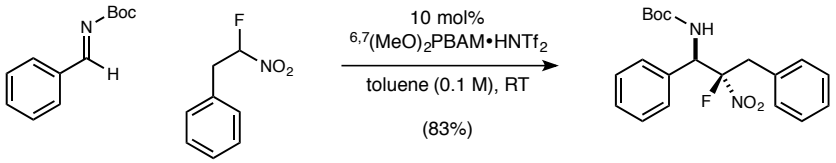
to be 3.5:1 dr and 94% ee for the major diastereomer and 84% ee for the minor diastereomer by chiral HPLC analysis (Chiralpak IA, 6% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 7.55 min, $t_r(d_2e_1$, minor/major) = 10.5 min, $t_r(d_1e_2$, major/minor) = 11.3 min, $t_r(d_2e_2$, minor/minor) = 14.5 min). R_f = 0.7 (25% EtOAc/hexanes); IR (film) 3387, 3064, 3034, 2980, 2929, 1697, 1564, 1514, 1163 cm^{-1}; Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 6.4 Hz, 2H), 7.39-7.35 (m, 3H), 7.30-7.22 (m, 4H), 7.10 (m, 1H), 6.14 (dd, J = 28.0, 10.0 Hz, 1H), 5.12 (d, J = 10.0 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.2, 133.7, 131.1, 129.1, 128.8, 128.6 (2C), 128.5, 126.0 ($^2J_{CF}$ = 90 Hz), 118.8 ($^1J_{CF}$ = 241 Hz), 80.9, 57.9 ($^2J_{CF}$ = 20 Hz), 28.0; ^{19}F NMR (376 Hz, $CDCl_3$) δ −139.4 (minor), −139.9 (major); HRMS (CI): Exact mass calcd for $C_{19}H_{22}FN_2O_4$ $[M+H]^+$ 361.1558, found 361.1557.



***tert*-Butyl ((1*R*,2*R*)-2-fluoro-2-nitro-2-phenyl-1-(pyridin-3-yl)ethyl)carbamate (140)**. This compound was prepared according to the general procedure employing 177 μmol of the nitroalkane with a 23 h reaction time. Column chromatography (SiO_2, 25-55% ethyl acetate in hexanes) afforded the adduct as a colorless oil (50 mg, 86%), which was found to be 6.9:1 dr and 95% ee for the major diastereomer by chiral HPLC analysis (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 11.7 min, $t_r(d_1e_2$, major/minor) = 14.1 min, $t_r(d_2e_2$, minor/minor) = 18.3 min, $t_r(d_2e_1$, minor/major) = 25.4 min). R_f = 0.3 (25% EtOAc/hexanes); IR (film) 3435, 3200, 2979, 2924, 1710, 1572, 1180 cm^{-1}; Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.50 (d, J = 4.4 Hz, 1H), 7.73 (d, J = 6.8 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.43-7.36 (m, 3H), 7.21-7.17 (m, 1H), 6.20 (dd, J = 29.2, 8.4 Hz, 1H), 5.62 (d, J = 10.0 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 150.2, 149.8, 136.3, 131.3, 130.6 ($^2J_{CF}$ = 23.0 Hz), 128.8, 125.8 ($^3J_{CF}$ = 9.0 Hz), 123.6, 119.4 ($^1J_{CF}$ = 243 Hz), 81.0, 56.2 ($^2J_{CF}$ = 17.0 Hz), 27.9; ^{19}F NMR (376 Hz, $CDCl_3$) δ −139.6; HRMS (ESI): Exact mass calcd for $C_{18}H_{21}FN_3O_4$ $[M+H]^+$ 362.1519, found 362.1507.

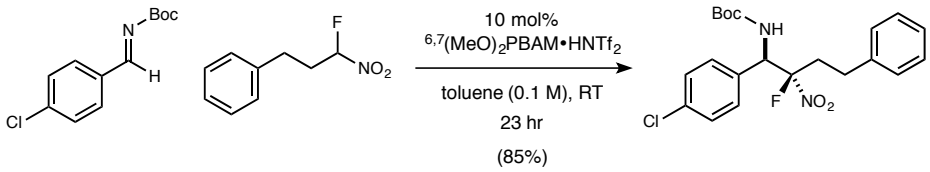


***tert*-Butyl ((1*R*,2*S*)-2-fluoro-2-nitro-1-phenyl-2-(pyridin-2-yl)ethyl)carbamate (141)**. This compound was prepared according to the general procedure using the nitroalkane (46.0 mg, 295 μmol) and imine (58.5 mg, 285 μmol) of the nitroalkane with a 24 h reaction time. Following filtration, the crude reaction was diluted with DCM and washed with 1.0 M KOH (to remove unreacted nitroalkane). The organics were combined, dried ($MgSO_4$), and filtered. Column chromatography (SiO_2, 15-20% ethyl acetate in hexanes) afforded the product as a colorless oil (83 mg, 81%), which was found to be 2.5:1 dr and 95% ee for the major diastereomer and 93% ee for the minor diastereomer by chiral HPLC analysis (Chiralpak IA, 7% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 12.7 min, $t_r(d_2e_1$, minor/major) = 13.7 min, $t_r(d_1e_2$, major/minor) = 15.9 min, $t_r(d_2e_2$, minor/minor) = 20.8 min). R_f = 0.3 (33% EtOAc/hexanes); IR (film) 3400, 3317, 3061, 2986, 2930, 1705, 1580, 1172 cm^{-1}; Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 4.8 Hz, 1H), 7.78 (ddd, J = 9.6, 4.0, 2.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.43-7.41 (m, 1H), 7.4-7.37 (m, 2H), 7.31-7.28 (m, 2H), 7.20 (m, 1H), 6.22 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) major diastereomer: ppm 154.2, 150.2 ($^2J_{CF}$ = 28 Hz), 149.2 ($^3J_{CF}$ = 3.0 Hz), 137.4, 134.5, 128.5, 128.5, 128.4, 125.6, 121.5 ($^3J_{CF}$ = 6.0 Hz), 117.5 ($^1J_{CF}$ = 240 Hz), 80.5, 58.0 (br d), 28.1; ^{19}F NMR (376 Hz, $CDCl_3$) δ −134.6 (major), −137.9 (minor); HRMS (ESI): Exact mass calcd for $C_{18}H_{20}FN_3NaO_4$ $[M+Na]^+$ 384.1336, found 384.1325.



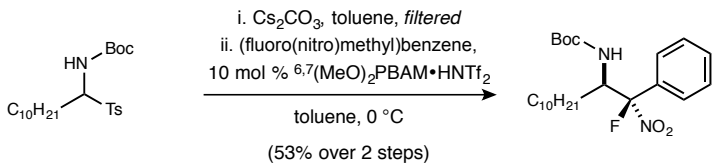
***tert*-Butyl ((1*R*,2*R*)-2-fluoro-2-nitro-1,3-diphenylpropyl)carbamate (142)**. This compound was prepared according to the general procedure using the nitroalkane (55.0 mg, 327 μmol) and the imine (61.0 mg, 297 μmol) with a 36 h reaction time. Column chromatography (SiO_2, 5-10% ethyl acetate in hexanes) afforded the product as a colorless oil (92 mg, 83%), which was found to be 6:1 dr and 97% ee for the major diastereomer and 84% ee for the minor diastereomer by chiral HPLC analysis (Chiralpak IB, 3% EtOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/major) = 9.1 min, $t_r(d_2e_2$, minor/minor) = 10.0 min, $t_r(d_1e_2$, major/minor) = 10.8 min, $t_r(d_2e_1$, minor/major) =

14.5 min). R_f = 0.7 (25% EtOAc/hexanes); IR (film) 3424, 3320, 3035, 2980, 2985, 1697, 1572, 1510, 1177 cm^{-1}; Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 5H), 7.27-7.24 (m, 3H), 7.07-7.06 (m, 2H), 5.65 (br d, *J* = 9.8 Hz, 1H), 5.12 (d, *J* = 20.0, 10.0 Hz, 1H), 3.57-3.44 (m, 1H), 3.06 (dd, *J* = 18.4, 9.8 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.3, 130.0, 129.2, 129.1, 128.7 (2C), 128.2, 128.0, 121.2 ($^1J_{CF}$ = 245 Hz), 80.9, 58.9 ($^2J_{CF}$ = 19 Hz), 41.0 ($^2J_{CF}$ = 20 Hz), 28.1; ^{19}F NMR (376 Hz, $CDCl_3$) δ −136.5 (minor), −139.5 (major); HRMS (CI): Exact mass calcd for $C_{20}H_{23}FN_2O_4$ $[M+]^+$ 374.16.[211]

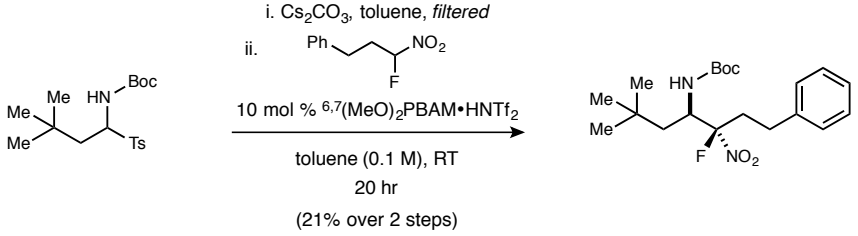


***tert*-Butyl ((1*R*,2*R*)-1-(4-chlorophenyl)-2-fluoro-2-nitro-4-phenylbutyl)carbamate (143)**. This compound was prepared according to the general procedure employing 102 μmol of the nitroalkane with a 23 h reaction time at room temperature. Column chromatography (SiO_2, 2-6% ethyl acetate in hexanes) afforded the adduct as a colorless oil (33 mg, 85%), which was found to be 5.0:1 dr and 93% ee for the major diastereomer by chiral HPLC analysis (Chiralpak IA, 5% EtOH/hexanes, 1.0 mL/min: $t_r(d_2e_1$, minor/major) = 9.2 min, $t_r(d_1e_1$, major/major) = 10.1 min, $t_r(d_1e_2$, major/minor) = 13.9 min, $t_r(d_2e_2$, minor/minor) = 17.7 min). R_f = 0.64 (15% EtOAc/hexanes); IR (film) 3421, 3324, 3027, 2979, 2931, 1710, 1572, 1496 cm^{-1}; Major diastereomer: ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.32-7.19 (m, 5H), 7.06 (d, *J* = 7.2 Hz, 2H), 5.57 (d, *J* = 9.6 Hz, 1H), 5.47 (dd, *J* = 20.4, 10.2 Hz, 1H), 2.76 (m, 1H), 2.61-2.53 (m, 1H), 2.50-2.42 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.3, 138.5, 135.3, 133.0, 129.3, 129.2, 128.7, 128.2, 126.7, 121.5 ($^1J_{CF}$ = 243 Hz), 81.1, 58.1 ($^2J_{CF}$ = 21.0 Hz), 36.7 ($^2J_{CF}$ = 21.0 Hz), 28.1, 28.0; ^{19}F NMR (376 Hz, $CDCl_3$) δ −137.0; HRMS (ESI): Exact mass calcd for $C_{21}H_{24}ClFN_2NaO_4$ $[M+Na]^+$ 445.1306, found 445.1300.

[211] Sample submitted for HRMS analysis at the time of this submission.

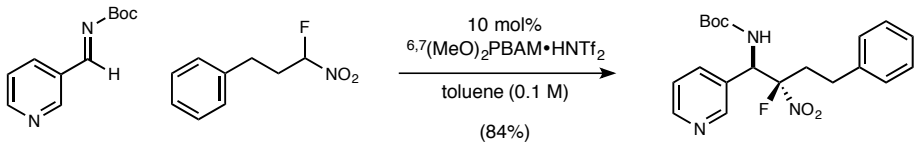


***tert*-Butyl ((1*R*,2*R*)-1-(4-chlorophenyl)-2-fluoro-2-nitro-2-phenylethyl)carbamate (144)**. A vial was charged with the sulfone (85 mg, 200 μmol), Cs_2CO_3 (324 mg, 1.00 mmol), and toluene (1 mL). The heterogeneous mixture was monitored by ^{1}H NMR and stirred at room temperature for 3.5 h. The mixture was carefully loaded onto a plug of Celite and flush through once with toluene (1 mL) into a separate reaction vial containing (fluoro(nitro)methyl)benzene (37 mg, 240 μmol). The mixture was chilled to 0 °C before the catalyst was added (18 mg, 20 μmol) and the reaction stirred for 20 h. The mixture was filtered through a plug of silica gel and concentrated. The residue was purified by column chromatography (SiO_2, 1-3% ethyl acetate in hexanes) to afford the adduct as a colorless oil (45 mg, 53% over 2 steps), which was found to be 6.1:1 dr and 88% ee for the major diastereomer by chiral HPLC analysis (Chiralpak OD-H, 2% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(d_1e_2, major/minor) = 5.2 min, t_r(d_1e_1, major/major) = 5.5 min, t_r(d_2e_1, minor/major) = 6.3 min, t_r(d_2e_2, minor/minor) = 8.1 min). R_f = 0.9 (25% EtOAc/hexanes); IR (film) 3425, 3349, 2927, 2858, 1708, 1579, 1175 cm^{-1}; Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.2 Hz, 2H), 7.43-7.38 (m, 3H), 5.18-5.06 (ddd, J = 21.6, 10.8, 10.8 Hz, 1H), 4.39 (d, J = 10.8 Hz, 1H), 1.47-1.33 (m, 4H), 1.31-1.20 (m, 23H), 0.87 (t, J = 8.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.9, 131.5 ($^2J_{CF}$ = 24 Hz), 128.9, 128.4, 125.9 ($^3J_{CF}$ = 10 Hz), 120.1 ($^1J_{CF}$ = 241 Hz), 80.1, 54.4 ($^2J_{CF}$ = 21 Hz), 31.9, 29.5 (2C), 29.4 (2C), 29.3, 29.0, 28.6 ($^4J_{CF}$ = 4 Hz), 28.0, 25.4, 14.1; ^{19}F NMR (376 Hz, $CDCl_3$) δ −141.4 (major), –140.8 (minor); HRMS (ESI): Exact mass calcd for $C_{23}H_{37}FN_2NaO_4$ $[M+Na]^+$ 447.2635, found 447.2635.



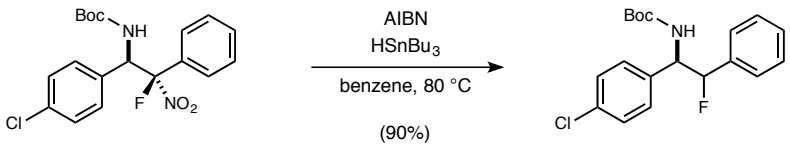
***tert*-Butyl ((3*R*,4*R*)-3-fluoro-6,6-dimethyl-3-nitro-1-phenylheptan-4-yl)carbamate (145)**. A vial was charged with the sulfone (36 mg, 100 μmol), Cs_2CO_3 (162 mg, 500 μmol), and toluene

(500 μL). The heterogeneous mixture was monitored by ^{1}H NMR and stirred at room temperature for 4.5 h. The mixture was carefully loaded onto a plug of Celite and flushed through once with toluene (500 μL) into a separate reaction vial containing the fluoronitroalkane (20 mg, 110 μmol). The mixture was chilled to 0 °C before the catalyst was added (9.1 mg, 10 μmol) and the reaction stirred for 20 h. The mixture was filtered through a plug of silica gel and concentrated. The residue was purified by column chromatography (SiO_2, 1-4% ethyl acetate in hexanes) to afford the adduct as a colorless oil (8 mg, 21% over 2 steps), which was found to be 10:1 dr and 84% ee for the major diastereomer by chiral HPLC analysis (Chiralpak AD-H, 3% EtOH/hexanes, 1.0 mL/min: t_r(e_1, major) = 5.5 min, t_r(e_2, minor) = 7.2 min). R_f = 0.8 (15% EtOAc/hexanes); IR (film) 3413, 3346, 2961, 2867, 1707, 1565 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31-7.27 (m, J = 7.2 Hz, 3H), 7.20 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 2H), 4.61-4.53 (ddd, J = 19.8, 14.4, 1.2 Hz, 1H), 4.44 (d, J = 10.2 Hz, 1H), 2.76-2.71 (ddd, J = 23.5, 12.0, 3.6 Hz, 1H), 2.67-2.57 (m, 1H), 2.53-2.48 (ddd, J = 25.2, 12.6, 4.8 Hz, 1H), 1.44 (d, J = 3.6 Hz, 2H), 1.42 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.0, 139.2, 128.6, 128.3, 126.5, 123.1 ($^1J_{CF}$ = 244 Hz), 80.7, 52.4 ($^2J_{CF}$ = 21 Hz), 42.6, 35.5 ($^2J_{CF}$ = 21 Hz), 30.0, 29.4, 28.3, 28.1 ($^3J_{CF}$ = 4 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −140.1 (major), –140.8 (minor); HRMS (ESI): Exact mass calcd for $C_{20}H_{31}FN_2NaO_4$ $[M+Na]^+$ 405.2166, found 405.2158.

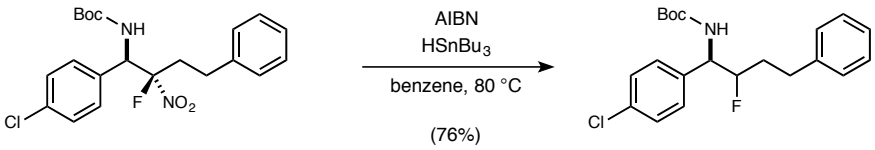


***tert*-Butyl ((*1R*,*2R*)-2-fluoro-2-nitro-4-phenyl-1-(pyridin-3-yl)butyl)carbamate (146)**. This compound was prepared according to the general procedure using the nitroalkane (23.0 mg, 126 μmol) and imine (23.5, 114 μmol) with a 22 h reaction time at room temperature. Column chromatography (SiO_2, 40% ethyl acetate in hexanes) afforded the product as a colorless oil (37 mg, 84%), which was found to be 4.4:1 dr and 96% ee for the major diastereomer and 90% ee for the minor diastereomer by chiral HPLC analysis (Chiralpak IA, 10% EtOH/hexanes, 1.0 mL/min: t_r(d_2e_2, minor/minor) = 9.6 min, t_r(d_2e_1, minor/major) = 10.4 min, t_r(d_1e_2, major/minor) = 12.8 min, t_r(d_1e_1, major/major) = 14.1 min). R_f = 0.5 (50% EtOAc/hexanes); IR (film) 3421, 3324, 3027, 2979, 2931, 1710, 1496 cm^{-1}; Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.33-7.23 (m, 3H), 7.19 (m, 1H), 7.06 (d, J = 6.6 Hz, 2H),

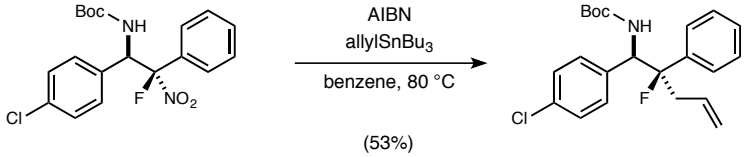
5.82 (br d, J = 9.0 Hz, 1H), 5.54 (dd, J = 20.4, 10.2 Hz, 1H), 2.80-2.75 (m, 1H), 2.64-2.54 (m, 1H), 2.49-2.45 (m, 1H), 2.11-2.09 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.7, 150.5, 149.2, 138.3, 135.3, 130.5, 128.7, 128.2, 126.8, 123.8, 121.3 ($^1J_{CF}$ = 244 Hz), 81.5, 56.7 ($^2J_{CF}$ = 21 Hz), 36.8 ($^2J_{CF}$ = 20 Hz), 29.7, 28.1; ^{19}F NMR (376 Hz, $CDCl_3$) δ −137.0 (major), –136.8 (minor); HRMS (ESI): Exact mass calcd for $C_{20}H_{25}FN_3O_4$ $[M+H]^+$ 390.1829, found 390.1823.



***tert*-Butyl ((1*R*)-1-(4-chlorophenyl)-2-fluoro-2-phenylethyl)carbamate** (**182**). To an oven-dried microwave vial was added the fluoronitroalkane (45 mg, 114 μmol) and benzene (500 μL). In a separate flame-dried vial was added AIBN (7.2 mg, 46 μmol), tributyltin hydride (153 μL, 570 μmol) and benzene (400 μL). Both solutions were subjected to freeze-pump-thaw cycles (-78 °C to RT, 3 cycles) and backfilled with argon. The fluoronitroalkane solution was heated to 80 °C and stirred. The AIBN/tributyltin hydride solution was then added in 4 portions over 40 min by syringe. After 2 h, the reaction mixture was cooled, the volatiles evaporated, and the remaining residue was purified by column chromatography (10% K_2CO_3 in SiO_2 by weight, 5-10% diethyl ether in hexanes) to afford the product as a white foam (36 mg, 90%), which was found to be ~2:1 dr. R_f = 0.8 (25% Et_2O/hexanes); IR (film) 3369, 2973, 2925, 1683, 1524, 1496, 1376 cm^{-1}; Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 1H), 7.29-7.25 (m, 2H), 7.24-7.16 (m, 3H), 7.02-6.97 (m, 3H), 5.80 (d, J = 31.2 Hz, 1H), 5.40 (br m, 1H), 5.07-4.96 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.9, 136.2 (d, $^2J_{CF}$ = 20.5 Hz), 134.8, 133.6, 129.4, 128.6, 128.2, 128.2, 125.9 (d, $^3J_{CF}$ = 7.5 Hz), 95.2 ($^1J_{CF}$ = 180 Hz), 80.1, 59.0 ($^2J_{CF}$ = 21 Hz), 28.3; ^{19}F NMR (376 Hz, $CDCl_3$) δ −194.5 (minor), –197.9 (major); HRMS (ESI): Exact mass calcd for $C_{19}H_{21}ClFNNaO_2$ $[M+Na]^+$ 372.1143, found 372.1152.

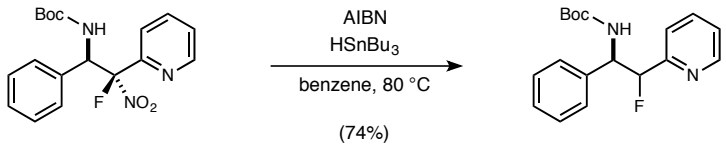


***tert*-Butyl ((1*R*)-1-(4-chlorophenyl)-2-fluoro-4-phenylbutyl)carbamate** (**183**). To an oven-dried microwave vial was added the fluoronitroalkane (28 mg, 66 μmol) and benzene (300 μL). In a separate flame-dried vial was added AIBN (4.2 mg, 25 μmol), tributyltin hydride (89 μL, 331 μmol) and benzene (600 μL). Both solutions were subjected to freeze-pump-thaw cycles (-78 °C to RT, 3 cycles) and backfilled with argon. The fluoronitroalkane solution was stirred and heated to 80 °C. The AIBN/tributyltin hydride solution was then added in 4 portions over 60 min by syringe. After 2 h, the reaction mixture was cooled, the volatiles removed by vacuum, and the remaining residue was purified by column chromatography (10% K_2CO_3 in SiO_2 by weight, 2-4-8% ethyl acetate in hexanes) to afford the product as a white foam (19 mg, 76%), which was found to be ~1:1 dr. R_f = 0.9 (25% EtOAc/hexanes); IR (film) 3424, 3320, 3049, 2966, 2918, 2862, 1711, 1496, 1378 cm^{-1}; Mixture of two diastereomers: ^1H NMR (600 MHz, $CDCl_3$) δ 7.32-7.27 (m, 8H), 7.24-7.17 (m, 8H), 7.11 (d, *J* = 7.2 Hz, 2H), 5.37-5.23 (br m, 2H), 4.80-4.52 (m, 4H), 2.85-2.71 (m, 2H), 2.67-2.62 (m, 1H), 2.16-2.01 (m, 1H), 1.93-1.87 (m, 1H), 1.75-1.60 (m, 3H), 1.44 (br s, 9H), 1.41 (br s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) major diastereomer: ppm 154.9, 140.6, 136.0, 133.5, 128.7, 128.5, 128.4, 128.2, 126.2, 94.6 ($^1J_{CF}$ = 176 Hz), 80.1, 57.1 ($^2J_{CF}$ = 18 Hz), 33.8 ($^2J_{CF}$ = 20 Hz), 31.3 ($^2J_{CF}$ = 18 Hz), 28.3; minor diastereomer: ppm 155.4, 140.6, 138.4, 133.8, 129.5, 128.8, 128.5, 128.4, 126.2, 94.7 ($^1J_{CF}$ = 176 Hz), 80.1, 56.3 ($^2J_{CF}$ = 19 Hz), 33.8 ($^2J_{CF}$ = 20 Hz), 31.3 ($^2J_{CF}$ = 18 Hz), 28.3; ^{19}F NMR (376 Hz, $CDCl_3$) δ −195.8 (minor), –196.5 (major); HRMS (ESI): Exact mass calcd for $C_{21}H_{26}ClFNO_2$ $[M+H]^+$ 378.1631, found 378.1629.



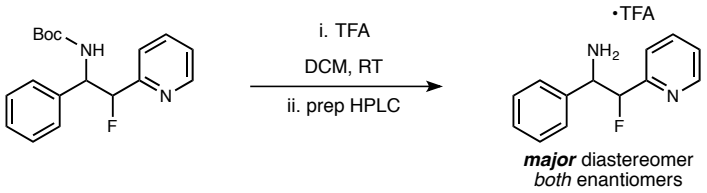
***tert*-Butyl ((1*R*,2*R*)-1-(4-chlorophenyl)-2-fluoro-2-phenylpent-4-en-1-yl)carbamate** (**184**). To an oven dried vial was added the fluoronitroalkane (25 mg, 63 μmol) and benzene (300 μL). In a separate flame-dried vial was added AIBN (4.2 mg, 25 μmol), tributyltin hydride (196 μL, 634 μmol) and benzene (800 μL). Both solutions were subjected to freeze-pump-thaw cycles (-78 °C

to RT, 3 cycles) and backfilled with argon. The fluoronitroalkane solution was heated to 80 °C and stirred. The AIBN/tributyltin hydride solution was then added in 4 portions over 60 min by syringe. After 2 h, the reaction mixture was cooled, the volatiles evaporated, and the remaining residue was purified by column chromatography (10% K_2CO_3 in SiO_2 by weight, 2-7% ethyl acetate in hexanes) to afford the adduct as a white foam (13 mg, 53%), which was found to be >10:1 dr. $[\alpha]_D^{20}$ +123 (*c* 0.35, $CHCl_3$); R_f = 0.9 (25% EtOAc/hexanes); IR (film) 3447, 3378, 2984, 2922, 2362, 1695, 1513, 1493, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.14 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 2H), 5.57-5.50 (m, 1H), 5.41 (d, *J* = 9.2 Hz, 1H), 5.06-4.99 (m, 3H), 3.08-3.03 (m, 1H), 2.88-2.80 (ddd, *J* = 21.6, 14.4, 6.6 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.3, 139.0 ($^2J_{CF}$ = 21 Hz), 136.5, 133.1, 129.7, 128.0, 127.9, 127.4, 124.9 ($^3J_{CF}$ = 12 Hz), 119.0, 100.8 ($^1J_{CF}$ = 243 Hz), 80.2, 60.9 ($^2J_{CF}$ = 20 Hz), 41.8 ($^2J_{CF}$ = 20 Hz), 28.4, 28.0; ^{19}F NMR (376 Hz, $CDCl_3$) δ −139.9; HRMS (ESI): Exact mass calcd for $C_{22}H_{25}ClFNNaO_2$ $[M+Na]^+$ 412.1456, found 412.1458.

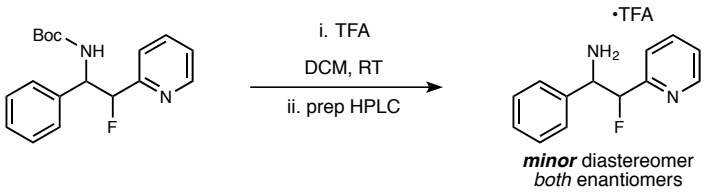


***tert*-Butyl ((1*R*)-2-fluoro-1-phenyl-2-(pyridin-2-yl)ethyl)carbamate (S29)**. To an oven-dried microwave vial was added the fluoronitroalkane (20 mg, 55 μmol) and benzene (300 μL). In a separate flame-dried vial was added AIBN (3.6 mg, 22 μmol), tributyltin hydride (75 μL, 277 μmol) and benzene (400 μL). Both solutions were subjected to freeze-pump-thaw cycles (-78 °C to RT, 3 cycles) and backfilled with argon. The fluoronitroalkane solution was stirred and heated to 80 °C. The AIBN/tributyltin hydride solution was then added in 4 portions over 40 minutes by syringe. After 2 hours, the reaction mixture was cooled, the volatiles evaporated, and the remaining residue was purified by column chromatography (10% K_2CO_3 in SiO_2 by weight, 25-30% diethyl ether in hexanes) to afford the product as an off-white foam (14 mg, 74%), which was found to be ~2:1 dr. R_f = 0.3 (33% Et_2O/hexanes); IR (film) 3428, 3317, 2979, 2924, 1710, 1503, 1179 cm^{-1}; Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 5.6, 0.8 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.29-7.26 (m, 4H), 7.24-7.21 (m, 1H), 7.20-7.16 (m, 1H), 7.07 (br m, 1H), 5.87-5.75 (m, 2H), 5.34 (br m, 1H), 1.33 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 156.7, 154.9, 148.8 (d, $^3J_{CF}$ = 3.0 Hz), 136.4, 128.3, 127.7, 127.6, 127.0, 123.1, 120.4 (d, $^3J_{CF}$ =

5.0 Hz), 94.9 ($^1J_{CF}$ = 180 Hz), 79.6, 57.2 ($^2J_{CF}$ = 21 Hz), 28.2; ^{19}F NMR (376 Hz, $CDCl_3$) δ −194.57 (minor), –197.9 (major); HRMS (ESI): Exact mass calcd for $C_{18}H_{21}FN_2O_2$ $[M+Na]^+$ 339.1485, found 339.1470.



2-Fluoro-1-phenyl-2-(pyridin-2-yl)ethan-1-amine (**187b,c**). To a flask was added the Boc-amine (80 mg, 253 μmol) in dichloromethane (3 mL) under argon. Trifluoroacetic acid (TFA) (580 μL, 7.59 mmol) was added in one portion and the mixture was stirred for 2.5 h. The mixture was diluted with dichloromethane and quenched with sat aq $NaHCO_3$. The organics were combined, dried ($MgSO_4$), filtered and concentrated to a yellow oil that was pure by ^{1}H NMR (54 mg, 98%). Separation of both diastereomers on reverse phase preparatory HPLC (5-25% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 15.0 min (major), 17.2 min (minor)) afforded the product as the TFA salt as a light yellow oil. $[\alpha]_D^{20}$ +44.6 (*c* 1.25, EtOH, (*R*)-amine)), $[\alpha]_D^{20}$ –52.7 (*c* 0.45, EtOH, (*S*)-amine); R_f = 0.1 (10% MeOH/CH_2Cl_2); IR (film) 3422, 3048, 2917, 2768, 2681, 1204, 1142 cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 8.59 (d, *J* = 5.8 Hz, 1H), 7.82 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.42-7.36 (m, 6H), 5.92 (dd, *J* = 47.2, 7.6 Hz, 1H), 5.09 (dd, *J* = 14.0, 7.6 Hz, 1H); ^{13}C NMR (150 MHz, MeOD) ppm 154.5 (d, $^2J_{CF}$ = 20.0 Hz), 150.6, 139.1, 133.8 (d, $^3J_{CF}$ = 5.0 Hz), 130.9, 130.3, 129.2, 126.2 (d, $^4J_{CF}$ = 2.0 Hz), 124.8 (d, $^3J_{CF}$ = 5.0 Hz), 94.9 ($^1J_{CF}$ = 179 Hz), 58.8 ($^2J_{CF}$ = 21 Hz); ^{19}F NMR (376 Hz, MeOD) δ −181.7; HRMS (ESI): Exact mass calcd for $C_{13}H_{14}FN_2$ $[M+H]^+$ 217.1141, found 217.1137.



2-Fluoro-1-phenyl-2-(pyridin-2-yl)ethan-1-amine (**187a,d**). To a flask was added the Boc-amine (80 mg, 253 μmol) in dichloromethane (3 mL) under argon. Trifluoroacetic acid (TFA)

(580 μL, 7.59 mmol) was added in one portion and the mixture was stirred for 2.5 h. The mixture was diluted with dichloromethane and quenched with sat aq $NaHCO_3$. The organics were combined, dried ($MgSO_4$), filtered and concentrated to a yellow oil that was pure by ^1H NMR (54 mg, 98%). Separation of both diastereomers on reverse phase preparatory HPLC (5-25% aqueous acetonitrile, 210 nm, flow rate: 8 mL/min, R_t = 14.8 min (major), 16.4 min (minor)) afforded the product as the TFA salt as a light yellow oil. $[\alpha]_D^{20}$ +22 (*c* 0.33, DMSO, (*R*)-amine)), $[\alpha]_D^{20}$ –54 (*c* 0.35, EtOH, (*S*)-amine); R_f = 0.1 (10% MeOH/CH_2Cl_2); IR (film) 3391, 3060, 2922, 2860, 2640, 1675, 1207, 1138 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 8.61 (dd, *J* = 4.2, 0.6 Hz, 1H), 7.69 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.35-7.29 (m, 4H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.06 (dd, *J* = 48.0, 3.6 Hz, 1H), 5.02 (dd, *J* = 24.6, 3.6 Hz, 1H); ^{13}C NMR (150 MHz, MeOD) ppm 155.7 (d, $^2J_{CF}$ = 24.0 Hz), 150.2, 138.7, 132.6, 130.6, 129.9, 129.5, 125.3, 122.5 (d, $^3J_{CF}$ = 7.5 Hz), 94.6 ($^1J_{CF}$ = 180 Hz), 59.1 ($^2J_{CF}$ = 21 Hz); ^{19}F NMR (376 Hz, MeOD) δ –197.9; HRMS (ESI): Exact mass calcd for $C_{13}H_{14}FN_2$ $[M+H]^+$ 217.1141, found 217.1137.

Determination of the Absolute Configuration of 132 (Single Crystal X-ray)

Crystal data and structure refinement for 15060.

Empirical formula	C19 H19 Cl2 F N2 O4	
Formula weight	429.26	
Crystal color, shape, size	colorless block, 0.31 × 0.29 × 0.24 mm^3	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1$	
Unit cell dimensions	a = 9.5907(2) Å	α= 90°.
	b = 17.2393(4) Å	β= 109.6016(11)°.
	c = 13.3259(3) Å	γ = 90°.
Volume	2075.58(8) $Å^3$	
Z	4	
Density (calculated)	1.374 Mg/m^3	
Absorption coefficient	0.348 mm^{-1}	
F(000)	888	

Data collection

Diffractometer	APEX II Kappa Duo, Bruker
Theta range for data collection	1.62 to 27.52°.
Index ranges	-12<=h<=12, -22<=k<=22, -17<=l<=17
Reflections collected	30851

Independent reflections	9578 [R(int) = 0.0330]
Observed Reflections	9047
Completeness to theta = 27.52°	99.9 %

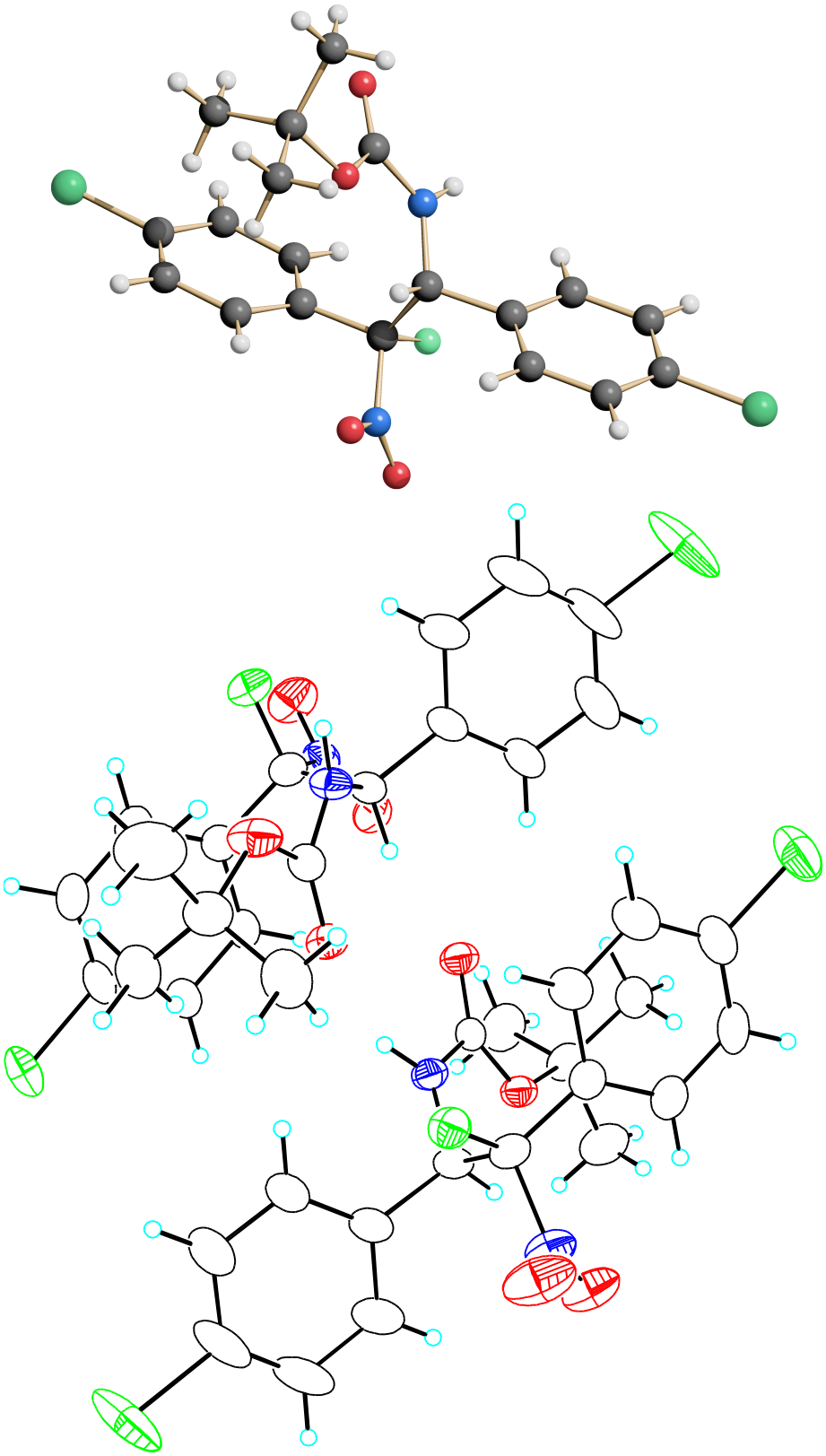
Solution and Refinement

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9211 and 0.8997
Solution	Intrinsic methods
Refinement method	Full-matrix least-squares on F^2
Weighting scheme	$w = [\sigma^2 Fo^2 + AP^2 + BP]^{-1}$, with
	$P = (Fo^2 + 2\,Fc^2)/3$, A = 0.0461, B = 0.4770
Data / restraints / parameters	9578 / 1 / 511
Goodness-of-fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0333, wR2 = 0.0864
R indices (all data)	R1 = 0.0358, wR2 = 0.0888
Absolute structure parameter	-0.01(3)
Largest diff. peak and hole	0.423 and -0.433 $e.Å^{-3}$

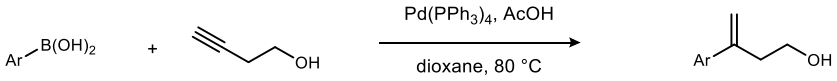
Structure solution and refinement

The space group $P2_1$ was determined based on intensity statistics and systematic absences. The structure was solved and refined using the SHELX suite of programs.[212] An intrinsic-methods solution was calculated, which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed, which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final anisotropic full-matrix least-squares refinement on F^2 with 511 variables converged at R1 = 3.32%, for the observed data and wR2 = 8.87% for all data. The goodness-of-fit was 1.023. The largest peak in the final difference electron density synthesis was 0.423 $e^-/Å^3$ and the largest hole was -0.433 $e^-/Å^3$ with an RMS deviation of0.039 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.374 g/cm^3 and F(000), 888 e^-. The remaining electron density is minuscule and located near bonds.

[212] A short history of *SHELX*, G. M. Sheldrick, *Acta Cryst*. A64, 112 - 122 (2008).

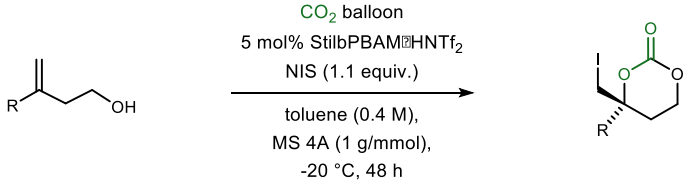


Formula unit (two crystallographically independent molecules).



Alcohols were prepared according to the procedure by Oh and coworkers[213] as follows. A flame–dried round–bottomed flask was charged with a stir bar, degassed 1,4-dioxane (0.4 M), tetrakis(triphenylphosphine)palladium(0) (5 mol%), 3-butyn-1-ol (1 equiv), and boronic acid (1.5 equiv). This mixture was stirred at room temperature for 10 min, acetic acid (20 mol%) was added, and the reaction mixture was heated to 80 °C for 13 h. The reaction mixture was cooled to room temperature, diluted with methanol to dissolve the solids, and then concentrated.[214] The resulting dark brown oil was filtered through a plug of silica using 50% ethyl acetate in hexanes. The resulting yellow oil was purified by flash column chromatography (SiO_2) to afford the desired alcohol.

General Procedure for the Enantioselective Iodocarbonation Reaction



A flame-dried vial equipped with a stir bar and molecular sieves 4A (1g/mmol) was backfilled with CO_2, and charged with the alcohol (1 equiv) and StilbPBAM·$HNTf_2$ (5 mol%). The vial was evacuated and refilled with CO_2 prior to the addition of dry toluene (0.4 M). The reaction mixture was cooled to -20 °C for 30 min under a balloon of CO_2, and then *N*-iodosuccinimide (1.2 equiv) was added. The reaction mixture immediately became bright pink in color and was stirred for 48 h. The resulting dark red mixture was treated with 0.5 M aq $Na_2S_2O_3$ at -20 °C and extracted with diethyl ether. The organic layers were combined, dried, and concentrated to a yellow residue that was purified by flash column chromatography (SiO_2, ethyl acetate in hexanes) to give the title compound.

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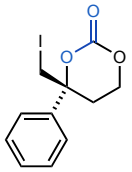
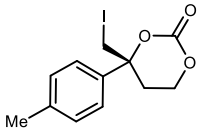
[213] Oh, C. H.; Jung, H. H.; Kim, K.S.; Kim, N. *Angew. Chem. Int. Ed.* **2003**, 42, 805–808.

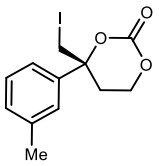
214 If not dissolved in this manner, solids will form and block the plug of silica when filtering.



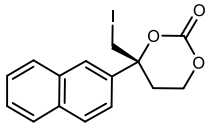
(*R*)-4-(Iodomethyl)-4-phenyl-1,3-dioxan-2-one (223). Prepared according to the general procedure using 3-phenylbut-3-en-1-ol (14.8 mg, 100 μmol), and purified by flash column chromatography (SiO_2, 30-45% ethyl acetate in hexanes) to give the title compound as a yellow solid (31.1 mg, 98%). The product was determined to be 91% ee by chiral HPLC analysis (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 21.0 min, t_r(minor) = 22.9 min; mp 59-64 °C; $[\alpha]_D^{20}$ -19 (*c* 0.95, $CHCl_3$); R_f = 0.5 (50% EtOAc/hexanes) visualized with *p*-anisaldehyde; IR (film) 3050, 3023, 2923, 2926, 1755, 1138 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.36 (m, 5H), 4.37 (ddd, *J* = 11.0, 5.0, 2.4 Hz, 1H), 4.06 (ddd, *J* = 12.0, 12.0, 3.2 Hz, 1H), 3.61 (s, 2H), 2.77 (ddd, *J* = 14.4, 12.2, 5.0 Hz, 1H) 2.47 (ddd, *J* = 14.4, 2.9, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 147.9, 138.3, 129.3, 129.1, 124.8, 83.7, 65.0, 31.4, 15.2 ppm; HRMS (ESI): Exact mass calcd for $C_{11}H_{11}IO_3$ $[M]^+$ 317.9747, found 317.9745



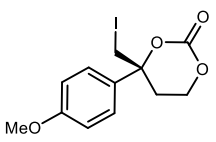
(*R*)-4-(Iodomethyl)-4-(*p*-tolyl)-1,3-dioxan-2-one (223b). Prepared according to the general procedure using 3-(*p*-tolyl)but-3-en-1-ol (16.7 mg, 103 μmol), and purified by silica gel chromatography (SiO_2, 20-30% ethyl acetate in hexanes) to afford a yellow oil (33 mg, 96%) and was determined to be 91% ee by chiral HPLC (Chiralpak IA: 15% EtOH /hexanes, 1.0 mL/min: t_r(minor) = 15.8 min, t_r(major) = 20.9 min). $[\alpha]_D^{20}$ -12.2 (*c* 0.28, $CHCl_3$); R_f = 0.6 (33% EtOAc/hexanes); IR (film) 3033, 2957, 2922, 2852, 1754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (m, 4H), 4.35 (ddd, *J* = 10.8, 4.8, 2.4 Hz, 1H), 4.04 (ddd, *J* = 12.0, 12.0, 3.2 Hz, 1H), 3.59 (d, *J* = 7.2 Hz, 1H), 3.56 (d, *J* = 7.2 Hz, 1H), 2.73 (ddd, *J* = 14.4, 12.0, 4.8 Hz, 1H), 2.44 (ddd, *J* = 14.4, 2.8, 0.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.0, 139.1, 135.5, 130.0 (2C), 124.7 (2C), 83.7, 65.1, 31.4, 21.0, 15.4; HRMS (ESI): Exact mass calcd for $C_{12}H_{13}INaO_3$ $[M+Na]^+$ 354.9807, found 354.9820.



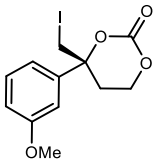
(*R*)-4-(Iodomethyl)-4-(*m*-tolyl)-1,3-dioxan-2-one (222c). Prepared according to the general procedure with a 48 h reaction time using 3-(*m*-tolyl)but-3-en-1-ol (21.9 mg, 135 μmol). The organic extracts were washed with 2 M aq NaOH, dried and concentrated to a yellow oil (42 mg, 96%) that was determined to be 93% ee by chiral HPLC (Chiralpak IA: 10% iPrOH /hexanes, 1.0 mL/min: t_r (major) = 13.6 min, t_r(minor) = 15.0 min). $[\alpha]_D^{20}$ -6.9 (*c* 0.16, $CHCl_3$); R_f = 0.4 (66% EtOAc/hexanes); IR (film) 3070, 2961, 2920, 2852, 1759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.6 Hz, 1H), 7.19 (m, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 4.35 (ddd, *J* = 10.8, 4.8, 2.4 Hz, 1H), 4.04 (ddd, *J* = 12.0, 3.2, 0.8 Hz, 1H), 3.59 (br s, 2H) 2.73 (ddd, *J* = 14.4, 12.0, 4.8 Hz, 1H), 2.44 (ddd, *J* = 14.4, 2.8, 0.8 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 148.0, 139.3, 138.2, 129.9, 129.2, 125.5, 121.8, 83.7, 65.0, 31.5, 21.6, 15.3; HRMS (ESI): Exact mass calcd for $C_{12}H_{13}INaO_3$ $[M+Na]^+$, 354.9807, found 354.9798.



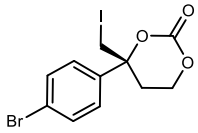
(*R*)-4-(Iodomethyl)-4-(naphthalen-2-yl)-1,3-dioxan-2-one (223d). Prepared according to the general procedure using 3-(naphthalen-2-yl)but-3-en-1-ol (19.8 mg, 100 μmol), and purified by flash column chromatography (SiO_2, 30-45% ethyl acetate in hexanes) to give the title compound as a yellow oil (32.5 mg, 88%). The product was determined to be 90% ee by chiral HPLC analysis (Chiralpak IB, 20% ^{i}PrOH/hexanes, 0.8 mL/min, t_r(major) = 24.2 min, t_r(minor) = 26.1 min; $[\alpha]_D^{20}$ -3.1 (*c* 0.10, $CHCl_3$); R_f = 0.5 (50% EtOAc/hexanes) visualized with *p*-anisaldehyde; IR (film) 3020, 2921, 1752, 1447, 1403, 1259, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.87 (dd *J* = 13.6, 3.3 Hz, 2H), 7.55 (ddd, *J* = 16.8, 9.4, 3.0 Hz, 2H), 7.38 (dd, *J* = 8.7, 1.9 Hz, 1H), 4.36 (dddd, *J* = 13.6, 11.1, 5.0, 2.6 Hz, 1H), 4.05 (ddd, *J* = 12.1, 11.2, 3.2 Hz, 1H), 3.69 (d, *J* = 2.5 Hz, 2H), 2.81 (ddd, *J* = 12.2, 7.1, 5.0 Hz, 1H), 2.60 (ddd *J* = 5.7, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 147.9, 135.4, 133.1, 133.0, 129.4, 128.3, 127.6, 127.2, 127.1, 124.8, 121.5, 83.8, 65.0, 31.4, 15.0; HRMS (ESI): Exact mass calcd for $C_{15}H_{13}INaO_3$ $[M+Na]^+$ 390.9807, found 390.9825.



(*R*)-4-(Iodomethyl)-4-(4-methoxyphenyl)-1,3-dioxan-2-one (223e). Prepared according to the general procedure using 3-(4-methoxyphenyl)but-3-en-1-ol (17.8 mg, 100 μmol) at -50 ºC, and purified by flash column chromatography (SiO_2, 30-45% ethyl acetate in hexanes) to give the title compound as a yellow oil (14.5 mg, 41%). The product was determined to be 71% ee by chiral HPLC analysis (Chiralpak IA, 10% EtOH/hexanes, 1 mL/min, t_r(minor) = 35.3 min, t_r(major) = 40.7 min; $[\alpha]_D^{20}$ -84 (*c* 0.63, $CHCl_3$); R_f = 0.4 (50% EtOAc/hexanes) visualized with *p*-anisaldehyde; IR (film) 2957, 2924, 2852, 1753, 1609, 1511, 1463, 1404, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 4.35 (d, *J* = 6.4 Hz, 1H), 4.11 (m, 1H), 3.82 (s, 3H), 3.56 (d, *J* = 6.5 Hz, 2H), 2.73 (ddd, *J* = 13.5, 4.7 Hz, 1H), 2.43 (ddd, *J* = 14.4, 3.2, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 160.0, 147.9, 130.0, 126.2, 114.6, 83.5, 65.0, 55.3, 31.2, 15.6; HRMS cannot be obtained due to instability of product during shipping.

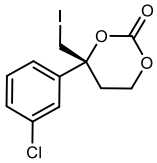


(*R*)-4-(Iodomethyl)-4-(3-methoxyphenyl)-1,3-dioxan-2-one (223f). Prepared according to the general procedure using 3-(3-methoxyphenyl)but-3-en-1-ol (18.8 mg, 103 μmol), and purified by silica gel chromatography (SiO_2, 40-45% ethyl acetate in hexanes) to afford a yellow oil (27 mg, 75%) that was determined to be 90% ee by chiral HPLC (Chiralpak IA: 15% EtOH/hexanes, 1.0 mL/min: t_r(major) = 20.2 min, t_r(minor) = 23.6 min. $[\alpha]_D^{20}$ -66.7 (*c* 0.24, $CHCl_3$); R_f = 0.5 (50% EtOAc/hexanes); IR (film) 3060, 2962, 2921, 2839, 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 1H), 6.94 (m, 3H), 4.35 (ddd, *J* = 10.8, 4.8, 2.4 Hz, 1H), 4.06 (ddd, *J* = 12.0, 3.2, 0.8 Hz, 1H), 3.83 (s, 3H), 3.59 (dd, *J* = 12.0, 11.2 Hz, 2H), 2.73 (ddd, *J* = 14.4, 12.0, 4.8 Hz, 1H), 2.44 (ddd, *J* = 14.4, 2.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.2, 147.8, 139.9, 130.4, 116.9, 114.1, 111.1, 83.6, 65.1, 55.4, 31.5, 15.1; HRMS (ESI): Exact mass calcd for $C_{12}H_{13}INaO_4$ $[M+Na]^+$, 370.9756, found 370.9766.

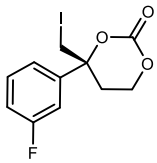


(*R*)-4-(4-Bromophenyl)-4-(iodomethyl)-1,3-dioxan-2-one (223g). Prepared according to the general procedure using 3-(4-bromophenyl)but-3-en-1-ol (22.7 mg, 100 μmol), and purified by flash column chromatography (SiO_2, 30-40% ethyl acetate in hexanes) to give the title compound as a yellow oil (26.1 mg, 65%). The product was determined to be 90% ee by chiral HPLC analysis (Chiralpak IA, 15% EtOH/hexanes, 1

mL/min, t_r(minor) = 19.5 min, t_r(major) = 27.7 min; $[\alpha]_D^{20}$ -7.0 (*c* 0.23, $CHCl_3$); R_f = 0.4 (50% EtOAc/hexanes); IR (film) 2922, 2852, 1755, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 4.36 (dddd, *J* = 14.0, 11.2, 5.0, 2.3 Hz, 1H), 4.06 (ddd, *J* = 11.5, 11.5, 3.3 Hz, 1H), 3.56 (d, *J* = *2*.4 Hz, 2H), 2.72 (ddd, *J* = 16.9, 14.5, 6.8 Hz, 1H) 2.45 (ddd, *J* = 14.5, 3.1, 3.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 147.5, 137.5, 132.1, 126.6, 125.4, 83.3, 64.8, 31.3, 14.5; HRMS (ESI): Exact mass calcd for $C_{11}H_{11}BrIO_3$ $[M+H]^+$ 396.8931, found 396.8921.

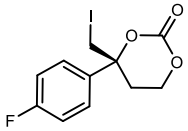


(*R*)-4-(3-Chlorophenyl)-4-(iodomethyl)-1,3-dioxan-2-one (223h). Prepared according to the general procedure using 10 mol % catalyst **133**•$HNTf_2$ and 3-(3-chlorophenyl)but-3-en-1-ol (24.0 mg, 135 μmol) with a 5 d reaction time, and purified by silica gel chromatography (SiO_2, 30-40% ethyl acetate in hexanes) to afford a yellow oil (21 mg, 44%) and was determined to be 87% ee by chiral HPLC (Chiralpak IA: 12% EtOH /hexanes, 1.0 mL/min: t_r(minor) = 18.2 min, t_r(major) = 20.5 min). $[\alpha]_D^{20}$ -3.4 (*c* 0.65, $CHCl_3$); R_f = 0.28 (30% EtOAc/hexanes); IR (film) 3067, 2957, 2922, 2846, 1754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.39 (m, 3H), 7.30 (m, 1H), 4.39 (ddd, *J* = 10.9, 4.8, 2.3 Hz, 1H), 4.06 (ddd, *J* = 12.0, 12.0, 3.2 Hz, 1H), 3.60 (d, *J* = 7.2 Hz, 1H), 3.56 (d, *J* = 7.2 Hz, 1H), 2.78-2.70 (m, 1H), 2.44 (ddd, 14.4, 14.4, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 147.5, 140.5, 135.6, 130.6, 129.4, 125.5, 123.2, 83.2, 64.9, 31.4, 14.5; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}ClINaO_3$ $[M+Na]^+$ 374.9261, found 374.9259.

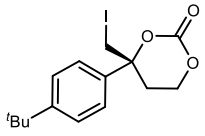


(*R*)-4-(3-Fluorophenyl)-4-(iodomethyl)-1,3-dioxan-2-one (223i). Prepared according to the general procedure using 10 mol % catalyst **133**•$HNTf_2$ and 3-(3-fluorophenyl)but-3-en-1-ol (13.8 mg, 83.0 μmol) with 96 h reaction time, and purified by silica gel chromatography (SiO_2, 30-40% ethyl acetate in hexanes) to afford a yellow oil (12 mg, 40%) that was determined to be 89% ee by chiral HPLC (Chiralpak IA: 15% EtOH /hexanes, 1.0 mL/min: t_r(minor) = 14.3min, t_r(major) = 16.7 min). $[\alpha]_D^{20}$ -2.3 (*c* 0.22, $CHCl_3$); R_f = 0.30 (30% EtOAc/hexanes); IR (film) 3064, 2919, 2857, 1762, 1103 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.44-7.31 (m, 1H), 7.18-7.16 (m, 1H), 7.13-7.10 (m, 2H), 4.40-4.37 (ddd, *J* = 13.2, 4.8,

3.0 Hz, 1H), 4.10-4.05 (ddd, *J* = 12.0, 3.0, 0.6 Hz, 1H), 3.59 (d, *J* = 11.4 Hz, 1H), 3.57 (d, *J* = 11.4 Hz, 1H), 2.76-2.72 (ddd, *J* = 9.6, 7.2, 3.0 Hz, 1H), 2.48-2.45 (ddd, 14.4, 6.0, 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 163.0 ($^1J_{CF}$ = 250 Hz), 147.5, 141.1, 131.1 ($^3J_{CF}$ = 7.5 Hz), 120.6 ($^4J_{CF}$ = 3 Hz), 116.2 ($^2J_{CF}$ = 21 Hz), 112.5 ($^2J_{CF}$ = 24 Hz), 83.3, 64.9, 31.5, 14.4 ppm; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}FINaO_3$ $[M+Na]^+$ 358.3556, found 358.0557.

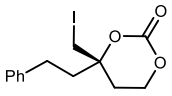


(*R*)-4-(4-Fluorophenyl)-4-(iodomethyl)-1,3-dioxan-2-one (223j). Prepared according to the general procedure using 3-(4-fluorophenyl)but-3-en-1-ol (16.6 mg, 100 μmol), and purified by flash column chromatography (SiO_2, 30-40% ethyl acetate in hexanes) to give the title compound as a yellow oil (18.1 mg, 54%). The product was determined to be 90% ee by chiral HPLC analysis (Chiralpak IA, 15% EtOH/hexanes, 1 mL/min, t_r(minor) = 16.4 min, t_r(major) = 19.6 min; $[\alpha]_D^{20}$ -5.4 (*c* 0.11, $CHCl_3$); R_f = 0.4 (50% EtOAc/hexanes) visualized with *p*-anisaldehyde; IR (film) 2960, 2917, 2847, 1745, 1600, 1507, 1403, 1257, 1126, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (ddd, *J* = 9.7, 8.9, 5.0 Hz, 2H), 7.13 (dd, *J* = 6.5 Hz, 2H), 4.38 (ddd, *J* = 11.2, 7.8, 2.2 Hz, 1H), 4.06 (dd, *J* = 11.6, 11.6, 3.3 Hz, 1H), 3.57 (d, *J* = 2.2 Hz, 2H), 2.74 (ddd, *J* = 14.5, 11.8, 5.0 Hz, 1H), 2.47 (ddd *J* = 14.5, 3.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 162.8 (d, $^1J_{CF}$ = 249.7 Hz), 147.6, 134.2 (d, $^4J_{CF}$ = 3.3 Hz), 127.9 (d, $^3J_{CF}$ = 8.3 Hz), 116.3 (d, $^2J_{CF}$ = 21.9 Hz), 83.4, 64.9, 31.4, 15.0; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}FINaO_3[M+Na]^+$ 358.9556, found 358.9542.

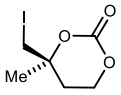


(*R*)-4-(4-(*tert*-Butyl)phenyl)-4-(iodomethyl)-1,3-dioxan-2-one (223j). Prepared according to the general procedure using 3-(4-(*tert*-butyl)phenyl)but-3-en-1-ol (19.8 mg, 97 μmol) with 96 h reaction time, and purified by washing the organic layers with 2 M aq NaOH, which were dried and concentrated to a yellow oil (36 mg, 99%) that was determined to be 91% ee by chiral HPLC (Chiralpak IA: 10% iPrOH/hexanes, 1.0 mL/min: t_r(minor) = 14.1 min, t_r(major) = 16.1 min). $[\alpha]_D^{20}$ -19.5 (*c* 0.19, $CHCl_3$); R_f = 0.8 (50% EtOAc/hexanes); IR (film) 3035, 2966, 2904, 1746, 1406 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 4.4, 2.4 Hz, 2H), 7.29 (dd, *J* = 4.4, 2.4 Hz, 2H), 4.34 (ddd, *J* = 10.8, 4.8, 2.4 Hz, 1H), 4.00 (ddd, *J* = 12.0, 3.2, 0.8 Hz, 1H), 3.59 (dd, *J* = 10.8, 11.2 Hz, 2H), 2.75 (ddd, *J* = 14.4, 12.0, 4.8 Hz, 1H), 2.44 (ddd, *J* = 14.4, 2.8, 0.8 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz,

$CDCl_3$) ppm 152.3, 148.0, 135.1, 126.2, 124.6, 83.6, 65.0, 34.6, 31.4, 31.3, 31.2; HRMS (ESI): Exact mass calcd for $C_{15}H_{19}INaO_3$ $[M+Na]^+$, 397.0277, found 397.0288.



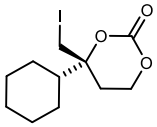
(*S*)-4-(Iodomethyl)-4-phenethyl-1,3-dioxan-2-one (223l). Prepared according to the general procedure using 10 mol % catalyst **133**•$HNTf_2$ and 3-methylene-5-phenylpentan-1-ol (16.2 mg, 92 μmol) with 72 h reaction time, and purified by silica gel chromatography (SiO_2, 35-45% ethyl acetate in hexanes) to afford a yellow oil (22 mg, 71%) that was determined to be 67% ee by chiral HPLC (Chiralpak IA: 15% EtOH/hexanes, 1.0 mL/min: t_r(minor) = 16.7 min, t_r(major) = 21.9 min). $[\alpha]_D^{20}$ -9.1 (*c* 0.27, $CHCl_3$); R_f = 0.4 (30% EtOAc/hexanes); IR (film) 3023, 2948, 2920, 2858, 1750, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.24-7.21 (m, 3H), 4.40 (dd, *J* = 7.2, 6.0 Hz, 2H), 3.51 (d, *J* = 10.8 Hz, 1H), 3.43 (d, *J* = 10.8 Hz, 1H) 2.85-2.80 (ddd, *J* = 13.2, 4.8, 4.8 Hz, 1H), 2.74-2.69 (ddd, *J* = 13.2, 7.2, 4.8 Hz, 1H), 2.39-2.34 (m, 1H), 2.92-2.16 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 148.3, 140.1, 128.7 (2C), 128.3 (2C), 126.5, 82.8, 64.3, 40.3, 30.3, 28.7, 9.1; HRMS (ESI): Exact mass calcd for $C_{13}H_{15}INaO_3$ $[M+Na]^+$ 368.9964, found 368.9949.



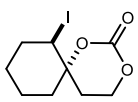
(*S*)-4-(Iodomethyl)-4-methyl-1,3-dioxan-2-one (214). Prepared according to the general procedure using 10 mol % catalyst **133**•$HNTf_2$ and 3-methyl-3-buten-1-ol (1.00 g, 11.6 mmol), and purified by flash column chromatography (SiO_2, 40% ethyl acetate in hexanes) to afford a viscous yellow oil (2.10 g, 72%) and 68% ee by chiral HPLC (Chiralpak IA: 6% EtOH/hexanes, 1 mL/min: t_r(major) = 40.6 min, t_r(minor) = 45.3 min). OR analysis was taken after recrystallization[215] on 80% ee material. $[\alpha]_D^{20}$ -31.9 (*c* 0.74, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (ddd, *J* = 5.2, 4.6, 1.5 Hz, 2H), 3.40 (dd, *J* = 11.7, 11.7 Hz, 2H), 3.68 (ddd, *J* = 14.2, 6.5, 5.8 Hz, 1H), 2.09 (ddd, *J* = 14.5, 5.1, 4.7 Hz, 1H), 1.66 (s, 3H). Analytical data matches that previously reported in literature.[216]

215 Recrystallized in 0.1 M diethyl ether at -20 °C.

216 Minakata, S.; Sasaki, I.; Ide, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 1309–1311



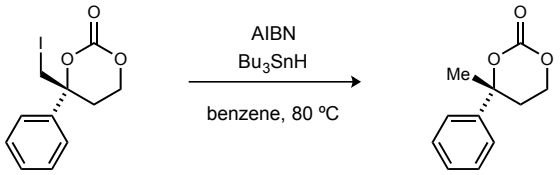
(*R*)-4-Cyclohexyl-4-(iodomethyl)-1,3-dioxan-2-one (223m). Prepared according to the general procedure using 10 mol % catalyst **8** and 3-cyclohexylbut-3-en-1-ol (18.8 mg, 103 μmol) with a 52 h reaction time, and purified by silica gel chromatography (SiO_2, 35-40% ethyl acetate in hexanes) to afford a tan oil (31 mg, 76%) and was determined to be 74% ee by chiral HPLC (Chiralpak IA: 20% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(major) = 14.5 min, t_r(minor) = 15.4 min). $[\alpha]_D^{20}$ -2.9 (*c* 0.18, $CHCl_3$); R_f = 0.20 (25% EtOAc/hexanes); IR (film) 2926, 2850, 1749, 1405, 1274, 1108 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41-4.19 (m, 2H), 3.49 (d, *J* = 11.2 Hz, 2H), 2.30-2.16 (m, 2H), 1.91-1.68 (m, 6H), 1.28-1.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 149.2, 84.6, 64.3, 45.2, 27.3, 26.4, 26.3, 26.1 (2C), 25.9, 10.8; HRMS (ESI): Exact mass calcd for $C_{11}H_{17}INaO_3$ $[M+Na]^+$ 347.0120, found 347.0120.



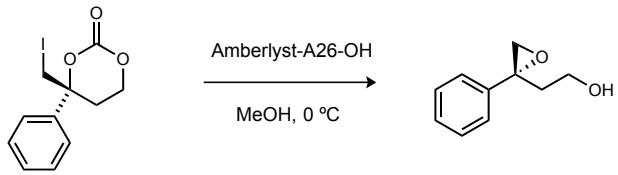
(6*S*,7*R*)-7-Iodo-1,3-dioxaspiro[5.5]undecan-2-one (223o). Prepared according to the general procedure using 2-(cyclohex-1-en-1-yl)ethan-1-ol (1.00 g, 8.00 mmol), and purified by flash column chromatography (SiO_2, 30-45% ethyl acetate in hexanes) to give the title compound as a yellow solid (1.93 g, 82%). The product was determined to be 67% ee by chiral HPLC analysis (Chiralpak IA, 10% EtOH/hexanes, 1 mL/min, t_r(major) = 18.4 min, t_r(minor) = 23.1 min; $[\alpha]_D^{20}$ -67 (*c* 0.70, $CHCl_3$)[217]; Mp 38-40 °C (dec); R_f = 0.55 (50% EtOAc/hexanes) visualized with *p*-anisaldehyde; IR (film) 2939, 2863, 1747, 1450, 1400 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (dd *J* = 7.0, 3.5 Hz, 1H), 4.38 (m, 2H), 2.38 (ddd, *J* = 14.4, 9.1, 5.1 Hz, 1H), 2.34 (ddd, *J* = 15.9, 8.2, 3.8 Hz, 1H), 2.19 (m, 2H), 1.93 (m, 1H), 1.85 (m, 2H), 1.68 (m, 1H), 1.54 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 148.5, 83.3, 63.9, 38.0, 33.5, 32.8, 31.6, 23.9, 21.0; HRMS could not obtained due to product instability during shipping.

217 Optical rotation measured using carbonate recrystallized from 2q: 82% ee

Derivatizations of Iodocarbonates



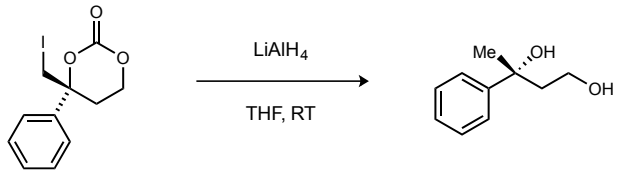
(*R*)-4-Methyl-4-phenyl-1,3-dioxan-2-one (239). A flame–dried microwave vial backfilled with N_2 was charged with a stir bar, degassed benzene (530 µL), (*R*)-4-(iodomethyl)-4-phenyl-1,3-dioxan-2-one (**2a**, 25.4 mg, 80.0 µmol, 89% ee), and tributyltin hydride (93.1 mg, 320 µmol). The reaction mixture was warmed in an oil bath to 80 °C for 5 min and then AIBN (2.0 mg, 12.0 µmol) was added, and the mixture was stirred for 1 h. The reaction mixture was concentrated to a colorless residue that was purified by flash column chromatography as described by Harrowven (10% powdered K_2CO_3 in SiO_2, 30-60% ethyl acetate in hexanes)[218] to give the title compound as a colorless oil (16.9 mg, 88%). The product was determined to be 88% ee by chiral HPLC analysis (Chiralpak IA, 12% EtOH/hexanes, 1.0 mL/min: t_r(major) = 17.4 min, t_r(minor) = 13.3 min. $[\alpha]_D^{20}$ -54.4 (*c* 0.85, $CHCl_3$) Analytical data matches that previously reported in literature .[219]



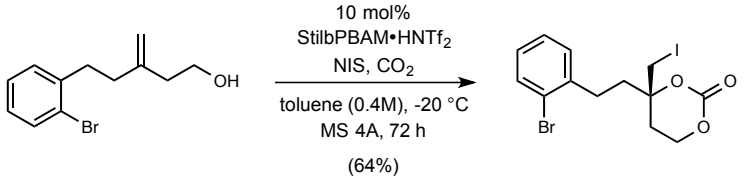
(*R*)-2-(2-Phenyloxiran-2-yl)ethan-1-ol (240). A vial backfilled with N_2 after drying was charged with a stir bar, (*R*)-4-(iodomethyl)-4-phenyl-1,3-dioxan-2-one (**2a**, 31.8 mg, 100 µmol, 91% ee) and methanol (250 µL). The reaction mixture was cooled to 0 °C for 30 min and then Amberlyst A-26 hydroxide form (120 mg, 1.20 g/mmol) was added and stirred for 3 h. The resulting mixture was filtered through a glass frit and washed with ethyl acetate. The solution was dried and concentrated to a colorless residue that was purified by flash column chromatography (SiO_2, 20-40% ethyl acetate in hexanes) to give the title compound as a colorless oil (14.9 mg, 90%). The product was determined to be 91% ee by chiral HPLC analysis

[218] Harrowven, D. C. *et al. Chem. Comm.* **2010**, 46, 6335–6337
[219] Kartika, R. *et al. Org. Lett.* **2012**, 14, 3676-3679

(Chiralpak AD-H, 5% ^{i}PrOH/hexanes, 1.0 mL/min: t_r(major) = 14.8 min, t_r(minor) = 16.5 min. $[\alpha]_D^{20}$ -4.7 (*c* 0.17, $CHCl_3$). Analytical data matches that previously reported in literature.[220]



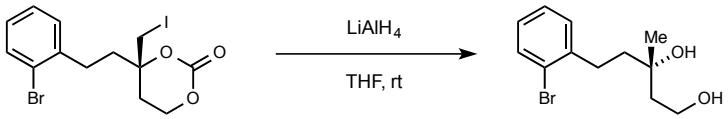
(*R*)-3-Phenylbutane-1,3-diol (241). A flame–dried vial was charged with $LiAlH_4$ (18.0 mg, 472 μmol) and dry THF (750 μL) under Ar. The carbonate (30 mg, 94 μmol, 91% ee) was added to the mixture as a solution in THF (200 μL) at rt and stirred for 1 h. The resulting mixture was quenched with satd aq NH_4Cl and extracted with ethyl acetate. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to a residue that was purified by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes) to give the title compound as a colorless oil (11 mg, 71%). The product was determined to be 91% ee by chiral HPLC analysis (Chiralpak IB, 6% EtOH/hexanes, 1.0 mL/min: t_r(major) = 13.1 min, t_r(minor) = 12.4 min. $[\alpha]_D^{20}$ +39 (*c* 0.36, $CHCl_3$); R_f = 0.3 (50% EtOAc/hexanes); IR (film) 3364 (br), 3060, 2970, 2922, 2853, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.2, Hz, 2H), 7.35 (m, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 3.78 (m, 1H), 3.57 (ddd, *J* = 12.0, 8.8, 3.2 Hz, 1H), 3.47 (br s, 1H), 2.42 (br s, 1H), 2.15-2.01 (m, 2H), 1.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 147.5, 128.2, 126.6, 124.7, 75.9, 60.4, 44.0, 31.0. HRMS (CI, GC/MS): Exact mass calcd for $C_{10}H_{13}O_1$ [M-OH] 149.0961, found 149.0962.



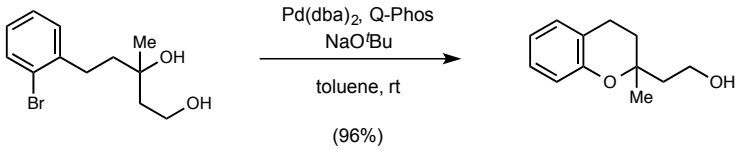
(*S*)-4-(2-Bromophenethyl)-4-(iodomethyl)-1,3-dioxan-2-one (253). The reaction was carried out over 72 h according to the general procedure. The crude material was separated by silica gel chromatography (SiO_2, 30% ethyl acetate in hexanes) to afford a clear oil (51 mg, 64%) that was determined to be 50% ee by chiral HPLC (Chiralcel IC: 20% EtOH /hexanes, 1.0 mL/min:

[220] Yamamoto *et al. J. Am. Chem. Soc.* **2010**, 132, 7878–7880

t_r(major) = 19.5 min, t_r(minor) = 30.2 min). $[\alpha]_D^{20}$ –7.8 (*c* 0.21, $CHCl_3$); R_f = 0.2 (25% EtOAc/hexanes); IR (film) 3052, 2927, 1750, 1404, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 2H), 7.12-7.07 (m, 1H), 4.42 (m, 2H), 3.53 (d, *J* = 11.2 Hz, 1H), 3.46 (d, *J* = 11.2 Hz, 1H), 2.94-2.89 (dt, *J* = 12.6, 5.2 Hz, 1H), 2.86-2.82 (dt, *J* = 12.8, 5.2 Hz, 1H), 2.42-2.35 (m, 1H), 2.28-2.14 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 148.3, 139.4, 133.0, 130.5, 128.3, 127.8, 124.2, 82.7, 64.3, 38.2, 29.9, 29.5, 9.57; HRMS (ESI): Exact mass calcd for $C_{13}H_{15}BrIO_3$ $[M+H]^+$ 446.9069, found 446.9083.

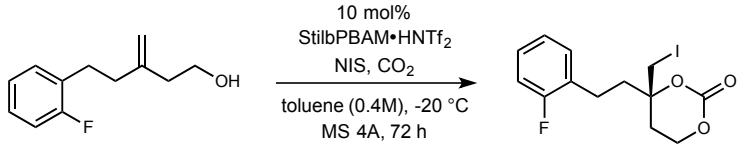


(*S*)-5-(2-Bromophenyl)-3-methylpentane-1,3-diol (264). A flame-dried vial was charged with $LiAlH_4$ (9.8 mg, 259 μmol) and dry THF (1.29 mL) under Ar. The iodocarbonate (55 mg, 129 μmol, 50% ee) was added to the mixture as a solution in THF (200 μL) at rt and stirred for 1 h. The resulting mixture was quenched with satd aq NH_4Cl and extracted with diethyl ether. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to a residue that was purified by flash column chromatography (SiO_2, 60% ethyl acetate in hexanes) to give the title compound as a colorless oil (35 mg, 94%). $[\alpha]_D^{20}$ –2.3 (*c* 0.35, $CHCl_3$); R_f = 0.35 (50% EtOAc/hexanes); IR (film) 3359 (br), 2924, 2855, 1467 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 7.2, 3.6 Hz, 2H), 7.05 (m, 1H), 3.96 (m, 2H), 2.80 (ddd, *J* = 13.2, 7.2, 2.4 Hz, 1H), 1.89 (ddd, *J* = 12.0, 7.8, 4.2 Hz, 1H), 1.83-1.75 (m, 2H), 1.58 (br s, 1H), 1.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 141.5, 132.8, 130.3, 127.6 (2C), 124.3, 73.6, 59.9, 42.9, 41.5, 31.0, 26.7; HRMS (ESI): Exact mass calcd for $C_{12}H_{15}BrO$ $[M–H_2O]^+$ 255.0379, found 255.0378.



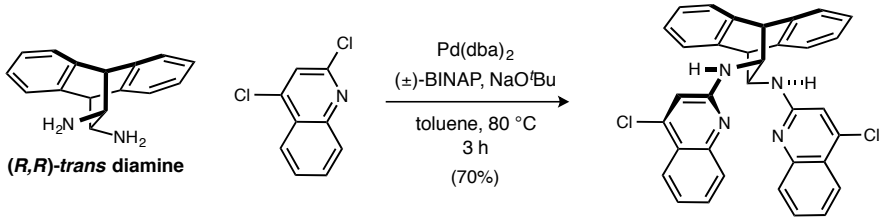
2-(2-Methylchroman-2-yl)ethan-1-ol (254). A flame-dried vial was charged with $Pd(dba)_2$ (1.7 mg, 2.9 μmol), Q-Phos (3.0 mg, 4.3 μmol), sodium *tert*-butoxide (1.8 mg, 19 μmol) under Ar. The *rac*-diol (3.9 mg, 14.3 μmol) was added as a solution in toluene (300 μL) under Ar at rt. The

mixture was heated to 80 °C and stirred for 90 min. The resulting mixture was cooled, filtered through Celite, and concentrated to a residue that was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to give the title compound as a colorless oil (2.6 mg, 96%). Two enantiomers of the racemic mixture were determined by chiral HPLC (Chiralcel IA: 10% EtOH /hexanes, 1.0 mL/min: t_r = 9.8 min, t_r = 10.6 min). R_f = 0.7 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (m, 2H), 6.84 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 3.94 (m, 1H). 3.87 (m, 1H), 2.80 (m, 2H), 2.27-1.76 (m, 4H), 1.34 (s, 3H). Analytical data matches that found for the same molecule previously reported: Ishikawa *et al. Eur. J. Org. Chem.* **2008**, 2759-2766.



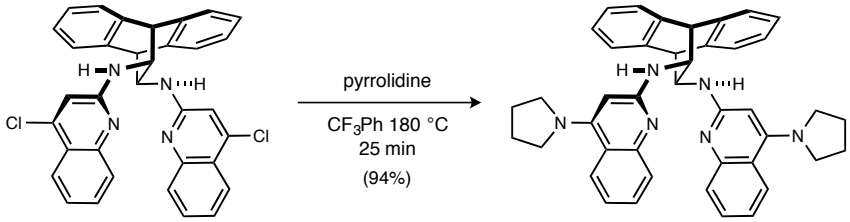
(*S*)-4-(2-Fluorophenethyl)-4-(iodomethyl)-1,3-dioxan-2-one (266). The reaction was carried out over 72 h according to the general procedure. The crude material was separated by silica gel chromatography (SiO_2, 25% ethyl acetate in hexanes) to afford a clear oil (30 mg, 63%) that was determined to be 57% ee by chiral HPLC (Chiralcel AD: 15% EtOH /hexanes, 1.0 mL/min: t_r(minor) = 18.7 min, t_r(major) = 22.7 min). R_f = 0.3 (25% EtOAc/hexanes); IR (film) 3052, 2927, 1750, 1404, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.19 (m, 2H), 7.10-7.00 (m, 2H), 4.41 (dd, J = 5.6, 5.6 Hz, 2H), 3.49 (dd, J = 25.6, 11.2 Hz, 2H), 2.87-2.71 (m, 2H). 2.41-2.34 (m, 1H), 2.29-2.16 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 161.2 (d, $^1J_{CF}$ = 244.0 Hz), 148.2, 130.5 (d, $^3J_{CF}$ = 5.0 Hz), 128.3 (d, $^3J_{CF}$ = 8.0 Hz), 126.9 (d, $^2J_{CF}$ = 15.0 Hz), 124.3 (d, $^4J_{CF}$ = 3.0 Hz), 115.4 (d, $^2J_{CF}$ = 22.0 Hz), 82.7, 64.3, 38.5, 29.8, 22.5 (d, $^3J_{CF}$ = 3.0 Hz), 9.25.

Synthesis of AnthPBAM (279) from (R,R)-Diamine 273



(11*R*,12*R*)-N^{11},N^{12}-Bis(4-chloroquinolin-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine (278). A 100 mL flask was charged with the diamine **273** (200 mg, 846 μmol), 2,4-dichloro-6-methoxyquinoline (335 mg, 1.69 mmol), $Pd(dba)_2$ (7.3 mg, 13 μmol), *rac*-BINAP (16

mg, 25 μmol), and sodium *tert*-butoxide (203 mg, 2.12 mmol) under an inert atmosphere. Toluene (6 mL) was added and the resulting suspension was heated at 80 °C and stirred for 3 h. The reaction mixture was cooled and filtered through a pad of Celite with CH_2Cl_2 and hexanes and concentrated under vacuum. The residue was diluted with CH_2Cl_2 and pushed through a plug of silica. The residue was recrystallized from CH_2Cl_2/hexanes (1:5) and vacuum filtered to provide a light yellow crystals (330 mg, 70%) and was pure by ^{1}H NMR. The product was determined to be > 98.5% ee by chiral HPLC (Chiralcel IA: 4% EtOH /hexanes, 1.0 mL/min: t_r(minor) = 5.5 min, t_r(major) = 6.0 min). $[\alpha]_D^{20}$ +111 (*c* 0.88, $CHCl_3$); R_f = 0.80 (50% EtOAc/hexanes); IR (film) 3404, 3279, 3064, 2946, 1607, 1524, 1399 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.57-7.48 (m, 6H), 7.32 (d, *J* = 6.8 Hz, 2H), 7.28-7.19 (m, 6H), 6.63 (s, 2H), 4.74 (d, *J* = 8.0 Hz, 2H), 4.71 (s, 2H), 4.29 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.5, 148.5, 142.6, 141.8, 139.3, 130.3, 12.8, 126.6, 126.6, 126.0, 124.7, 123.9, 122.9, 121.8, 111.8, 59.7, 49.1; HRMS (ESI): Exact mass calcd for $C_{34}H_{25}Cl_2N_4$ $[M+H]^+$ 559.1456, found 559.1448.



(*R*,*R*)-^{4}PyrrolidineQuin-AnthBAM (273). A 0.5-2 mL microwave vial was charged with the (*R*,*R*)-^{4}ClQuin-AnthBAM (213 mg, 381 μmol), pyrrolidine (126 μL, 1.53 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 180 °C and stirred in the microwave for 25 min. The reaction was monitored by TLC, cooled, and concentrated. The residue was dissolved in benzene (~5 mL), precipitated by the slow addition of hexanes (~20 mL) over the course of 30 min, and the solid was vacuum filtered. This solid was dissolved in CH_2Cl_2 and then washed with 3 M aq NaOH, water, dried ($MgSO_4$), and filtered to afford a light brown powder (225 mg, 94%). $[\alpha]_D^{20}$ –7.4 (*c* 1.8, $CHCl_3$); R_f = 0.1 (50% EtOAc/hexanes); IR (film) 3397, 3272, 3057, 2960, 2862, 1586, 1524, 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.44-7.37 (m, 6H), 7.25-7.20 (m, 4H), 7.02 (m, 2H), 5.65 (s, 2H), 4.62 (br s, 2H), 4.57 (s, 2H), 4.04 (s, 2H), 3.31 (m, 4H), 3.20 (m, 4H), 1.65 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.0, 153.8, 149.9, 141.8, 139.3, 128.6, 126.7, 126.5,

126.5, 126.2, 124.8, 124.5, 119.5, 118.3, 90.6, 60.4, 51.7 (2C), 49.9, 25.5 (2C); HRMS (ESI): Exact mass calcd for $C_{42}H_{41}N_6$ $[M+H]^+$ 629.3393, found 629.3387.

Determination of the Absolute Configuration of 223 (Single Crystal X-ray)

A single crystal of purified iodocarbonate **2a** was grown by the vapor-diffusion method in diethyl ether under hexanes atmosphere, and the absolute stereochemistry was determined by X-ray crystallography.

Crystal data

$C_{11}H_{11}IO_3$	D_x = 1.849 Mg m^{-3}
M_r = 318.10	Mo $K\alpha$ radiation, λ = 0.71073 Å
Orthorhombic, $P2_12_12_1$	Cell parameters from 9901 reflections
a = 7.4336 (3) Å	θ = 2.7–30.1°
b = 8.2693 (3) Å	μ = 2.79 mm^{-1}
c = 18.5884 (7) Å	T = 150 K
V = 1142.64 (8) Å^3	Block, yellowish
Z = 4	0.31 × 0.29 × 0.22 mm
F(000) = 616	

Data collection

Kappa diffractometer	3365 independent reflections
Radiation source: fine-focus sealed tube	3318 reflections with $I > 2\sigma(I)$
Graphite monochromator	R_{int} = 0.028
Detector resolution: 83.33 pixels mm^{-1}	θ_{max} = 30.1°, θ_{min} = 2.2°
ω and phi scans	h = -10→10
Absorption correction: multi-scan *SADABS*, R. Blessing; 1995	k = -11→11
T_{min} = 0.479, T_{max} = 0.579	l = -26→19
15981 measured reflections	

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighboring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.015	H-atom parameters constrained
$wR(F^2)$ = 0.038	$w = 1/[\sigma^2(F_o^2) + (0.0143P)^2 + 0.2525P]$ where $P = (F_o^2 + 2F_c^2)/3$
S = 1.16	$(\Delta/\sigma)_{max}$ = 0.001
3365 reflections	$\Delta\rho_{max}$ = 0.35 e Å^{-3}

136 parameters

0 restraints

Primary atom site location: structure-invariant direct methods

$\Delta\rho_{min}$ = -0.61 e Å^{-3}

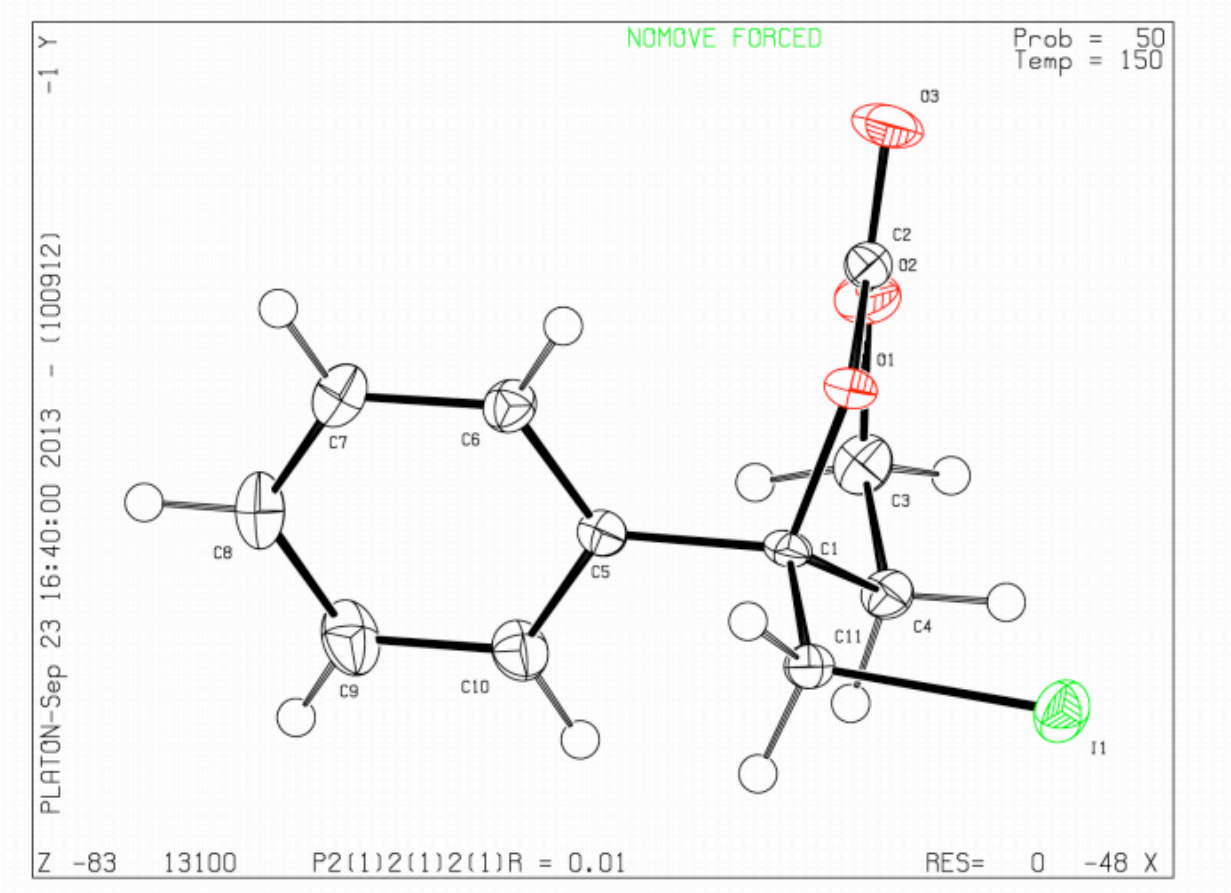
Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881

Absolute structure parameter: 0.004 (14)

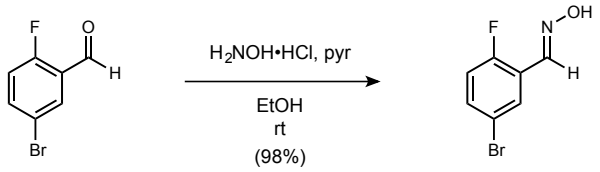
Figure 43. Crystal structure of **223** *(Special details)*

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

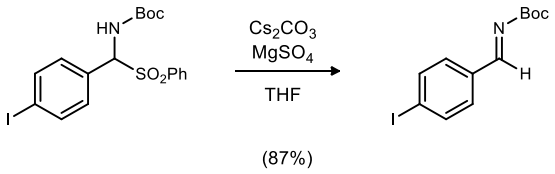
Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.



Supporting Compounds

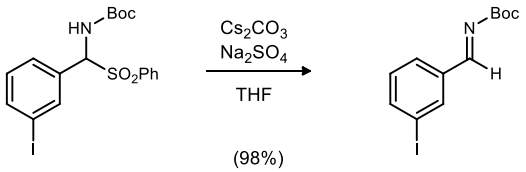


(*E*)-5-Bromo-2-fluorobenzaldehyde oxime (S1). Aldehyde (2.0 mL, 16.8 mmol), hydroxyl amine hydrochloride (1.40 g, 20.2 mmol), pyridine (2.45 mL, 30.3 mmol), and ethanol (5.6 mL) were combined in a flask at room temperature. The mixture was stirred for 10 h and ethanol was evaporated under reduced pressure. The mixture was diluted with EtOAc, washed twice with 1 M aq HCl, once with satd aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a white crystalline solid (3.6 g, 98%). Mp = 76-77 ºC; R_f = 0.6 (CH_2Cl_2); IR (film) 3285 (br), 3079, 3017, 1904, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.30 (s, 1H), 7.89 (dd, *J* = 8.8, 4.0 Hz, 1H). 7.46 (m, 1H), 6.97 (t, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 161.0 (d, $^1J_{CF}$ = 255 Hz), 143.1 (d, $^3J_{CF}$ = 3 Hz), 134.2, 129.6 (d, $^3J_{CF}$ = 3 Hz), 121.8, 117.7 (d, $^2J_{CF}$ = 22 Hz), 117.1 (d, $^3J_{CF}$ = 3 Hz); HRMS (APCI): Exact mass calcd for C_7H_5BrFNO $[M]^+$ 216.9533, found 216.9539.

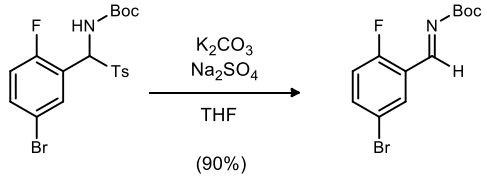


(*E*)-*tert*-Butyl 4-iodobenzylidenecarbamate (S2). To a flame dried round bottom flask equipped with a stir bar was added $MgSO_4$ (888 mg, 7.40 mmol) and sulfone (175 mg, 370 μmol). The solids were suspended in THF (2.8 mL) and stirred for 20 minutes at room temperature, after which Cs_2CO_3 (240 mg, 0.74 mmol) was added. The mixture was stirred for 4.5 hours at room temperature, then filtered through a bed of celite on an oven dried frit and washed with DCM. Concentration of the filtrate revealed a white oil (106 mg, 87%) that solidified after sitting in a freezer at -20 °C overnight to give a white waxy solid. Mp = 46 °C; R_f = 0.40 (20% EtOAc/hexanes); IR (film) 2978, 2931, 1715, 1629, 1584, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 1.60 (s, 9H); ^{13}C

NMR (100 MHz, $CDCl_3$) ppm 168.6, 162.3, 138.2, 133.4, 131.2, 101.2, 82.5, 27.8; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}INNaO_2$ $[M+Na]^+$ 353.9961, found 353.9955.

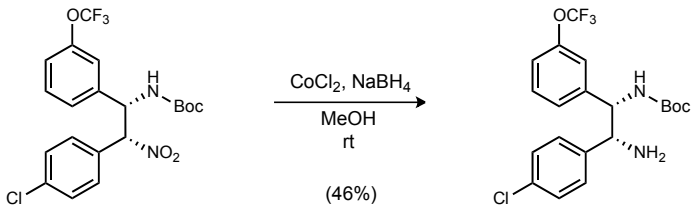


(*E*)-*tert*-Butyl 3-iodobenzylidenecarbamate (S3). To a flame dried flask was added Cs_2CO_3 (488 mg, 1.50 mmol), Na_2SO_4 (850 mg, 5.99 mmol), then the sulfone (355 mg, 749 μmol) and toluene (7.7 mL). The mixture was vigorously stirred for 2.5 h and monitored by ^{1}H NMR. The reaction mixture was filtered through a plug of Celite with excess CH_2Cl_2 and concentrated to a clear oil containing analytically pure aldimine. IR (film) 2978, 2930, 1719, 1631, 1367, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.31 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.8, 162.1, 142.1, 138.2, 136.0, 130.5, 129.7, 94.5, 82.7, 27.9 (3C); HRMS (ESI): Exact mass calcd for $C_{12}H_{14}INNaO_2$ $[M+Na]^+$ 353.9967, found 353.9961.

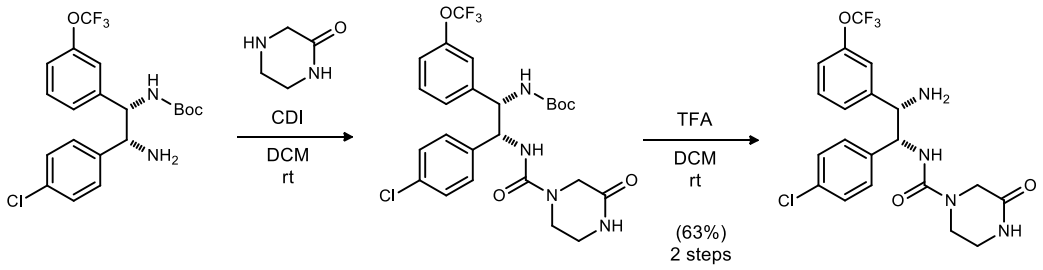


(*E*)-*tert*-Butyl 5-bromo-2-fluorobenzylidenecarbamate (S4). To a flame dried flask equipped with a magnetic stir bar were added the sulfone (3.11 g, 7.0 mmol), sodium sulfate (7.95 g, 56 mmol), potassium carbonate (6.77 g, 49 mmol), and THF (70 mL). The mixture was refluxed for 7 hours, cooled, filtered through an oven dried frit, and concentrated *in vacuo* to reveal a white oil (1.881 g, 89%) which solidified to a white waxy solid after being stored at -20 °C. Mp = 39-40 °C; R_f = 0.47 (30% EtOAc/hexanes); IR (film) 2982, 2930, 1728, 1621, 1584 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.27 (d, J = 6.0 Hz, 1H), 7.63 (m, 1H), 7.05 (dd, J = 9.2, 9.2 Hz, 1H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.7 (d, $^1J_{CF}$ = 256 Hz), 161.1 (d, $^4J_{CF}$ = 5 Hz), 137.7 (d, $^4J_{CF}$ = 8 Hz), 130.8 (d, $^3J_{CF}$ = 15 Hz), 123.6 (d, $^3J_{CF}$ = 10 Hz), 117.8 (d, $^2J_{CF}$ =

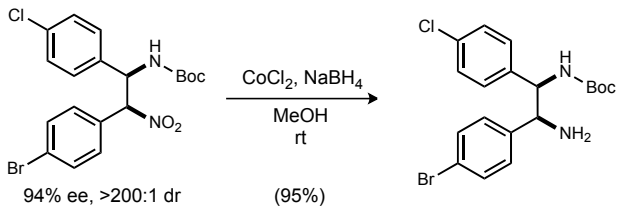
22 Hz), 117.5 (d, $^4J_{CF}$ = 3 Hz), 82.9, 27.8; HRMS (ESI): Exact mass calcd for $C_{12}H_{14}BrFNO_2$ $[M+H]^+$ 302.0192, found 302.0193.



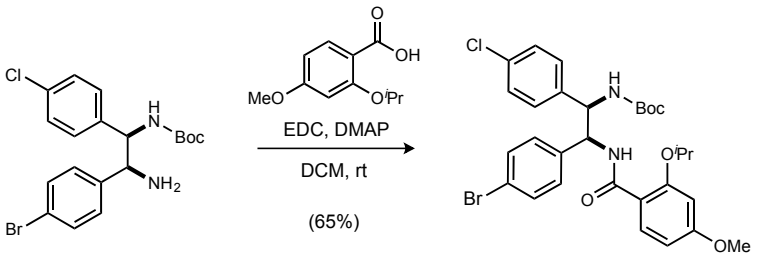
***tert*-Butyl ((1*R*,2*S*)-2-amino-2-(4-chlorophenyl)-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (S5).** The aza-Henry adduct (140 mg, 304 μmol) and $CoCl_2$ (46.0 mg, 304 μmol) were added to methanol (1.2 mL) in a flask and chilled to 0 °C before $NaBH_4$ (57 mg, 1.5 mmol) was added in three portions over 5 h. The reaction mixture was stirred at 0 °C for an additional 15 m before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc aq NH_4OH and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 40-60% ethyl acetate in hexanes) afforded the product as a white foam (60 mg, 46%) in about 15:1 dr (by ^{1}H NMR). R_f = 0.40 (50% EtOAc/hexanes); IR (film) 3378, 3302, 2977, 2929, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.94 (m, 1H), 6.86 (s, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 4.84 (br dd, 1H), 4.26 (br d, 1H), 1.50 (br m, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.1, 149.0, 140.1, 133.4, 130.6, 129.4, 128.4, 128.2, 125.9, 121.6, 120.3 (q, $^1J_{CF}$ = 251 Hz), 120.0, 119.9, 119.1 79.9, 59.1, 28.2; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}ClF_3N_2O_3$ $[M+H]^+$ 431.1249, found 431.1366.



***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-2-(3-oxopiperazine-1-carboxamido)-1-(3-(trifluoromethoxy) phenyl)ethyl)carbamate (S6).** Amine **S5** (60 mg, 139 μmol) was added carbonyl diimidazole (29.4 mg, 181 μmol) in dichloromethane (0.5 mL). The mixture was stirred at room temperature for 90 m (or until no starting material remains by TLC) at which point the oxopiperazine (27.8 mg, 278 μmol) was added. The mixture was stirred for 16 h, and then diluted with dichloromethane and water. The aqueous layer was extracted with dichloromethane and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to an off-white oil. The residue was washed with hexanes (4 mL) and the wash layer was decanted to afford the desired product as a 1:1 mixture with imidazole. This was used without further purification. The urea (47 mg, 84 μmol) was dissolved in dichloromethane (2.0 mL), and treated with TFA (180 μL, 3.3 mmol), and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, poured into satd aq $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to an oil. The residue was washed with hexanes and the wash layer was decanted to afford the desired product as a yellow foam (40 mg, 63% over 2 steps) in about 20:1 dr (by ^{1}H NMR). R_f = 0.1 (5% MeOH/CH_2Cl_2); IR (film) 3344, 3262, 2924, 1668 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.04 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 1H), 6.00 (d, *J* = 7.2 Hz, 1H), 5.03 (dd, *J* = 12.6, 1.8 Hz, 1H), 4.33 (d, *J* = 4.8 Hz, 1H), 4.07 (dd, *J* = 17.4, 12.6 Hz, 2H), 3.60 (m, 2H), 3.31 (m, 2H), 1.24 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.5, 155.7, 149.1, 144.5, 136.6, 133.4, 129.8, 128.8 (2C), 128.3 (2C), 125.2, 120.1, 119.5, 59.4, 59.0, 47.5, 40.9, 39.6, 14.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{21}ClF_3N_4O_3$ $[M+H]^+$ 457.1254, found 457.1268.

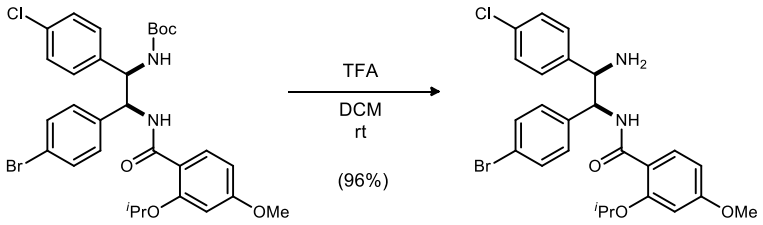


***tert*-Butyl ((1*R*,2*S*)-2-amino-2-(4-bromophenyl)-1-(4-chlorophenyl)ethyl)carbamate (S7).** The β-nitro Boc-amine (470 mg, 1.03 mmol) and $CoCl_2$ (134 mg, 1.03 mmol) were added to methanol (4.1 mL) in a flask and chilled to 0 °C before $NaBH_4$ (194 mg, 5.15 mmol) was added in three portions over 2 h. The reaction mixture was stirred at 0 °C for an additional 15 m before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc aq NH_4OH and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a white foam (416 mg, 95%). $[\alpha]_D^{20}$ +44 (*c* 0.80, $CHCl_3$); R_f = 0.40 (50% EtOAc/hexanes); IR (film) 3378, 3274, 2977, 1698, 1526, 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 7.2 Hz, 2H), 6.94 (d, *J* = 7.2 Hz, 2H), 5.46 (d, *J* = 6.8 Hz, 1H), 4.79 (br t, 1H), 4.22 (br d, 1H), 1.56 (br s, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.1, 140.8, 133.4, 132.6, 128.7 (2C), 128.3, 121.41, 120.3, 79.8, 59.3, 28.3 (3C); HRMS (ESI): Exact mass calcd for $C_{19}H_{23}BrClN_2O_2$ $[M+H]^+$ 425.0631, found 425.0643.

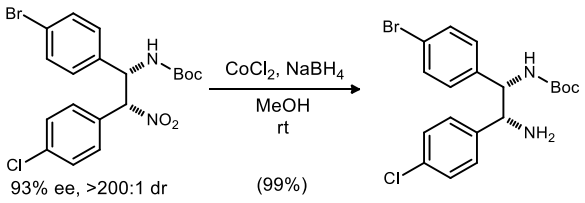


***tert*-Butyl ((1*R*,2*S*)-2-(4-bromophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)carbamate (S8).** The amine (383 mg, 900 μmol) and carboxylic acid (189 mg, 900 μmol) were dissolved in CH_2Cl_2 (4.5 mL), chilled to 0 °C, and treated with EDC•HCl (224 mg, 1.17 mmol) and DMAP (10 mg, 90 μmol). The reaction was stirred and allowed to gradually warm to room temperature over 2 h. After 16 h, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water, satd aq $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was washed with a 3:7 mixture of CH_2Cl_2/hexanes and decanted to

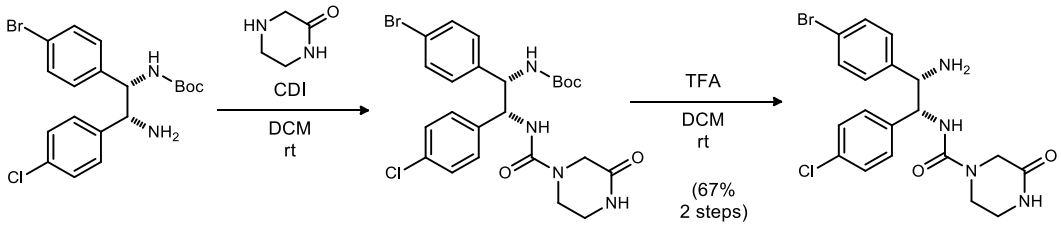
afford a white solid (438 mg, 79%) >95% pure by ^{1}H NMR. $[\alpha]_D^{20}$ -17 (*c* 0.39, $CHCl_3$); mp = 223-225 °C; R_f = 0.9 (10% MeOH/CH_2Cl_2); IR (film) 3350, 2978, 1685, 1631, 1611, 1530, 1496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.8 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.94 (m, 4H), 6.59 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.46 (d, *J* = 1.2 Hz, 1H), 5.87 (d, *J* = 4.8 Hz, 1H), 5.75 (d, *J* = 5.6 Hz, 1H), 5.08 (d, *J* = 3.6 Hz, 1H), 4.68 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.84 (s, 3H), 1.38 (s, 9H), 1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.6, 163.7, 157.2, 155.1, 137.3, 134.4, 133.4, 131.5, 128.9, 128.7, 128.4, 121.7, 114.2, 105.3, 100.3, 80.0, 71.5, 59.5, 56.7, 55.5, 31.6, 28.3, 22.6, 22.0, 21.6, 14.1; HRMS (ESI): Exact mass calcd for $C_{30}H_{34}BrClN_2NaO_5$ $[M+Na]^+$ 639.1237, found 639.1248.



***N*-((1*S*,2*R*)-2-Amino-1-(4-bromophenyl)-2-(4-chlorophenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S9).** The amide (374 mg, 605 μmol) was dissolved in CH_2Cl_2 (6.0 mL), and treated with TFA (1.8 mL, 24 mmol), and stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2, poured into satd aq $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a white foam (300 mg, 96%). $[\alpha]_D^{20}$ -103 (*c* 1.07, $CHCl_3$); R_f = 0.6 (10% MeOH/CH_2Cl_2); IR (film) 3371, 2991, 2929, 1643, 1609, 1519, 1498 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 5.40 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.75 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 1.70 (br, 2H), 1.44 (d, *J* = 6.0 Hz, 3H), 1.43 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 164.6, 163.3, 157.2, 140.7, 137.3, 134.1, 133.1, 131.1, 129.5, 128.4, 128.3, 121.4, 114.9, 105.1, 100.3, 71.5, 58.9, 58.6, 55.5, 22.2, 22.0; HRMS (ESI): Exact mass calcd for $C_{25}H_{26}BrClN_2NaO_3$ $[M+Na]^+$ 539.0713, found 539.0696.

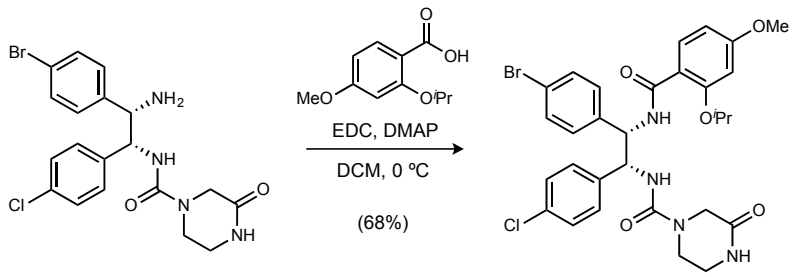


***tert*-Butyl ((1*S*,2*R*)-2-amino-1-(4-bromophenyl)-2-(4-chlorophenyl)ethyl)carbamate (S10).** The β-nitro Boc-amine (265 mg, 581 μmol) and $CoCl_2$ (75.4 mg, 581 μmol) were added to methanol (3 mL) in a flask and chilled to 0 °C before $NaBH_4$ (110 mg, 2.91 mmol) was added in three portions over 45 m. The reaction mixture was stirred at 0 °C for an additional 15 m before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc aq NH_4OH and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a white foam (260 mg, 99%). $[\alpha]_D^{20}$ +40 (*c* 0.27, $CHCl_3$); R_f = 0.31 (50% EtOAc/hexanes); IR (film) 3371, 2976, 2982, 2859, 1697, 1489, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.45 (br s, 1H), 4.77 (br s, 1H), 4.23 (s, 1H), 1.36 (s, 9H), 1.25 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 140.3, 133.3, 131.5, 131.2, 129.1, 128.4, 128.3, 121.5, 59.1, 28.3 (3C); HRMS (ESI): Exact mass calcd for $C_{19}H_{23}BrClN_2O_2$ $[M+H]^+$ 425.0631, found 425.0641.



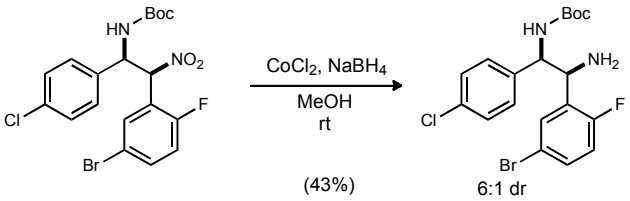
***N*-((1*R*,2*S*)-2-Amino-2-(4-bromophenyl)-1-(4-chlorophenyl)ethyl)-3-oxopiperazine-1-carboxamide (S11).** To the amine (241 mg, 566 μmol) was added carbonyl diimidazole (119 mg, 736 μmol) in CH_2Cl_2 (2.0 mL). The mixture was stirred at room temperature for 3 h (or until no starting material remains by TLC) at which point the oxopiperazine (113 mg, 1.13 mmol) was added. The mixture was stirred for 16 h, and then diluted with CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to an off-white solid. The solid was washed with 1:1 CH_2Cl_2/hexanes (6 mL)

and the wash layer was decanted to afford the desired product as a 1:1 mixture with imidazole. This was used without further purification. The urea (230 mg, 417 μmol) was dissolved in CH_2Cl_2 (5.0 mL), and treated with TFA (1.26 mL, 16.0 mmol), and stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2, poured into satd aq $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a brown oil (170 mg, 67% over 2 steps). $[\alpha]_D^{20}$ +32 (*c* 0.24, $CHCl_3$); R_f = 0.23 (10% MeOH/CH_2Cl_2); IR (film) 3344, 3262, 3069, 2924, 2848, 1675, 1537, 1496 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.84 (br s, 1H), 5.89 (d, *J* = 7.2 Hz, 1H), 5.00 (t, *J* = 6.4 Hz, 1H), 4.26 (d, *J* = 4.8 Hz, 1H), 4.05 (s, 2H), 3.60 (d, *J* = 2.8 Hz, 2H), 3.33 (br d, 2H), 1.85 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.3, 155.7, 140.8, 136.7, 133.4, 131.4, 128.8, 128.5 (2C), 128.3, 121.5 (2C), 59.3, 59.1, 47.6, 40.9, 39.7, 29.7; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}BrClN_4O_2$ $[M+H]^+$ 451.0536, found 451.0536.

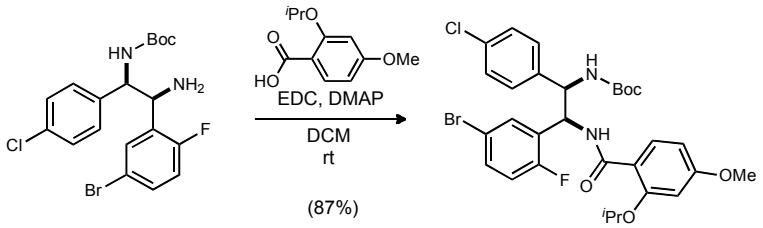


***N*-((1*R*,2*S*)-2-(4-Bromophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S12).** The amine (116 mg, 257 μmol) and carboxylic acid (54.0 mg, 257 μmol) were dissolved in CH_2Cl_2 (1.3 mL), chilled to 0 °C, and treated with EDC•HCl (64.0 mg, 334 μmol) and DMAP (3.1 mg, 26 μmol). The reaction was stirred and allowed to gradually warm to room temperature over 2 h. After 5 h, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water, satd aq $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 0-6% methanol in dichloromethane) afforded the amide as a white solid (112 mg, 68%). $[\alpha]_D^{20}$ +32 (*c* 0.65, $CHCl_3$); mp = 169 ºC; R_f = 0.60 (10% MeOH/CH_2Cl_2); IR (film) 3367, 2978, 2934, 1638, 1604, 1532, 1492, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 4.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* =

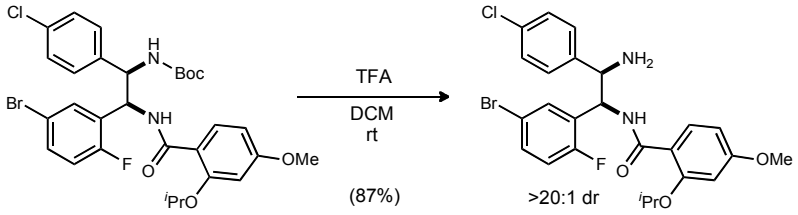
8.4 Hz, 2H), 6.85 (br s, 1H), 6.60 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 5.76 (dd, *J* = 8.0, 2.8 Hz, 1H), 5.10 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.65 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.10 (d, *J* = 3.2 Hz, 2H), 3.84 (s, 3H), 3.70 (m, 1H), 3.58 (m, 1H), 3.37 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.9, 167.2, 164.0, 157.2, 156.0, 137.1, 136.5, 134.4, 133.3, 131.6, 129.4, 128.7, 128.1, 121.9, 113.5, 105.4, 100.3, 71.5, 61.7, 60.4, 57.7, 55.6, 47.5, 41.1, 40.0, 22.0, 21.5, 21.0, 14.2; HRMS (ESI): Exact mass calcd for $C_{30}H_{32}BrClN_4NaO_5$ $[M+Na]^+$ 665.1142, found 665.1165.



***tert*-Butyl ((1*R*,2*S*)-2-amino-2-(5-bromo-2-fluorophenyl)-1-(4-chlorophenyl)ethyl)carbamate (S13).** The β-nitro Boc-amine (430 mg, 0.908 μmol) and $CoCl_2$ (118 mg, 0.908 μmol) were added to methanol (3.7 mL) in a flask and chilled to 0 °C before $NaBH_4$ (343 mg, 9.08 mmol) was added in two portions over 1 h. The reaction mixture was stirred at 0 °C for an additional 15 m before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc aq NH_4OH and the aqueous layer was extracted with EtOAc. The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 20-40% ethyl acetate in hexanes) afforded the product as a white oil (172 mg, 43%) in 6:1 dr (by ^{1}H NMR). R_f = 0.71 (50% EtOAc/hexanes); IR (film) 3378, 2975, 2920, 1691, 1527, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 4.0, 4.0 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 4.8 Hz, 1H), 7.03, (d, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 8.8 Hz, 1H), 5.50 (d, *J* = 6.4 Hz, 1H), 4.79 (br d, 1H), 4.46 (d, *J* = 6.4 Hz, 1H), 1.40 (br m, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.6 (d, $^1J_{CF}$ = 255 Hz), 133.6, 131.9, 131.8, 131.1 (d, $^3J_{CF}$ = 4 Hz), 128.6, 128.5, 128.2, 117.2 (d, $^2J_{CF}$ = 24 Hz), 116.8 (d, $^3J_{CF}$ = 4 Hz), 79.0, 58.6, 53.4, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}BrClFN_2O_2$ $[M+H]^+$ 443.0537, found 443.0547.

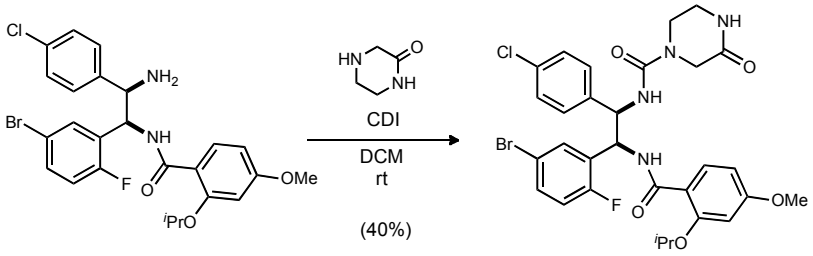


***tert*-Butyl ((1*R*,2*S*)-2-(5-bromo-2-fluorophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)carbamate (S14).** The amine (172 mg, 388 μmol) and carboxylic acid (81.6 mg, 388 μmol) were dissolved in CH_2Cl_2 (1.75 mL) at room temperature. The solution was chilled to 0 °C and EDC•HCl (96.6 mg, 504 μmol) and DMAP (4.8 mg, 39 μmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature over 2 h. After 17 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with water, satd aq $NaHCO_3$, and once more with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2, 20-30% ethyl acetate in hexanes) afforded the amide as a clear foam (213 mg, 87%). R_f = 0.77 (50% EtOAc/hexanes); IR (film) 3373, 3318, 2980, 2925, 2247, 1714, 1645, 1604, 1536 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 9.2 Hz, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 7.37 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 8.8 Hz, 1H), 6.54 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.44 (s, 1H), 5.97 (dd, *J* = 9.2, 9.2 Hz, 1H), 5.74 (m, 1H), 5.08 (m, 1H), 4.69 (qq, *J* = 6.0, 6.0 Hz, 1H), 3.82 (s, 3H), 1.32 (br s, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.3, 163.7, 157.2 (d, $^1J_{CF}$ = 244 Hz), 134.4, 133.6, 132.3 (2C), 132.2, 128.7, 128.6, 128.5 (d, $^3J_{CF}$ = 4 Hz), 117.6 (d, $^2J_{CF}$ = 22 Hz), 116.5 (d, $^3J_{CF}$ = 4 Hz), 114.0, 105.5, 100.1, 77.2, 71.5, 55.5, 28.1, 21.8, 21.7; HRMS (ESI): Exact mass calcd for $C_{30}H_{33}BrClFN_2NaO_5$ $[M+Na]^+$ 657.1143, found 657.1113.



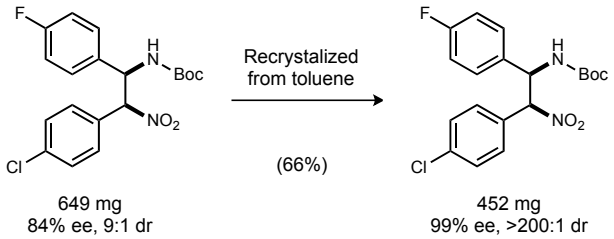
***N*-((1*S*,2*R*)-2-Amino-1-(5-bromo-2-fluorophenyl)-2-(4-chlorophenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S15).** The amide (210 mg, 330 μmol) was dissolved in CH_2Cl_2 (3.0 mL) and treated with TFA (758 μL, 9.91 mmol). The mixture was stirred at room temperature for 3 h,

then diluted with CH_2Cl_2, poured into satd aq $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Column chromatography (SiO_2, 30-50% ethyl acetate in hexanes) afforded the product as a foam (153 mg, 87%) and >20:1 dr by ^{1}H NMR. R_f = 0.15 (50% EtOAc/hexanes); IR (film) 3382, 2980, 2945, 1648, 1606, 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.41, (dd, *J* = 6.4, 2.0 Hz, 1H), 7.34 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.88 (t, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.71 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.73 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.43 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 3H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.36 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.8, 163.4, 160.8 (d, $^1J_{CF}$ = 245 Hz), 157.2, 139.9, 134.2, 133.4, 132.5 (d, $^3J_{CF}$ = 4 Hz), 132.0 (2C), 128.9, 128.8, 128.5, 128.4, 117.5 (d, $^2J_{CF}$ = 24 Hz), 116.6 (d, $^3J_{CF}$ = 4 Hz), 114.6, 105.8, 104.1, 100.2, 77.2, 71.4, 63.8, 58.4, 55.5, 54.0, 21.9 (2C); HRMS (ESI): Exact mass calcd for $C_{25}H_{26}BrClFN_2O_3$ $[M+H]^+$ 535.0799, found 535.0790.

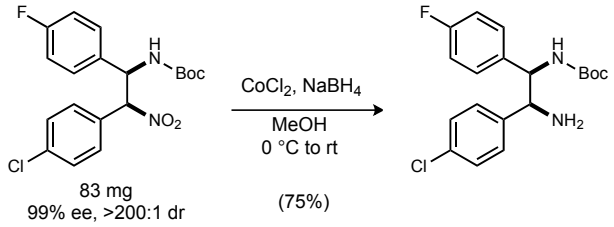


***N*-((1*R*,2*S*)-2-(5-Bromo-2-fluorophenyl)-1-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S16).** To the amine (150 mg, 277 μmol) was added carbonyl diimidazole (53.0 mg, 332 μmol) in CH_2Cl_2 (6.5 mL). The mixture was stirred at room temperature for 3 hours, or until no starting material remained by TLC, at which point oxopiperazine (55.0 mg, 554 μmol) was added. The mixture was stirred for 16 h. The reaction mixture was concentrated and purified by column chromatography (SiO_2, 40-100% ethyl acetate in hexanes) to afford the product as a white solid (68 mg, 40%). $[\alpha]_D^{20}$ +90 (*c* 0.20, $CHCl_3$); Mp = 150-152 °C (dec.); R_f = 0.61 (10% MeOH/CH_2Cl_2); IR (film) 3371, 3260, 3074, 2977, 2928, 1650, 1602, 1533 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.39 (m, 1H), 7.31 (d, *J* = 9.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.97 (m 3H), 6.55 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.44 (d, *J* = 1.6 Hz, 1H), 6.07 (dd, *J* = 9.2, 9.2 Hz, 1H), 5.13 (m, 1H), 4.67 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.10 (d, *J* = 1.6 Hz, 2H), 3.83 (s,

3H), 3.68 (m, 1H), 3.56 (m, 1H), 3.38 (br m, 2H), 1.26 (dd, J = 6.0, 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.9, 166.6, 163.9, 159.1 (d, $^1J_{CF}$ = 246 Hz), 157.3, 155.8, 137.0, 134.4, 133.5, 132.4 (2C), 131.1 (d, $^3J_{CF}$ = 4 Hz), 129.2, 128.3, 128.1, 117.7 (d, $^2J_{CF}$ = 24 Hz), 116.4 (d, $^3J_{CF}$ = 4 Hz), 113.4, 105.2, 100.2, 71.6, 60.1, 55.5, 52.2, 47.4, 41.1, 39.9, 21.9, 21.6; HRMS (ESI): Exact mass calcd for $C_{30}H_{31}BrClFN_4NaO_5$ $[M+Na]^+$ 683.1048, found 683.1021.

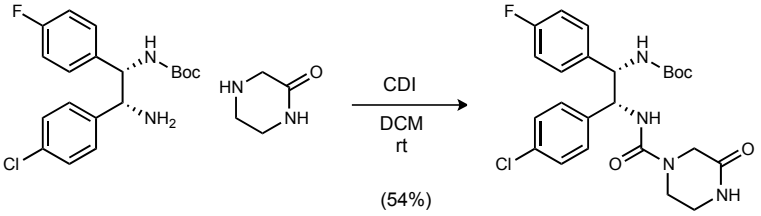


***tert*-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-1-(4-fluorophenyl)-2-nitroethyl)carbamate (S17)**. The β-amino nitroalkane that was 84% ee and 9:1 dr (694 mg, 1.65 mmol) was recrystallized from toluene (16.5 mL, 0.1 M) over the course of 12 h. The crystals were vacuum filtered to afford the adduct as fluffy white crystals that were found to be 99% ee and >200:1 dr by chiral HPLC (66%). $[\alpha]_D^{20}$ +153 (*c* 1.0, $CHCl_3$).

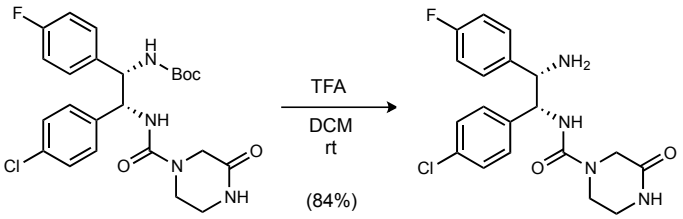


***tert*-Butyl ((1*S*,2*R*)-2-amino-2-(4-chlorophenyl)-1-(4-fluorophenyl)ethyl)carbamate (S18).** The aza-Henry adduct (301 mg, 760 μmol), methanol (2.9 mL), and cobalt (II) chloride (49.3 mg, 379 μmol) were combined and stirred. The solution was cooled to 0 °C and sodium borohydride (431 mg, 11.2 mmol) was added in 5 portions over 1 h. The reaction mixture was stirred at 0 °C for an additional 30 min before the mixture was quenched with satd aq NH_4Cl. The reaction mixture was adjusted to pH 10 with conc aq NH_4OH. The mixture was added to a glass frit, washed with water, and the aqueous layer was collected. The remaining solid was thoroughly washed with CH_2Cl_2 and collected in a separate flask. The organic layers were dried

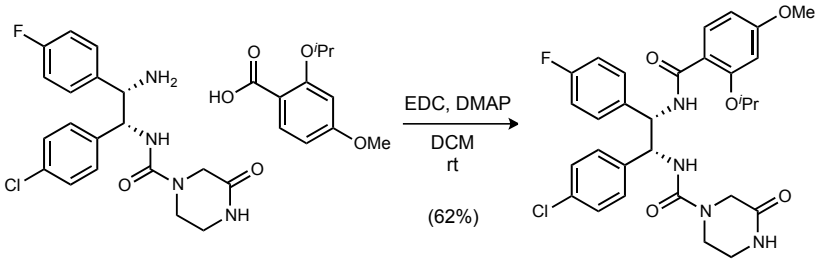
($MgSO_4$), filtered and concentrated to afford a white solid (221 mg, 75%). $[\alpha]_D^{20}$ –45 (*c* 0.84, $CHCl_3$); mp 144-146 °C; R_f = 0.36 (50% EtOAc in hexanes); IR (film) 3371, 2970, 2922, 2355, 1692, 1602, 1512 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ7.58 (d, *J* = 8.4 Hz, 2H), 7.02-6.92 (m, 6H), 4.81 (br m, 1H), 4.24 (br d, 1H), 1.48-1.38 (m, 12H); ^{13}C NMR (100 MHz, CD_3OD) ppm 163.7 (d, $^1J_{CF}$ = 244 Hz), 157.2, 142.2, 137.6, 134.2, 130.7 (d, $^3J_{CF}$ = 8.0 Hz), 130.4, 129.3, 116.2 (d, $^2J_{CF}$ = 22.0 Hz), 80.2, 61.5, 60.9, 28.6; HRMS (ESI): Exact mass calcd for $C_{19}H_{23}ClFN_2O_2$ $[M+H]^+$ 361.1677, found 361.1689.



***tert*-Butyl ((1*S*,2*R*)-2-(4-chlorophenyl)-1-(4-fluorophenyl)-2-(3-oxopiperazine-1-carboxamido)ethyl)carbamate (S19).** To a mixture of free amine (210 mg, 575 μmol) and methylene chloride (2.9 mL), carbonyl diimidazole (112 mg, 689 μmol) was added and left to stir at rt for 1 h before adding oxopiperazine (115 mg, 1.15 mmol). The resulting mixture was stirred for 5 h before quenching with water and extracting with methylene chloride. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford a white solid (166 mg, 54%). $[\alpha]_D^{20}$ +16 (*c* 0.09, CH_3COCH_3); Mp: 216-218 °C; R_f = 0.54 (10% MeOH in CH_2Cl_2); IR (film) 3379 (br), 2981, 1505, 1682, 1608 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.68 (s, 1H), 7.45-7.40 (m, 4H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.05 (dd, *J* = 8.8 Hz, 8.0 Hz, 4H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 3.90 (d, *J* = 17.6 Hz, 1H), 3.72 (d, *J* = 17.6 Hz, 1H), 3.62-3.42 (m, 1H), 3.37-3.36 (m, 1H), 3.10 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) ppm 169.9, 163.5 (d, $^1J_{CF}$ = 243 Hz), 157.9, 157.3, 140.9, 138.2, 136.2, 134.2, 130.7, 130.6 (d, $^3J_{CF}$ = 8.0 Hz), 129.2, 116.0 (d, $^2J_{CF}$ = 21 Hz), 80.3, 59.5, 58.5, 48.2, 41.33, 41.26, 28.6; HRMS (ESI) Exact mass cald for $C_{24}H_{28}ClFN_4NaO_4$ $[M+Na]^+$ 513.1681, found 513.1704.

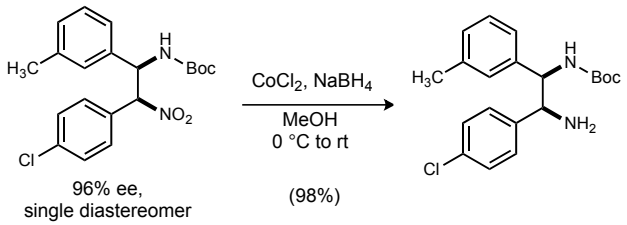


***N*-((1*R*,2*S*)-2-Amino-1-(4-chlorophenyl)-2-(4-fluorophenyl)ethyl)-3-oxopiperazine-1-carboxamide (S20).** Boc-protected urea (150 mg, 306 μmol) was dissolved in CH_2Cl_2 (3.0 mL), and treated with TFA (702 μL, 9.80 mmol), and stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and poured into satd aq $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to an off white oil (100 mg, 84%). $[\alpha]_D^{20}$ −1.8 (*c* 0.61, MeOH); R_f = 0.36 (10% MeOH in CH_2Cl_2); IR (film) 3352 br, 3067, 2936, 2890, 1664, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H), 7.03 (m, 6H), 5.97 (d, *J* = 7.2 Hz, 1H), 4.99 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.28 (d, *J* = 5.6 Hz, 1H), 4.01 (d, *J* = 5.6 Hz, 2H), 3.60-3.56 (m, 2H), 3.29 (br m, 2H), 1.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.5, 162.1 (d, $^1J_{CF}$ = 243 Hz), 155.7, 137.5 (d, $^4J_{CF}$ = 3 Hz), 137.0, 133.3, 128.9, 128.4, 128.3 (d, $^3J_{CF}$ = 9 Hz), 115.1 (d, $^2J_{CF}$ = 21 Hz), 59.4, 58.9, 47.5, 40.8, 39.6; HRMS (ESI) Exact mass cald for $C_{19}H_{20}ClFN_4NaO_2$ $[M+Na]^+$ 413.1157, found 413.1145.



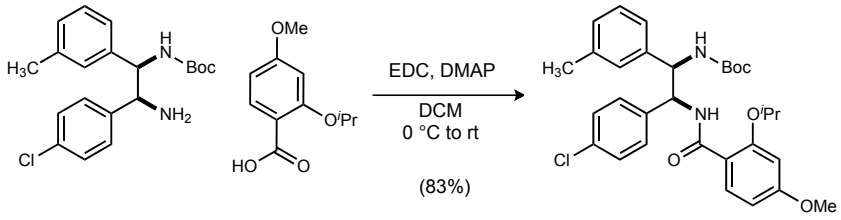
***N*-((1*R*,2*S*)-1-(4-Chlorophenyl)-2-(4-fluorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S21).** The amine (80.0 mg, 205 μmol) and 2-isopropoxy-4-methoxybenzoic acid (43.1 mg, 205 μmol) were combined in dichloromethane (1.0 mL). The solution was chilled 0 °C and DMAP (2.5 mg, 21 μmol) and EDC·HCl (51.0 mg, 266 μmol) were added. The mixture gradually warmed to room temperature and stirred for 24 h before diluting with dichloromethane and water. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified via column chromatography (0-6%

methanol in dichloromethane) to afford an off white oil (74 mg, 62%). $[\alpha]_D^{20}$ +61 (*c* 0.36, $CHCl_3$); R_f = 0.56 (10% MeOH in CH_2Cl_2); IR (film) 3369, 3259, 2975, 2926, 1666, 1646, 1542, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.6 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 5.2 Hz, 1H), 7.27 (br m, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.00 (m, 4H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.58 (dd, *J* = 9.2, 8.8 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 5.77 (dd, *J* = 8.0, 7.6 Hz, 1H), 5.08 (dd, *J* = 3.2, 3.2 Hz, 1H), 4.64 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.10 (s, 2H), 3.83 (s, 3H), 3.66 (m, 1H), 3.56 (m, 1H), 3.35 (br m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.1, 167.0, 163.9, 162.3 (d, $^1J_{CF}$ = 244 Hz), 157.2, 155.9, 136.7, 134.2 (d, $^2J_{CF}$ = 27 Hz), 134.0, 133.2, 129.4, 128.8, 128.0, 115.3 (d, $^2J_{CF}$ = 21 Hz), 113.5, 105.4, 100.3, 71.4, 61.7, 57.5, 55.0, 47.4, 40.9, 40.0, 21.9, 21.5; HRMS (ESI) Exact mass cald for $C_{30}H_{33}ClFN_4O_5[M+H]^+$ 583.2124, found 583.2134.

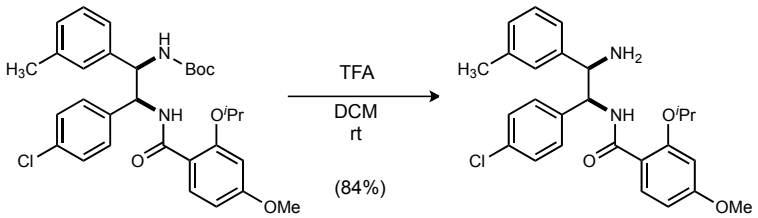


***tert*-Butyl ((1*R*,2*S*)-2-amino-2-(4-chlorophenyl)-1-(*m*-tolyl)ethyl)carbamate (S22).** To a round bottom flask equipped with a stir bar and argon balloon was added nitroalkane (200 mg, 510 μmol) and methanol (6.8 mL). The mixture was stirred at room temperature to dissolve the nitroalkane and then cooled to 0 °C. To the stirring solution was added $NaBH_4$ (289 mg, 7.65 mmol) in three portions over 90 min. The reaction was allowed to stir for an additional 30 min and then quenched with 1 M HCl, adjusting to pH 2. The solution was readjusted to ~10 with 1 M aq NH_4OH before vacuum filtration through a glass frit funnel, washing with deionized water. The aqueous wash was discarded and the solid remaining on the filter was washed heavily with dichloromethane. The organic filtrate was collected, dried with $MgSO_4$, and concentrated to give the title compound as a white/gray solid (181 mg, 98%). $[\alpha]_D^{20}$ -33 (*c* 0.11, $CHCl_3$); mp = 119-121 °C; R_f = 0.32 (5% MeOH/CH_2Cl_2); IR (film) 3378, 2978, 1687, 1522, 1367, 1289, 1252, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, 2 H), 7.18 (m, 2H), 7.10 (br s, 2H), 5.31 (br d, 1H), 4.79 (br dd, 1H), 4.23 (br d, 1 H), 2.31 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.0, 140.7, 138.4, 137.8, 133.0, 128.5, 128.3, 128.4, 124.3, 79.5, 59.7,

29.6, 28.2, 21.3; HRMS (ESI): Exact mass calcd for $C_{31}H_{39}ClN_2O_5$ $[M+H]^+$ 553.2469, found 553.2469.

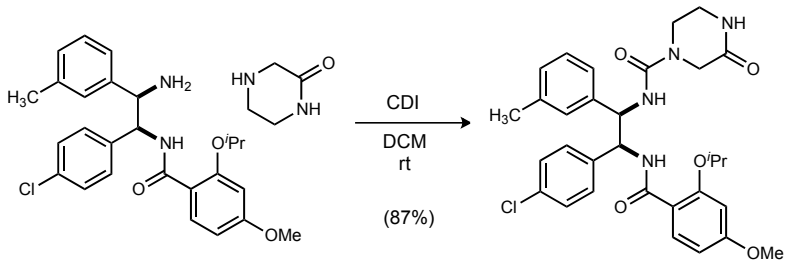


tert-Butyl ((1*R*,2*S*)-2-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(*m*-tolyl)ethyl)carbamate (S23). The amine (200 mg, 550 μmol) and carboxylic acid (115 mg, 550 μmol) were dissolved in dichloromethane at room temperature and then cooled to 0 °C with stirring under argon atmosphere. To the cold solution was added EDC·HCl (138 mg, 720 μmol) and DMAP (6.7 mg, 55 μmol) and the reaction was allowed to stir for 16 h while gradually warming to room temperature. The reaction was then diluted with dichloromethane and water and extracted three times. The organic layers were combined and dried ($MgSO_4$) and concentrated to afford the desired product as a white solid (253 mg, 83%). $[\alpha]_D^{20}$ -42 (*c* 0.12, $CHCl_3$); mp = 208-210 °C; R_f = 0.71 (5% MeOH/CH_2Cl_2); IR (film) 3352, 2975, 2927, 1682, 1532, 1255, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (br s, 1 H), 8.19 (d, *J* = 8.8 Hz, 1 H), 7.26 (m, 2 H), 7.16 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.06 (br m, 4H), 6.83 (m, 2H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.49 (s, 1H), 5.75 (br d, 1H), 5.51 (br dd, 1H), 5.12 (br d, 1H), 4.71 (br dd, 1H), 3.86 (s, 3H), 2.27 (s, 3H), 1.40 (s, 9H), 1.32 (bs s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.2, 163.4, 157.1, 155.1, 138.3, 137.7, 137.1, 134.2, 133.3, 128.7, 128.2, 128.1, 123.4, 114.5, 112.4, 105.1, 100.2, 79.8, 71.4, 59.3, 56.9, 55.5, 31.5, 28.3, 22.6, 22.0, 21.6, 21.4, 14.0. HRMS (ESI): Exact mass calcd for $C_{31}H_{38}ClN_2O_5$ $[M+H]^+$ 553.2469, found 553.2469.



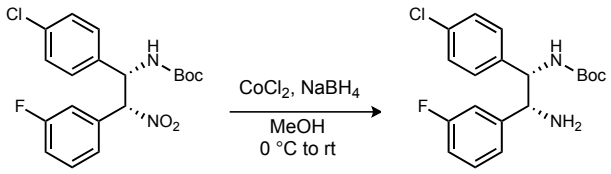
N-((1*S*,2*R*)-2-amino-1-(4-chlorophenyl)-2-(*m*-tolyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S24). The amide (200 mg, 360 μmol) was dissolved in dichloromethane

(4.0 mL) in a round bottom flask equipped with a stir bar and argon balloon. To the solution was added TFA (1.10 mL, 14.5 mmol) and the reaction was allowed to stir for 18 h. The reaction was quenched with saturated aq $NaHCO_3$ and extracted with dichloromethane. The organic layers were dried ($MgSO_4$), filtered, and concentrated, affording the product as a viscous foam (138 mg, 84%). $[\alpha]_D^{20}$ -123 (*c* 0.11, $CHCl_3$); R_f = 0.23 (5% MeOH/CH_2Cl_2); IR (film) 3381, 2978, 2930, 1644, 1605, 1492, 1259, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.19 (m, 3H), 7.07 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.96 (s, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.57 (dd, J = 8.9, 2.3 Hz, 1H), 6.51 (d, J = 2.1 Hz, 1H), 5.45 (dd, J = 7.8, 5.2 Hz, 1H), 4.78 (qq, *J* = 6.0, 6.0 Hz, 1H), 4.37 (d, *J* = 5.0 Hz, 1H), 3.83 (s, 3H), 2.29 (s, 3H), 1.48 (d, J = 6.3 Hz, 3H), 1.47 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.5, 163.2, 157.2, 142.4, 137.8, 137.2, 134.0, 132.9, 129.2, 128.1, 127.9, 127.7, 123.7, 115.2, 105.0, 100.7, 100.3, 71.4, 59.5, 58.7, 55.4, 29.6, 22.2, 21.9, 21.3; HRMS (ESI): Exact mass calcd for $C_{26}H_{30}ClN_2O_3$ $[M+H]^+$ 453.1945, found 453.1953.

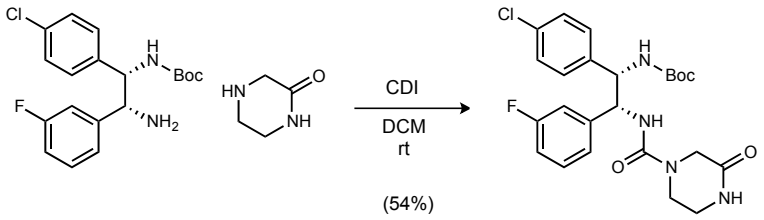


N-((1*R*,2*S*)-2-(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)-1-(*m*-tolyl)ethyl)-3-oxopiperazine-1-carboxamide (S25). To a round bottom flask equipped with a magnetic stir bar and argon balloon was added amine (100 mg, 220 μmol), CDI (45.0 mg, 280 μmol), and dichloromethane (1.25 mL). The mixture was stirred for one hour before oxopiperazine (44 mg, 440 μmol) was added. The reaction was then allowed to stir for 20 h before diluting with dichloromethane and water and extracting with water three times. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a light yellow solid (111 mg, 87%). $[\alpha]_D^{20}$ +45 (*c* 0.10, $CHCl_3$); mp = 115-117 °C; R_f = 0.19 (5% MeOH/CH_2Cl_2); IR (film) 3373, 2978, 2930, 1639, 1605, 1532, 1493, 1345, 1259, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.4 Hz, 1 H), 8.27 (d, J = 9.2 Hz, 1 H), 7.39 (d, J = 6.0 Hz, 1 H), 7.3-6.99 (3 H), 6.95 (d, J = 8.0 Hz, 2 H), 6.77 (d, J = 7.6 Hz, 1 H), 6.71 (br s, 1 H), 6.61 (dd, J = 8.8, 2.4 Hz, 1 H), 6.44 (d, J = 2.0 Hz, 1 H), 6.38 (br d, 1 H), 5.76 (dd, J = 8.0 Hz, 2.8 Hz, 1 H), 5.12 (dd, J = 5.6, 2.8 Hz, 1 H), 4.63

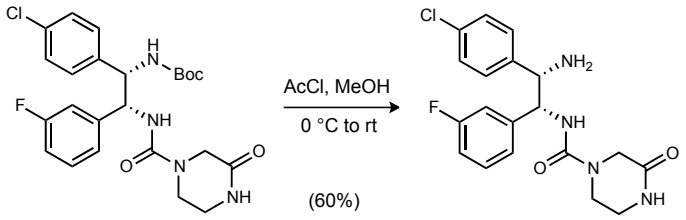
(qq, 1 H), 4.12 (d, J = 2.0 Hz, 2 H), 3.85 (s, 3 H), 3.70 (m, 1 H), 3.60 (m, 1 H), 3.39 (br m, 2 H), 2.20 (s, 3 H), 1.18 (d, J = 6.0 Hz, 3 H), 1.14 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.8, 166.8, 163.8, 157.2, 156.0, 137.6, 137.2, 137.0, 134.4, 133.5, 129.2, 128.9, 128.6, 128.34, 128.25, 128.1, 127.8, 124.8, 113.8, 105.2, 100.3, 71.4, 61.7, 57.9, 55.5, 47.5, 41.1, 40.0, 21.9, 21.5, 21.4; HRMS (ESI): Exact mass calcd for $C_{31}H_{36}ClN_4O_5$ $[M+H]^+$ 579.2374, found 579.2365.



***tert*-Butyl *((1S,2R)*-2-amino-1-(4-chlorophenyl)-2-(3-fluorophenyl)ethyl)carbamate (S26).** Nitroalkane (500 mg, 1.27 mmol) and $CoCl_2$ (165 mg, 1.27 mmol) were dissolved in methanol (16.7 mL) at rt and then cooled to 0 °C with stirring. $NaBH_4$ (716 mg, 19.0 mmol) was added in three portions over 1 h. The reaction was then allowed to stir for 1 h and then acidified to pH 2 with 1 M HCl. The pH of this solution was readjusted to 10 with 1 M aq NH_4OH and filtered through a glass frit, washing with deionized water. The solid on the filter was washed heavily with dichloromethane and the filtrate collected, dried ($MgSO_4$), filtered, and concentrated to yield the product as a white solid (355 mg, 77%). Mp = 141-143 °C; R_f = 0.51 (10% $MeOH/CH_2Cl_2$); IR (film) 3380, 2981, 2935, 1682, 1523, 1490, 1249, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 6.5 Hz, 1 H), 7.23 (d, *J* = 8.3 Hz, 3 H), 6.95 (m, 3 H), 6.99 (d, *J* = 7.7 Hz, 1 H), 6.83 (d, *J* = 9.5 Hz), 5.55 (br d, *J* = 6.5 Hz, 1 H), 4.84 (br dd, 1 H), 4.27 (br d, 1 H), 1.39 (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.6 (d, $^1J_{CF}$ = 244 Hz), 155.0, 144.7, 144.6, 133.3, 129.8, 129.7, 128.6, 128.2, 127.7, 122.5, 114.5, 114.3, 113.9, 113.7, 79.7, 59.3, 28.2. HRMS (ESI): Exact mass calcd for $C_{19}H_{23}ClFN_2O_2$ $[M+H]^+$ 361.1683, found 361.1678.

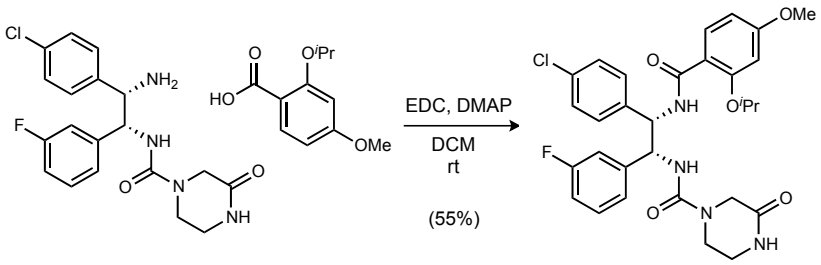


***tert*-Butyl ((1*S*,2*R*)-1-(4-chlorophenyl)-2-(3-fluorophenyl)-2-(3-oxopiperazine-1-carboxamido)ethyl)carbamate (S27).** Amine (300 mg, 820 μmol) was dissolved in dichloromethane (9.7 mL) at room temperature. To the solution was added CDI (174 mg, 1.07 mmol) with stirring under argon. Oxopiperazine (164 mg, 1.64 mmol) was delivered after 1 h and the reaction stirred for 18 h. The reaction was then concentrated by rotary evaporation, triturated with dichloromethane, and filtered through qualitative filter paper, washing with a small amount of dichloromethane. The product was removed from the filter paper and dried under high vacuum to yield the title compound as a light yellow solid (217 mg, 54%). Mp = 181-184 °C; R_f = 0.36 (10% MeOH/CH_2Cl_2); IR (film) 3366, 2980, 2930, 1678, 1632, 1526, 1250, 1168; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (br d, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.44-7.27 (m, 6 H), 7.03 (br m, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 4.93 (m, 2 H), 3.76 (d, *J* = 16.8 Hz, 1 H), 3.53 (d, *J* = 18 Hz, 1 H), 3.27 (m, 2 H), 2.92 (br, 2 H), 1.15 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 166.9, 155.8, 154.9, 145.5, 141.4, 131.9, 129.9, 129.8, 128.2, 124.7, 118.4, 115.0, 114.8, 113.7, 78.2, 58.0, 56.6, 55.3, 47.6, 28.4. HRMS (ESI): Exact mass calcd for $C_{24}H_{28}ClFN_4NaO_4$ $[M+Na]^+$ 513.1681, found 513.1704.



***tert*-Butyl ((1*S*,2*R*)-2-amino-1-(4-chlorophenyl)-2-(3-fluorophenyl)ethyl)carbamate (S28).** The urea (178 mg, 360 μmol) was dissolved in methanol (16 mL) at room temperature and then cooled to 0 °C. Acetyl chloride (206 μL, 2.90 mmol) was added via syringe to the cold solution and the reaction stirred under Ar atmosphere for 15 h, at which point the solvent was removed by rotary evaporation and high vacuum. The solid was redissolved in dichloromethane and $NaHCO_3$ and extracted once. The aqueous layer was back extracted five times with dichloromethane to afford the deprotected amine as a light yellow solid (84 mg, 60%). Mp = 139-142 °C; R_f = 0.21 (10% MeOH/CH_2Cl_2); IR (film) 3329, 3054, 2926, 1669, 1636, 1542, 1343, 1245 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (br s, 1 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.34 (m, 3 H), 7.25 (d, *J* = 10.8 Hz, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 7.05 (m, 3 H), 6.75 (d, *J* = 8.8 Hz, 1 H), 4.73 (dd, *J* = 9.2, 9.2 Hz, 1 H), 4.10 (d, *J* = 9.6 Hz, 1 H), 3.85 (m, 1 H), 3.61 (m, 1 H), 2.99 (br m, 2 H), 1.93

(br m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) ppm 166.7, 161.2, 156.0, 145.6, 144.1, 131.4, 129.9, 129.6, 128.0, 124.7, 115.0, 114.8, 114.0, 113.8, 60.8, 58.9, 47.7. HRMS (ESI): Exact mass calcd for $C_{19}H_{21}ClFN_4O_2$ $[M+H]^+$ 391.1337, found 391.1342.



N-((1*R*,2*S*)-2-(4-chlorophenyl)-1-(3-fluorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S29). To a glass vial equipped with a magnetic stir bar and argon balloon was added amine (49 mg, 125 μmol), carboxylic acid (26.3 mg, 125 μmol), and dichloromethane (1.0 mL). The mixture was cooled to 0 °C with stirring before addition of EDC·HCl (31 mg, 163 μmol) and DMAP (1.6 mg, 13 μmol). The reaction was allowed to stir for 18 h before dilution with dichloromethane and aqueous extraction. The combined organic layers were dried with $MgSO_4$ and concentrated to a light yellow solid (62 mg, 85%). The solid was redissolved in dichloromethane and purified by column chromatography (2-10% MeOH/CH_2Cl_2, 55%). Mp = 123-136 °C; R_f = 0.27 (10% MeOH/CH_2Cl_2), IR (film) 3369, 2933, 1639, 1605, 1533, 1493, 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 1 H), 8.27 (d, *J* = 9.2 Hz, 1 H), 7.71 (d, *J* = 4.8 Hz), 7.28 (s, 1 H), 7.15 (m, 1 H), 6.55 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 10.0 Hz, 1 H), 6.66 (d, *J* = 7.2 Hz, 1 H), 6.62 (dd, *J* = 9.2, 2.4 Hz, 1 H), 6.46 (d, *J* = 2.0 Hz, 1 H), 6.43 (s, 1 H), 5.80 (dd, *J* = 8.0, 2.4 Hz, 1 H), 5.13 (dd, *J* = 4.8, 2.8 Hz, 1 H), 4.67 (qq, *J* = 6.0, 6.0 Hz, 1 H), 4.14 (s, 2 H), 3.85 (s, 3 H), 3.70 (m, 1 H), 3.60 (m, 1 H), 3.41 (br m, 2 H), 1.22 (d, *J* = 6.0 Hz, 3 H), 1.15 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.0, 167.1, 163.9, 162.1 (d, $^1J_{CF}$ = 243 Hz), 157.2, 156.0, 140.8, 140.7, 136.6, 134.4, 133.8, 129.3, 129.2, 128.6, 128.4, 124.1, 114.9, 114.6, 114.5, 114.3, 113.5, 105.3, 100.3, 71.4, 61.8, 57.5, 55.5, 47.4, 41.0, 40.0, 22.0, 21.3. HRMS (ESI): Exact mass calcd for $C_{30}H_{33}ClFN_4O_5$ $[M+H]^+$ 583.2124, found 583.2126.