Title
Enantio- and Diastereoselective Additions to Nitroalkenes via N-Sulfinyl Urea Organocatalysis

Author
Kimmel, Kyle Lawrence

Publication Date
2012

Peer reviewed|Thesis/dissertation

Enantio- and Diastereoselective Additions to Nitroalkenes via *N*-Sulfinyl Urea Organocatalysis

by

Kyle Lawrence Kimmel

A dissertation submitted in partial satisfaction of the requirements for the degree of
Doctor of Philosophy in Chemistry
in the Graduate Division of the University of California, Berkeley

Thesis Committee:
Professor Robert G. Bergman, Chair
Professor Richmond Sarpong
Professor Alex Bell

Fall 2012

Abstract

Enantio- and Diastereoselective Additions to Nitroalkenes via *N*-Sulfinyl Urea Organocatalysis

by

Kyle Lawrence Kimmel

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Robert G. Bergman, Chair

Chapter 1. An introduction to my work with sulfinyl ureas as a new class of hydrogen-bonding catalysts is presented. The conception of this type of catalysis is discussed, and highlights in the sulfinyl urea-catalyzed additions of thioacetic acid and Meldrum's acid are presented.

Chapter 2. The sulfinyl urea-catalyzed enantioselective addition of thioacetic acid to a broad range of β- and cyclic α,β-disubstituted nitroalkenes is described. This method is shown to be useful for accessing pharmaceutically relevant 1,2-aminothiol products.

Chapter 3. The enantio- and diastereoselective addition of cyclohexyl Meldrum's acid to β- and α,β-disubstituted nitroalkenes is presented. This method is demonstrated to be a viable route to γ-amino acid derivatives with multiple stereocenters.

Chapter 4. The conjugate addition-enantioselective protonation of Meldrum's acid with terminal nitroalkenes is described. This process utilizes a sulfinyl urea catalyst that is chiral solely at the sulfinyl group. Rapid conversion of the addition products to pharmaceutically relevant α,γ-disubstituted γ-lactams is demonstrated.

Table of Contents

Acknowledgements

As is traditional in Ellman group theses, I will proceed to thank everyone who has contributed to my successes, helped me in any way, or made any impression on me whatsoever within my research sphere. As is also customary in the Ellman group, each expression of gratitude will be accompanied by a memorable fact or observation, a quintessential characteristic or a defining synopsis of the referenced person.

First and foremost, I would like to thank my PhD advisor, Professor Jonathan Ellman. Jon has been a truly superb advisor and research director. His intelligence and capacity for retaining large amounts of information have always bewildered and impressed me. His quick and sharp wit, tenacity and dedication, and humility in spite of his great successes are all to be commended and remembered.

Next I would like to give special thanks to my undergraduate research advisor, Professor Keith Woerpel. Keith was truly, in all senses of the word, my mentor. He was my original inspiration to study organic chemistry. He has bestowed upon me scientific knowledge, professional guidance, and most importantly friendship that continues to this day. As an unconditional supporter of me and as my fellow inquisitor and friend, I give him my thanks.

I would like to thank Professor Bob Bergman for his mentorship and support. Bob has always represented an icon of success, in-depth knowledge and wisdom in my eyes. In my experience as his teaching assistant for graduate physical organic chemistry, I can say with all honesty that he was one of the best teachers I have ever known. His thoroughness, patience, depth of understanding and ability to convey complex ideas simply and clearly will always impress me.

Though it is not customary to thank future employers, in my case it is more than warranted. In this economy, jobs are scarce and one must never take for granted the opportunities they are given. Thus I would like to thank Dart Neuroscience for having faith in me and granting me a position as a research chemist working toward the goal of enhanced long-term memory.

And now on to the wonderful and colorful group of individuals we call 'the Ellman group.'

Andy "Pat" Patterson was a jovial guy who always seemed to know what he was doing and complete it easily. Denise Colby is quite possibly the smartest person I have met, or at least embodies that persona. Either way, it was justification to bug her with questions whenever possible. Melissa Herbage was the first of a long train of Melissas in the Ellman group – a true trendsetter in name and in chemistry.

Two years above me was the army of the four women who ruled the dynamic of the Ellman group for several years – Katherine Rawls, Melissa Leyva, MaryAnn Robak and Katrien Brak. Katherine was the master of no-nonsense approaches to chemistry and life. Melissa took on the thankless (because we never won) job of being our softball captain. MaryAnn was the first person I worked with and as such was a valuable mentor and guide. Katrien was my neighbor in the lab, the senior student I looked up to and a friend. I still remember how I could recruit her to go join me for lunch outside on the lawn and we would chat about whatever was on our minds.

The class one year above me was the quirkiest and coolest trio – Andy Tsai, Pete Marsden and Sirilata "Van" Yotphan. Pete and Van were an inseparable but dysfunctional duo. Pete was without a doubt the most "chill" person the Ellman group has seen. Andy Tsai has been one of my closest friends in the group, which is ironic because he claims to be antisocial. Andy is a true Renaissance man, capable and interested in tackling every problem or situation one could think of, along with situations that one cannot even conceive. I wish him the best and demand that he

stays in touch. Rest assured, we will continue to celebrate his birthday in his absence, which may hopefully someday beget his return from the faraway land called Florida.

Rhia Martin is my best friend in the lab and has been with me since the beginning. We have shared many experiences, including apprehensions about minimeeting, exciting new results and five years of battling side-by-side with misbehaving chemicals. I wish her all the success and joy that life could bring.

Tyler "Thai-ler" Baguley has a way of making every situation funny and I'll miss that. Andrew Buesking is one of the most respectable people I know. Imagining Andrew doing something offensive or illegal is more difficult than thinking up a new synthesis of taxol.

The last class of graduate students that I will know consists of James Phelan, Apiwat Wangweerawong (it's phonetic, don't worry) and Shuming Chen. James should really go on "Who Wants to be a Millionaire" someday because his constant expounding of random little-known facts never ceases to surprise me. Apiwat is in all aspects a cool person and I wish him the best. Shuming really needs to deliver lessons in Mandarin Chinese that she has promised me so we can converse as if I were not a white person. I will always admire Shuming's sincere passion for learning and pursuit of knowledge no matter how remote, difficult or inaccessible.

There have been numerous postdoctoral researchers, visiting scientists and exchange students in the group that I would like to acknowledge for their help and friendship – Somenath Chowdhury, Gopal Datta, Masakazu Wakayama, Matt Soellner, Eric Phillips, Simon Duttwyler, Jimmie Weaver, Kevin Hesp, Hyung Jung, Yuji Matshushima, Joseph Stringer, Haichao Xu, Michael Ischay, Morten Storgaard, Tatjana Huber and Yajing Lian. Somenath is the most hospitable man I know. Masa was the best softball player we ever had. Eric is especially talented at chemistry and will undoubtedly be successful. Michael needs to relax because he is smart and everything will be fine. Tatjana is the kind of person who always puts people around her in a better mood. Joey is a good friend and very respectable gentleman. Simon is a person I would trust with any advice – from the finest details of chemistry to the most dubious life problems. Jimmie has been my "partner in crime" for the last two years, and together we have uncovered some really cool chemistry. It has truly been a pleasure working with him and I wish him great success as a professor at Oklahoma State University.

Finally, there are the undergraduates in the Ellman group – Stephen Thomas, Melissa Lee, Irene Cai and Colin Lu. Colin is apparently too smart for his own good, as he has been known to interrupt statements prior to the main clause with an honest "I know." Irene is a dedicated student but I unfortunately cannot help her with the task of finding Andrew. Stephen was the first student I mentored and has gone on to a productive graduate career at Columbia University. Finally, Melissa Lee has been my student for almost three years now and has been a truly wonderful person to work with. I hope that she keeps in touch with me for years to come.

I also want to thank my friends outside our lab – Jane Wang, Rachel Zeldin, Steve Heller, Pam Wang, Jen Nguyen, Yifei Yang, Alex Xenakis and Christina Woo – for their support throughout the years.

Lastly, I want to thank my wife, Ms. Crystal Su, for putting up with my many flaws and continuing to give me a chance. It is my hope that with the completion of this dissertation, I can enter into a new phase of life whereby I can return the many favors and sacrifices that she has made for me.

Chapter 1: Introduction

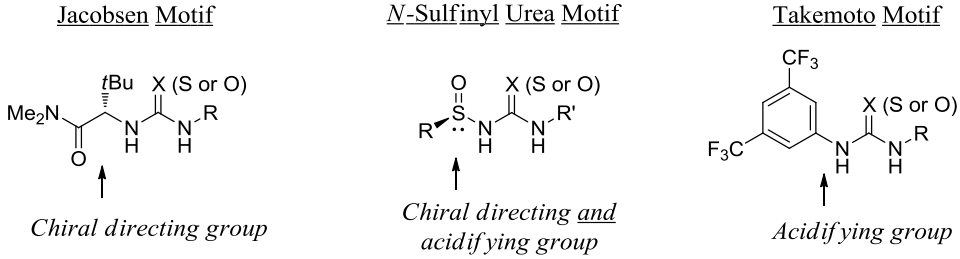
Recently in the Ellman group, N-sulfinyl ureas were discovered as a new class of hydrogen-bonding catalysts in which the sulfinyl moiety serves uniquely as both an acidifying and chiral directing group. This catalyst scaffold was then used to promote the first highly enantio- and diastereoselective additions of thioacetic acid and Meldrum's acid to nitroalkenes. The high level of acyclic diastereoselectivity we observed for the addition of Meldrum's acid to α,β-disubstituted nitroalkenes led to the development of the first enantioselective protonation of nitronates. Together, these methods represent new and efficient strategies to access biologically significant classes of compounds such as 1,2-aminothiols and γ-amino acid derivatives with β,γ or α,γ-substitution.

Introduction

In recent years, there have been an ever-increasing number of reports in the field of asymmetric organocatalysis. The high level of interest the organic chemistry community has expressed in this type of catalysis may reflect inherent advantages of organocatalysis over transition metal-based approaches, including low cost, low toxicity, facile preparation of catalysts, ease of handling due to low moisture and air sensitivity, and the possibility of enzyme-like selective catalysis.[1] Particularly, hydrogen-bonding catalysis has generated significant interest, and chiral ureas have been heavily utilized as asymmetric hydrogen-bonding catalysts.[1,2]

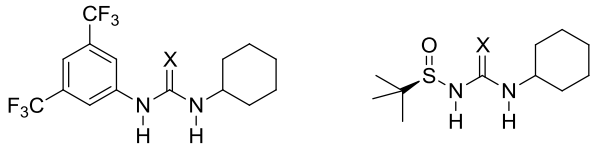
The activity of a urea-based catalyst with respect to electrophilic substrate activation can be enhanced by increasing the acidity of the urea protons and thus the strength of the hydrogen bond between the urea and the substrate. Takemoto developed a chiral 1,2-cyclohexanediamine-based asymmetric catalyst, in which Schreiner's 3,5-bis(trifluoromethyl)phenyl group[3] was utilized as an acidifying functionality to achieve a more active catalyst.[4] Jacobsen has taken an alternative approach in tuning the selectivity of urea-based hydrogen-bonding catalysts by adding an amino acid backbone to the urea to introduce additional chiral centers and appropriate steric bulk.[5] Both of these concepts have been invaluable in the discovery of new and improved urea-based catalysts, but rarely does a single moiety possess both acidifying and chiral directing properties. The insight that led to the original development of sulfinyl urea catalysis was the realization that a sulfinyl moiety did possess this unique combination of attributes (Figure 1.1).[6,7]

Figure 1.1. Acidifying and Chiral Directing Effects of the Sulfinyl Moiety



The greater acidifying power of a sulfinyl group was quantified by MaryAnn Robak at the inception of the sulfinyl urea project. Sulfinyl and Takemoto-type cyclohexyl ureas were synthesized and the pK_as of the more acidic urea proton were measured via spectroscopic methods in DMSO.[6a] In this study, the sulfinyl urea was found to be 3-4 pK_a units more acidic than its 3,5-bis(trifluoromethyl)phenyl counterpart (Figure 1.2).[6a]

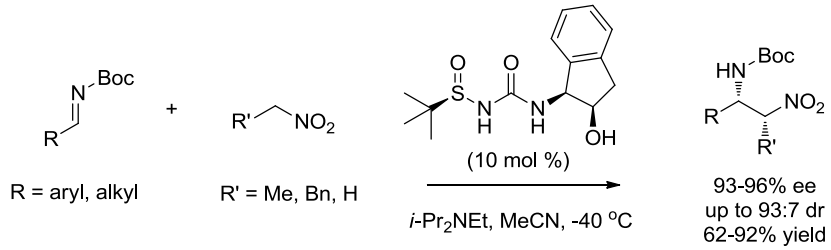
Figure 1.2. DMSO Acidities of Sulfinyl and Takemoto-type Ureas and Thioureas



Ellman and Robak then demonstrated the viability of sulfinyl ureas as a catalyst scaffold in an enantio- and diastereoselective aza-Henry reaction, achieving up to 96% ee and 93:7 dr for a range of N-Boc imines (Scheme 1.1).[6a] This reaction was a benchmark for initial work on

sulfinyl urea catalysis, proving to be competitive with known methods and representing an improvement in the case of aliphatic imines.[8]

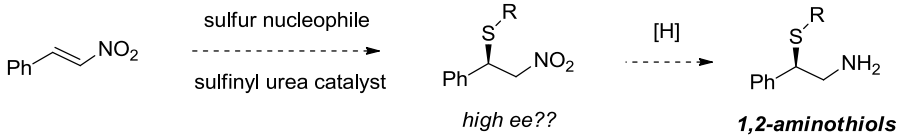
Scheme 1.1. Enantio- and Diastereoselective Aza-Henry Reaction



Addition of Thioacetic Acid to Nitroalkenes

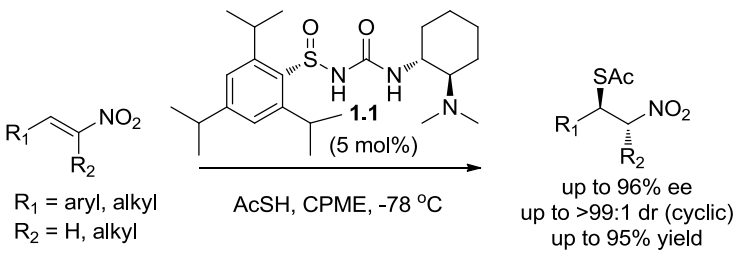
After the initial discovery of sulfinyl ureas as a viable scaffold for hydrogen-bonding organocatalysis and the demonstration of their viability with the enantio- and diastereoselective aza-Henry reaction, we were interested in applying this catalyst system to reactions for which no good organocatalytic method existed. One such transformation was enantioselective sulfa-Michael additions to nitroalkenes,[9-11] which upon reduction of the nitro group would afford biologically and pharmaceutically relevant 1,2-aminothiols (Figure 1.3). My first project was therefore to develop an efficient asymmetric method for this sulfa-Michael addition using sulfinyl urea catalysis.

Figure 1.3. Strategy for Accessing 1,2-Aminothiols



Trisylsulfinyl urea **1.1** was subsequently shown to catalyze the addition of thioacetic acid (Chapter 2) to a variety of aromatic and aliphatic β-substituted nitroalkenes as well as cyclic α,β-disubstituted nitroalkenes (Scheme 1.2).[6b] Method development was followed by application to the asymmetric synthesis of the known drug Sulconazole and catalyst structure-activity relationship studies to elucidate the role of the sulfinyl group in catalysis.[6c]

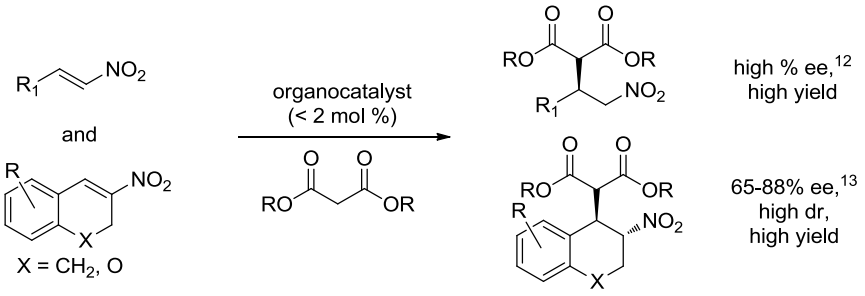
Scheme 1.2. Enantio- and Diastereoselective Addition of Thioacetic Acid to β- and Cyclic α,β-Disubstituted Nitroalkenes



Addition of Meldrum's Acid to Nitroalkenes

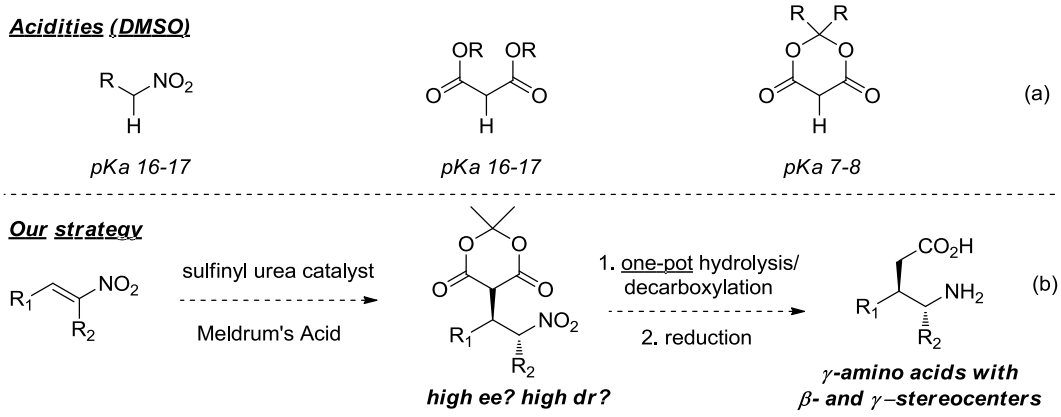
After developing a method for thioacetic acid addition that leads to 1,2-aminothiols, we were interested in expanding sulfinyl urea catalysis to include other classes of pharmaceutically useful compounds. One class of compounds that is prevalent in a variety of biologically active and pharmaceutically relevant structures is γ-amino acids. A survey of the literature at the time revealed that addition of malonate nucleophiles to β-substituted nitroalkenes was well precedented,[12] but additions to α,β-disubstituted nitroalkenes, which could lead to more complex γ-amino acids, were limited to very specific cyclic systems (Figure 1.4).[13]

Figure 1.4. Malonate Additions to β-Substituted and *Cyclic* α,β-Disubstituted Nitroalkenes.



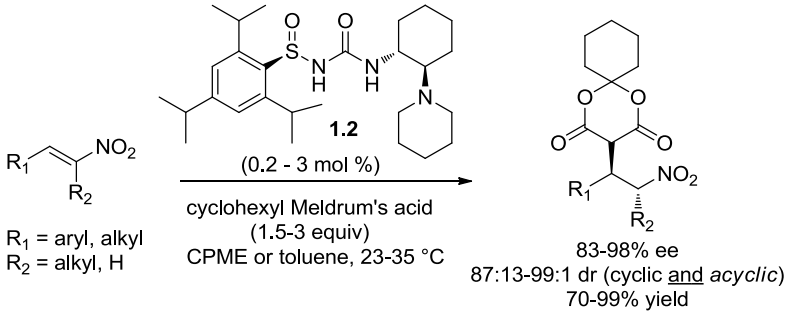
Additions to acyclic α,β-disubstituted nitroalkenes with high stereoselectivity at the α-nitro stereocenter introduce a significant challenge. Due to the comparable pK_as of the malonate nucleophile and the nitroalkane product (both ~16-17[14] in DMSO, Figure 1.5a), the α-nitro stereocenter in the addition product would necessarily epimerize under the reaction conditions. A more acidic pronucleophile, and thus less basic active nucleophile, would therefore be required in order to carry out this task. We posited that Meldrum's acid,[15] a significantly more acidic malonate derivative (pK_a 7-8[14] in DMSO, Figure 1.5a) could serve as a viable alternative for this endeavor, potentially enabling additions to nitroalkenes that set and preserve both the α- and β-stereocenters to allow access to more complex γ-amino acid derivatives (Figure 1.5b). The use of Meldrum's acid would also be advantageous synthetically because the acetal framework of the Meldrum's acid-derived products can be hydrolyzed and decarboxylated in a single step under acidic conditions.

Figure 1.5. Strategy for Accessing γ-Amino Acid Derivatives with Multiple Stereocenters



We found that using sulfinyl urea catalyst **1.2**, the addition of Meldrum's acid (Chapter 3) to β- and α,β-disubstituted nitroalkenes could be achieved in high enantio- and diastereoselectivity (Scheme 1.3).[6d] In particular, the addition to *acyclic* α,β-disubstituted nitroalkenes proceeded with diastereoselectivies of ~20:1.[16] The practicality and utility of this chemistry was further demonstrated by performing the reaction on mole scale at only 0.2 mol % catalyst loading.

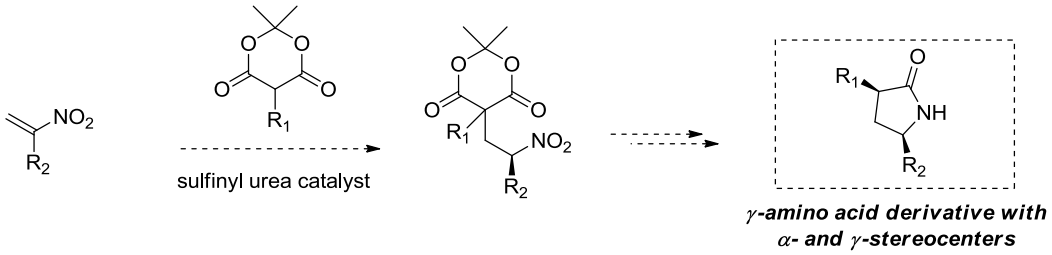
Scheme 1.3. Enantio- and Diastereoselective Addition of Cyclohexyl Meldrum's Acid to β- and α,β-Disubstituted Nitroalkenes



Conjugate Addition-Enantioselective Protonation of Terminal Nitroalkenes

The high diastereoselectivity observed in the Meldrum's acid addition to α,β-disubstituted nitroalkenes led us to consider the possibility of setting the α-nitro stereocenter in an enantioselective protonation reaction[17] for nitroalkene substrates with substitution only at the α-position (Figure 1.6). Analysis of the product structure reveals that nitro reduction without epimerization,[18] cyclization, and then a diastereoselective decarboxylative protonation[19] could provide γ-lactams with α- and γ-stereocenters. A survey of the literature revealed that competitive methodology did not exist for accessing these products.[20] The state of the art at the time consisted of a lengthy sequence starting from pyroglutamic acid[21] or diastereoselective alkylations and reductions that rely on expensive starting materials and stoichiometric amounts of toxic reagents.[20] The proposed sequence would therefore provide a more rapid, efficient and desirable route to these important structures.

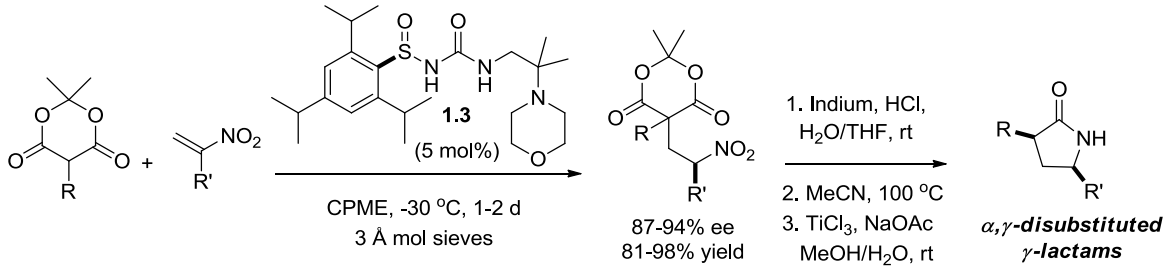
Figure 1.6. Strategy for Enantioselective Protonation Reaction



Our initial investigation began with our optimal catalyst system from the previous methodology, which relies on a cooperative interaction between the sulfinyl and 1,2-diamine stereocenters.[6b-d] Although this catalyst scaffold did not provide high levels of enantioselectivity, we were able to develop an effective new catalyst scaffold that for the first

time relies only on the sulfinyl stereocenter. With catalyst **1.3**, the enantioselective protonation reaction (Chapter 4) was achieved in 87-94% ee and 81-98% yield over a range of Meldrum's acid and nitroalkene substrates (Scheme 1.4).[6e] A simple three-step sequence was then developed for conversion of the addition products to γ-lactams with α- and γ-stereocenters in good yields and with high diastereoselectivity.

Scheme 1.4. Conjugate Addition-Enantioselective Protonation of Terminal Nitroalkenes



Conclusion

In conclusion, the breadth of sulfinyl urea catalysis has been extended from the seminal report of an enantio- and diastereoselective aza-Henry reaction to a full-fledged active class of hydrogen-bonding organocatalysts. In my first project we developed sulfinyl urea catalysis for the highly enantio- and diastereoselective thioacetic acid addition to nitroalkenes that was a considerable improvement over existing literature precedent in both selectivity and scope. Next we developed an enantio- and diastereoselective addition of Meldrum's acid that for the first time provides a general strategy toward efficiently accessing complex γ-amino acid derivatives with both α- and β-stereocenters. Finally, sulfinyl urea catalysis was used to achieve a novel enantioselective protonation of nitronates that upon reduction, cyclization, and diastereoselective decarboxylative protonation led to an important class of γ-lactams with α- and γ-stereocenters – a substitution pattern that is difficult to access by other means.

References

(1) For reviews of asymmetric organocatalysis, see: (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (b) Gaunt, M. J.; Johansson, C. C.; McNally, A.; Ngoc, T. V. *Drug Discovery Today* **2007**, *12*, 8.

(2) For reviews of H-bonding organocatalysis, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (e) Terada, M. *Synthesis* **2010**, *12*, 1929. (f) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem. Eur. J.* **2010**, *16*, 9350.

(3) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.

(4) (a) Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (b) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (c) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, *1*, 137.

(5) (a) Sigman M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

(6) For examples of *N*-sulfinyl urea catalysis, see: (a) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (b) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754. (c) Kimmel, K. L.; Robak, M. T.; Thomas, S.; Lee, M.; Ellman, J. A. *Tetrahedron* **2012**, *68*, 2704. (d) Kimmel, K. L.; Weaver, J. W.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121. (e) Kimmel, K. L.; Weaver, J. D.; Lee, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *Accepted*.

(7) For other examples of organocatalysts containing sulfinamide, see: (a) Beck, E. M.; Hyde, A. M.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 4260. (b) Tan, K. L.; Jacobsen, E. N.; *Angew. Chem., Int. Ed.* **2007**, *46*, 1315. (c) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913. (d) Wang, C.; Wu, X.; Zhou, L.; Sun, J. *Chem.- Eur. J.* **2008**, *14*, 8789. (e) Pei, D.; Zhang, Y.; Wei, S.; Wang, M.; Sun, J. *Adv. Synth. Catal.* **2008**, *350*, 619.

(8) For a review on the aza-Henry reaction, see: Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151.

(9) For a review on asymmetric Michael additions of thiols, see: Enders, D.; Luettgen, K.; Narine, A. A. *Synthesis* **2007**, *7*, 959. For organocatalytic enantioselective Michael additions of sulfur nucleophiles to α,β-unsaturated carbonyl compounds, see: (a) Dai, L.; Yang, H.; Niu, J.; Chen, F-E. *Synlett* **2012**, *23*, 314. (b) Dong, X-Q.; Fang, X.; Wang, C-J. *Org. Lett.* **2011**, *13*, 4426. (c) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418. (d) Marigo, M.; Schulte, T.; Franzen, J.; Jorgensen, K. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (e) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (f) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth Catal.* **2008**, *350*, 49. For metal-catalyzed enantioselective Michael additions of sulfur nucleophiles to α,β-unsaturated carbonyl compounds, see: (g) Abe, A. M.; Sauerland, S. J.; Koskinen, A. M. *J. Org. Chem.* **2007**, *72*, 5411. (h) Nishamura, K.; Tomioka, K. *J. Org. Chem.* **2002**, *67*, 431. (i) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589. (j) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675. (k) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (l) Dong, X-Q.; Fang, X.; Wang, C.-J. *Org. Lett.* **2011**, *13*, 4426. (m) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089. (n) Hui, Y.-H.; Jiang, J.; Wang, W.-T.; Chen, W.-L.; Cai, Y.-F.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4290.

(10) For Michael additions of sulfur nucleophiles to nitroalkenes, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Li, H.; Wang, J.; Zu, L.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 2585. (c) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823. To obtain a reasonable ee (58%), stoichiometric cinchona alkaloid catalyst was required.

(11) Several publications have appeared on asymmetric sulfa-Michael additions to nitroalkenes since the initial publication of our method. See: (d) Palacio, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849. (e) Lu, H-H.; Zhang, F-G.; Meng, X-G.; Duan, S-W.; Xiao, W-J. *Org. Lett.* **2009**, *11*, 3946.

(12) Many examples of organocatalytic enantioselective additions to nitroalkenes have been accomplished using malonate esters. For select examples, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673. (b) Ye, J.; Dixon, D. J.;

Hynes, P. S. *Chem. Commun.* **2005**, 4481-4483. (c) Li, H.; Wang, L. T.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907. (d). Xu, F.; Corley, E.; Zacuto, M.; Conlon, D. A.; Pipik, B.; Humphrey, G.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2010**, *75*, 1343-1353.(e) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367-6370. (f) Zhang, L.; Lee, M-M.; Lee, S-M.; Lee, J.; Cheng, M.; Jeong, B-S.; Park, H-G.; Jew, S-S. *Adv. Synth. Catal.* **2009**, *351*, 3063-3066. For select examples of highly enantioselective metal-catalyzed additions of malonate esters to nitroalkenes, see: (g) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097-13105. (i) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958-9959.

(13) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673. (b) Chen, W-Y.; Li, P.; Xie, J-W.; Li, X-S. *Catal. Commun.* **2011**, *12*, 502-504.

(14) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.

(15) Meldrum's acid additions had only been reported for simple β-substituted nitroalkenes and procceded with low to modest enantioselectivity. See: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673. (b) Bassas, O.; Huuskenon, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340-1351. (c) Kleczkowska, E.; Sas, W. *Polish Journal of Chemistry* **2007**, *81*, 1457-1464.

(16) Typically, one would expect poor diastereocontrol in conjugate additions that produce acyclic diastereomers, reflecting the almost equal thermodynamic energies of the two diastereomers. For an example of addition to acyclic α,β-disubstituted nitroalkenes in which low dr was observed, see: Ganesh, M.; Namboothiri, I. N. N. *Tetrahedron* **2007**, *63*, 11973-11983.

(17) For a review on enantioselective protonation, see: Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nature Chemistry* **2009**, *1*, 359.

(18) Epimerization of the α-nitro stereocenter occurs under many common reduction conditions, including $Pd/C/H_2$ and Ni/H_2. It was therefore necessary to investigate reduction conditions that would allow for preservation of the α-nitro stereocenter. In Chapter 4, it will be discussed that metallic indium under acidic conditions was optimal for the enantioselective protonation chemistry.

(19) (a) Diastereoselective decarboxylative protonation of 3-substituted pyrrolidinones had only been reported with ~3:1 dr for an N-H pyrrolidinone and with 55:45 dr for an *N*-pivaloyl pyrrolidinone. See: Hook, D.; Thomas, R.; Bernhard, R.; Wietfeld, B.; Sedelmeier, G.; Napp, M.; Baenziger, M.; Hawker, S.; Ciszewski, L.; Waykole, L. M. New Process. WO2008083967 (A2). (b) In analogy with Meyers' alkylations of simple *N*-methyl-5-methyl pyrrolidinone enolates, it was expected that the decarboxylative protonation should also take place from the face opposite the 5-substituent, and that the magnitude of diastereoselectivity would be greater for N-H than *N*-carbamoyl pyrrolidinones. For an excellent explanation of this phenomenom, see: Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565.

(20) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3.

(21) Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749.

Chapter 2: Enantio- and Diastereoselective Addition of Thioacetic Acid to Nitroalkenes via *N*-Sulfinyl Urea Catalysis

The enantioselective addition of thioacetic acid to nitroalkenes was achieved using N-sulfinyl urea catalysis. Initially, it was discovered that thioacetic acid could be added with high enantioselectivity (up to 96% ee) to aromatic β-substituted nitroalkenes, and with moderate enantioselectivity (up to 84% ee) to aliphatic β-substituted nitroalkenes. Subsequently, the scope of the reaction was extended to the enantio- and diastereoselective thioacetic acid addition to cyclic α,β-disubstituted nitroalkenes (up to >99:1 dr, up to 94% ee). The developed method was applied to the first asymmetric synthesis of the antifungal drug Sulconazole in 96% ee and 32% overall yield over five steps. Finally, the role of the sulfinyl group was investigated by replacing it with a variety of aryl and sulfonyl groups (15 catalysts), and it was found that the sulfinyl group was of crucial importance for attaining high selectivity in the thioacetic acid addition. This work has been published in a communication and a subsequent article (Kimmel, K. L.; Robak, M. T.; Ellman, J. A. J. Am. Chem. Soc. ***2009****, 131, 8754, and Kimmel, K. L; Robak, M. T.; Lee, M.; Ellman, J. A. Tetrahedron,* ***2012****, 68, 2704).*

Authorship

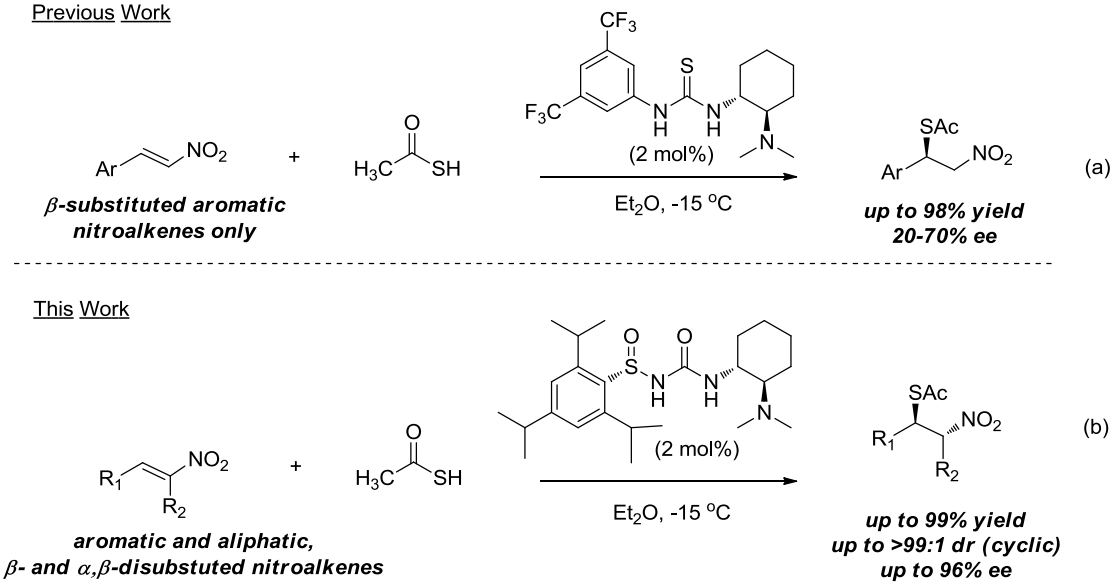
The work on enantio- and diastereoselective addition of thioacetic acid to nitroalkenes was conducted in collaboration with MaryAnn Robak, Stephen Thomas, and Melissa Lee.

Introduction

Asymmetric hydrogen-bonding organocatalysis is a rapidly expanding field of organic chemistry, spanning a variety of structural frameworks or hydrogen bonding motifs for the catalysts, including chiral ureas and thioureas, cinchona alkaloids, squaramides, guanidines, diols and phosphoric acids.[1] *N*-Sulfinyl ureas have recently emerged as a successful new class of hydrogen-bonding organocatalysts[2] in which the sulfinyl group can serve as an easily tunable, chiral acidifying group.[3] The sulfinyl moiety offers the advantage over other acidifying groups of achieving sufficient steric demand and good catalyst solubility in nonpolar solvents while simultaneously introducing chirality. The utility of *N*-sulfinyl urea catalysts has previously been demonstrated for the aza-Henry reaction with enantioselectivities of 93-96% for a variety of aryl and alkyl *N*-Boc imine substrates.[2]

To expand the scope of *N*-sulfinyl urea catalysis, we chose to explore thioacetic acid additions to nitroalkenes, where the only previous report gave only modest enantioselectivities ranging from 20-70% using Takemoto's thiourea organocatalyst **2.3**, and for which only aromatic β-substituted nitroalkene additions were demonstrated (Figure 2.1a).[4,5,6] Herein we report that appropriately substituted *N*-sulfinyl ureas catalyze the enantio- and diastereoselective addition of thioacetic acid to a variety of nitroalkenes with selectivities up to 96% ee and up to >99:1 dr (Figure 2.1b).

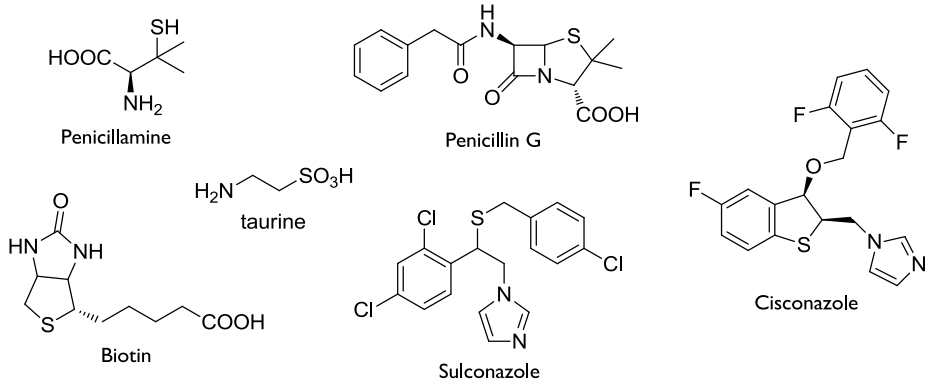
Figure 2.1. Literature Precedent for Enantioselective Thioacetic Acid Addition



Notably, nitroalkene thioacid addition products are versatile intermediates for the preparation of 1,2-aminothiol derivatives, which are prevalent in biologically active compounds such as penacillamine, penicillin, biotin, the clinically used azole anti-fungal drug Sulconazole, [7] and the

biologically significant aminosulfonic acid taurine (Figure 2.2).[8] The utility of the developed sulfinyl urea-catalyzed enantioselective thioacetic acid addition was hereby demonstrated with the first asymmetric synthesis of Sulconazole, affording the drug in 96% ee and 32% overall yield in only five synthetic steps.

Figure 2.2. Biologically and Pharmaceutically Relevant 1,2-Aminothiol Derivatives

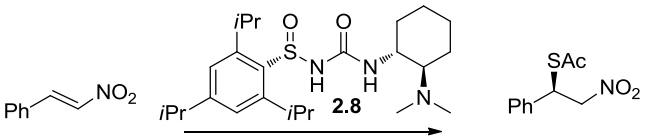


Results and Discussion

I. Reaction Development

In an initial catalyst screen, the *N*-trisylsulfinyl urea **2.8** was identified as the most selective catalyst, promoting the addition of thioacetic acid to *trans*-β-nitrostyrene (**2.1a**) with 87% ee in cyclopentyl methyl ether (CPME), which has seen increasing use as a solvent for large scale industrial applications,[9] at -78 ^{o}C (Table 2.1, entry 1). At this temperature no background reaction is observed; however, side reactivity was observed, decreasing the yield of desired product **2.2a**. To increase the yield of **2.2a**, the catalyst loading, substrate concentration and equivalents of thioacetic acid were optimized (Table 1). It was found that by lowering the concentrations of reagents (entry 2), avoiding a large excess of thioacetic acid (entries 3 and 4), and increasing the catalyst loading (entries 5 and 6), the yield of desired addition product could be increased and side reactivity minimized (entry 7). Though using 2 mol % of catalyst loading under dilute conditions (entry 2) gave a higher overall NMR yield than 5 mol % of catalyst loading (entry 7), the former gave greater quantities of undesired impurities which are more difficult to separate from the product than residual starting material, thus making 5 mol % catalyst loading at 0.1 M the preferred conditions for attaining an optimal isolated yield.

Table 2.1. Optimization of Thioacetic Acid Addition



entry	mol % of catalyst	conc. (M)	equiv of thioacid	NMR yield[a]	ee[b] (%)
1	2.0	0.4	2.0	71	87
2	2.0	0.1	2.0	86	90
3	2.0	0.4	1.0	42	88
4	2.0	0.4	5.0	32	82
5	5.0	0.4	2.0	85	87
6	0.5	0.4	2.0	42	80
7	5.0	0.1	2.0	82	90

[a]NMR yield of product was determined by ^{1}H NMR analysis of the ratio of product to starting material and side products derived from the starting material. [b]Enantiomeric excess was determined by chiral HPLC analysis.

Under these optimized reaction conditions, a variety of sulfinyl catalysts, as well as Takemoto's urea and thiourea catalysts, were evaluated for selectivity and catalytic activity (Table 2.2, Figure 2.3). Takemoto's thiourea catalyst **2.3**, though highly active, gave low selectivity (entry 1), whereas the less acidic Takemoto urea catalyst **2.4** was less active and gave improved but still modest enantioselectivity (entry 2). *tert*-Butanesulfinyl ureas **2.5** and **2.6** also were only moderately selective (entries 3 and 4), but switching to the more sterically demanding trisyl sulfinyl ureas, **2.7** and its diastereomer **2.8**, brought the enantioselectivity up to 80 and 90% ee, respectively (entries 5 and 6). Additionally, the more acidic and achiral trisyl *sulfonyl* group present in urea **2.9** gave diminished enantioselectivity as compared to the sulfinyl catalysts (entry 7). Overall, from this catalyst screen, sulfinyl urea **2.8**, with a *syn* relationship between the sulfinyl and 1,2-diamine stereocenters, provided the highest selectiviy (90% ee) and with good conversion within 2 days at -78 °C.

Figure 2.3. Catalysts Tested in Enantioselective Thioacetic Acid Addition

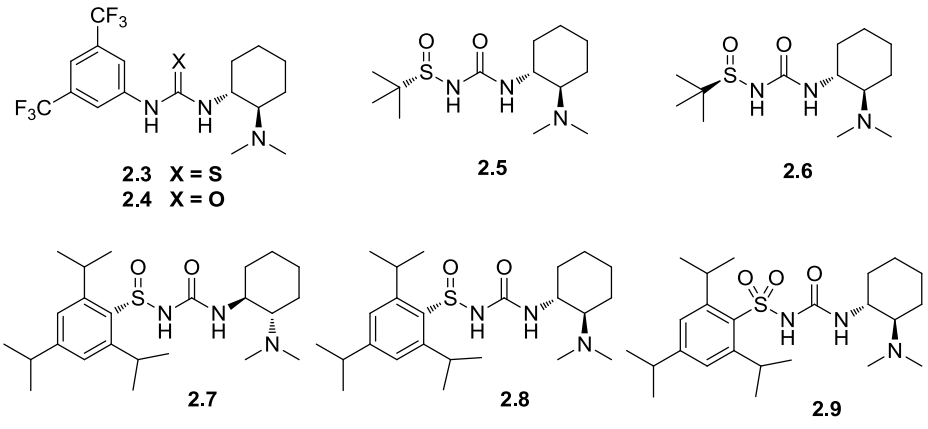
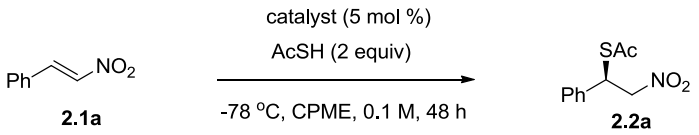


Table 2.2. Catalyst Screen Under Optimized Conditions



entry	catalyst	conv[a] (%)	ee[b] (%)
1	**2.3**	99	32[c]
2	**2.4**	65	68
3	**2.5**	99	46
4	**2.6**	99	50
5	**2.7**	89	80[c]
6	**2.8**	86	90
7	**2.9**	99	53

[a]Conversion was determined by ^{1}H NMR analysis based upon the ratio of product to starting material. [b]Enantiomeric excess was determined by chiral HPLC analysis. [c]Opposite enantiomer obtained as the major product.

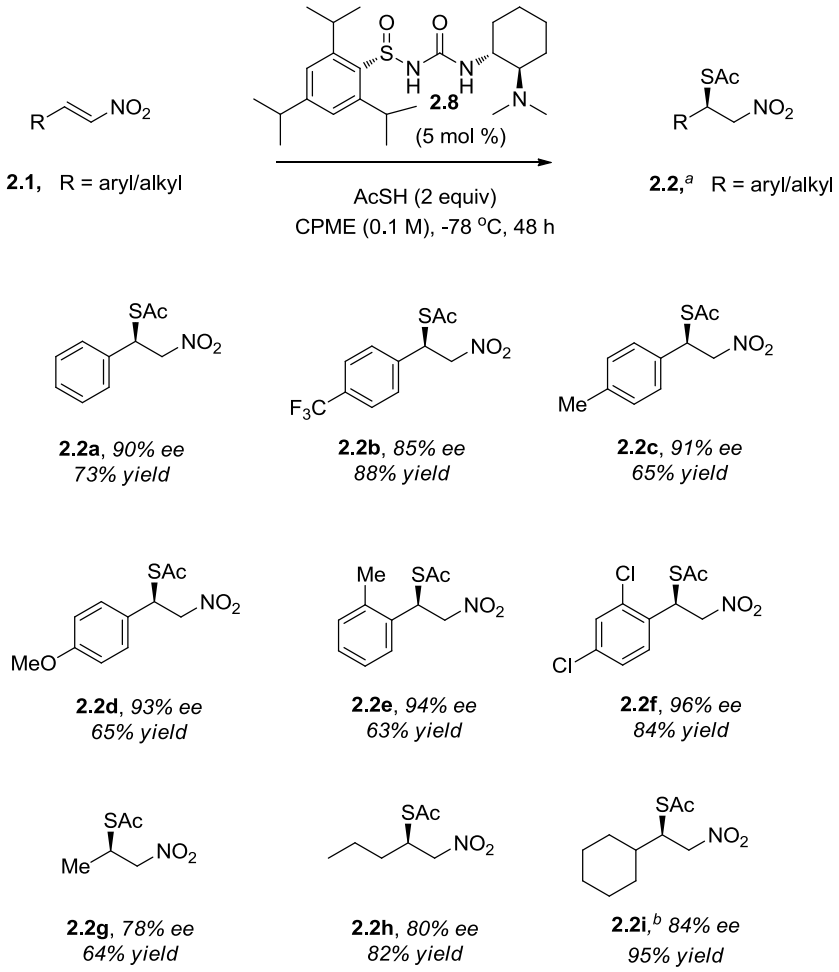
Identifying conditions for the isolation of these compounds proved challenging. After aqueous extraction and purification by silica gel chromatography using hexanes/ethyl acetate as the eluent, pure addition product **2.2a** was analyzed for enantiomeric excess. Much to our surprise, the observed enantiomeric purity after chromatography was <20% ee. This raised the question of whether the enantiomeric purity determined on unpurified material was accurate or whether racemization had in fact occurred during purification. We imagined that instability of the thioacid adducts could be causing the product to racemize during chromatographic purification. To probe the stability of the product toward various conditions, we devised an experiment wherein the crude product **2.2a** was partitioned and subjected to a 1% solution of mild base, mild acid, or strong acid and then analyzed. Acetic acid exposure preserved the enantiomeric purity (90% ee), hydrochloric acid caused crystallization and enhanced enantiomeric purity (98% ee), and triethylamine caused complete racemization (0% ee) and partial decomposition to the starting nitroalkene. These results suggest that racemization had occurred during chromatography through a process of base-promoted E_2 elimination of thioacetate, followed by nonselective re-addition. Due to the observed acid-stability of the products, chromatographic purification through use of acetic-acid buffered silica gel enabled straightforward isolation of pure product without racemization.

II. Synthetic Scope

The scope of the reaction was then explored for both aromatic and aliphatic nitroalkenes (Scheme 2.1). The product of addition to *trans*-β-nitrostyrene was isolated in 90% ee and 73% yield. Electronic variation via para substitution shows that more electron-deficient nitroalkenes (products **2.2b** and **2.2f**) provide a higher yield, while electron-rich derivatives provide higher enantioselectivities (products **2.2c-e**). Ortho substitution also results in an increase in enantioselectivity (product **2.2e**). Significantly, 2,4-dichloro-*trans*-β-nitrostyrene, which can be converted to sulconazole (*vide infra*), provides both high yield and enantioselectivity (product **2.2f**). Aliphatic nitroalkenes also undergo the addition reaction in good yield for both linear

(products **2.2g** and **2.2h**) and branched (product **2.2i**) substrates although with somewhat reduced enantioselectivity relative to the aryl substrates. In contrast to the other substrates, the cyclohexyl product **2.2i** was obtained with higher selectivity (84% ee) with catalyst **2.7** than catalyst **2.8** (70% ee), suggesting that the role of the *N*-sulfinyl configuration is complex and requires further investigation (*vide infra*).

Scheme 2.1. Catalytic Enantioselective Addition of Thioacetic Acid to Aromatic and Aliphatic β-Substituted Nitroalkenes

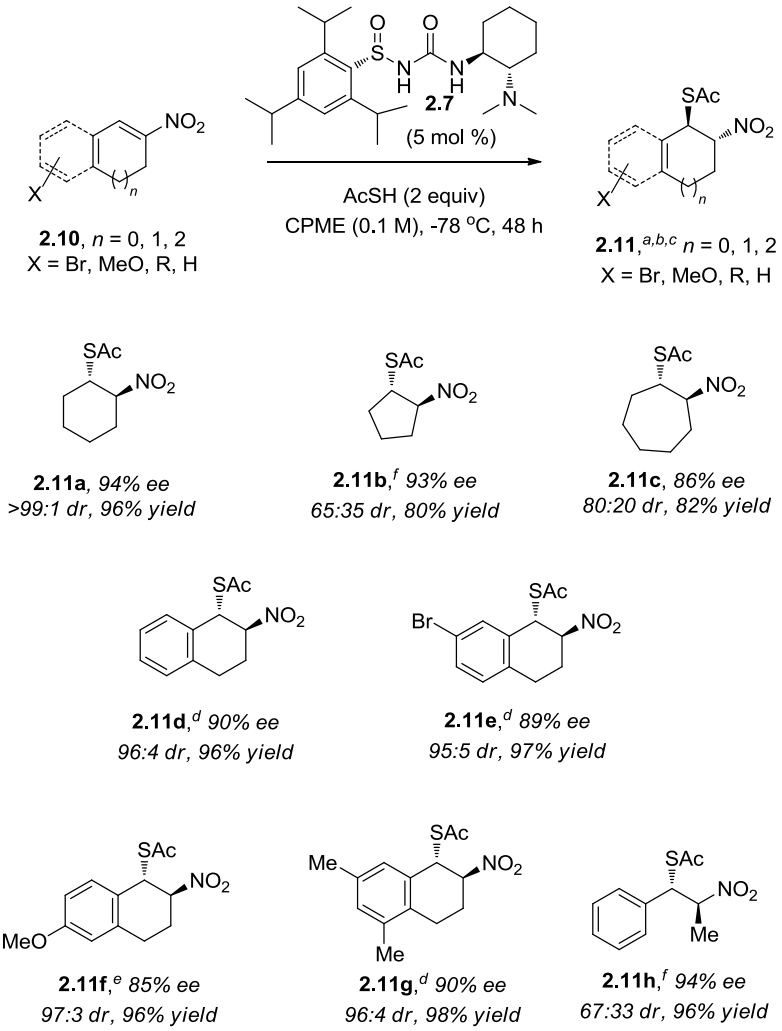


[a]Isolated yield of analytically pure material after chromatography. [b]Catalyst **2.7** was used.

In addition to the *trans*-β-substituted nitroalkenes discussed above, the enantioselective thioacetic acid addition can also be applied to the more complex α,β-disubstituted nitroalkenes (Scheme 2.2), in which two stereocenters are set in the addition reaction. Though the addition of thioacetic acid to nitrocyclohexene only proceeded in ~70% ee using sulfinyl catalyst **2.8**, diastereomeric sulfinyl catalyst **2.7** promoted the reaction in an impressive 94% ee (product **2.11a**). Additionally, the reaction was completely diastereoselective, affording exclusively the *trans*-product in 96% yield. Though variation of the substrate ring size tended to reduce the diastereoselectivity, both nitrocyclopentene (product **2.11b**) and nitrocycloheptene (product **2.11c**) underwent thioacetic acid addition with high enantioselectivities (93 and 86% ee,

respectively) and good yields (80-82%). The thioacetic acid addition proceeds with high enantio- and diastereoselectivity for a variety of six-membered substrate analogs, including electron-deficient, electron-rich and sterically demanding 2-nitro-3,4-dihydronaphthalene substrates (85-90% ee, 95:5-97:3 dr, products **2.11d-g**). Additionally, the chemical yields are excellent for the entire range of substrates (96-98%). The acyclic substrate *trans*-β-methyl-β-nitrostyrene gave quite high enantioselectivity (94% ee, product **2.11h**), albeit with only modest (~2:1) diastereoselectivity.

Scheme 2.2. Catalytic Enantio- and Diastereoselective Addition of Thioacetic Acid to α,β-Disubstituted Nitroalkenes



[a]Isolated yield of an analytically pure diastereomeric mixture after chromatography. [b]Diastereomeric ratios were determined by ^{1}H NMR and HPLC analysis. [c]Enantiomeric excess was determined by chiral HPLC analysis. [d]Reaction carried out at 0.4 M [**2.10**]. [e]Reaction performed using 5 equiv of thioacetic acid. [f]Reaction performed at 0.04 M [**2.10**] using 3 equiv of thioacetic acid.

III. Catalyst Structure-Activity Relationships

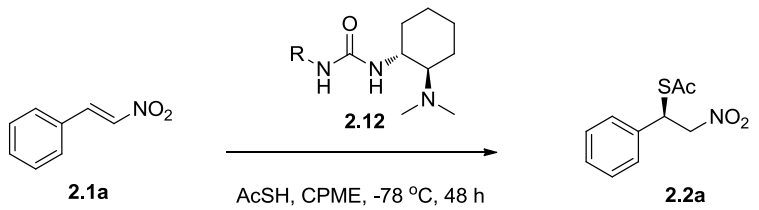
Though trisylsulfinyl urea catalysts **2.7** and **2.8** promote highly enantioselective additions for a broad variety of nitroalkene substrates, the role of sulfinyl stereochemistry is perplexing particularly because the preferred diastereomer of the catalyst seems to change somewhat arbitrarily across substrates (see Scheme 2.1, products **2.2a-h;** Scheme 2.1, product **2.2i;** and Scheme 2.2, products **2.11**). Moreover, for the less selective *tert*-butanesulfinyl urea catalysts **2.5** and **2.6**, the sulfinyl stereochemistry of the catalyst had a negligible effect (Table 2.2, entries 5 and 6). These results prompted us to pose the question: Does the catalyst require sulfinyl chirality at all or can the sulfinyl group be replaced with a simpler, more inexpensive *achiral* urea substituent with optimal steric and electronic properties?

To probe this question, a plethora of catalysts **2.12** that contain *achiral* replacements for the sulfinyl group, derived from readily available anilines or sulfonamides, were synthesized and tested in the enantioselective addition of thioacetic acid to *trans*-β-nitrostyrene (Table 2.3). These catalysts can be easily assembled using the standard carbonyldiimidazole-mediated coupling of the conserved 1,2-cyclohexanediamine component with a sulfinamide, sulfonamide or aniline input. Both aniline and sulfonamide-based catalysts were surveyed with a range of steric and electronic properties. It quickly became apparent that although catalytic efficiency was high for all catalysts surveyed, attaining high enantioselectivity was a more significant challenge. The benchmark for aniline-based catalysts, Takemoto's 3,4-bis(trifluoromethyl)phenyl urea **2.4** (Table 2.3, entry 1), afforded the product in 68% ee. The analogous 3,4-dinitrophenyl urea **2.12a** performed similarly, providing the adduct in 71% ee (entry 2). A variety of 2,4,6-trisubstituted aryl ureas **2.12b-e** were synthesized and surveyed and displayed overall mediocre selectivities (entries 3-6). Additionally, other highly activated scaffolds, such as the 2,6-dinitrophenyl urea **2.12f** (entry 7) and the pentafluorophenyl urea **2.12g** (entry 8), were also tested but displayed only moderate enantioselectivities. It should be noted that these catalysts span a broad range of urea acidities, from substantially less acidic than Takemoto's urea **2.4** to more acidic catalyst **2.12f**, but none outperformed Takemoto's catalyst. In addition, these catalysts span a range of steric properties, even up to the incredibly hindered 2,4,6-tri-*tert*-butylphenyl urea **2.12b**, but even this catalyst only provided 26% enantioselectivity (entry 3).

Much like with the aniline-based catalysts, sulfonamide-based catalysts spanning a range of acidities, steric profiles, and substitution patterns were tested (Table 2.3). A range of substituted aryl sulfonamides with increasing acidity were surveyed from the 4-dimethylaminophenyl and 2,4-dimethoxyphenyl sulfonyl ureas **2.12h** and **2.12i** with highly attenuated acidity (entries 9-10), to the 4-methoxyphenyl sulfonyl urea **2.12j** (entry 11) of comparable acidity to a sulfinyl urea to the more acidic sulfonyl ureas **2.9** and **2.12h-o** (entry 12). Within this sequence of electronic variation, no linear trend was observed, but rather more of a parabolic pattern was noted, wherein the peak of selectivity corresponded to an intermediate acidity, that of the *p*-methoxyphenyl sulfonyl urea **2.12j** (68% ee, entry 11). Additionally, both 2,4,6-trisubstituted and 3,5-disubstituted aryl sulfonyl ureas of varying steric bulk were evaluated (entries 12-16). Among both the 2,4,6-trisubstituted and 3,5-disubstituted series, increasing the steric bulk of the sulfonamide increased the enantioselectivity but only up to a maximum of 66% ee, with the original trisyl sulfonyl urea **2.9** as the best candidate (entry 14). Similarly, the *tert*-butylsulfonyl urea **2.12o**, with slightly attenuated acidity as compared to the aryl sulfonyl ureas but with similar steric bulk, did not surpass the benchmark 68% ee of Takemoto's catalyst (entry 17).

Despite several of these catalysts exhibiting similar steric bulk and acidity to trisyl *sulfinyl* urea **2.8**, none achieved selectivity even remotely close to the enantioselectivity of catalyst **2.8** (90% ee).

Table 2.3. Catalyst Structure-Activity Relationship Study

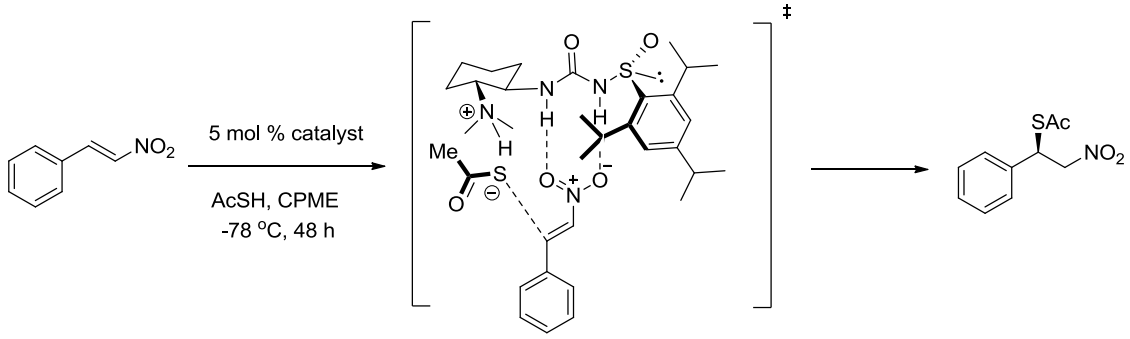


entry	catalyst	R	conv[a,b] (%)	ee[c] (%)
1	**2.4**	3,5-$(CF_3)_2$Ph	65	68
2	**2.12a**	3,5-$(NO_2)_2$Ph	54	71
3	**2.12b**	2,4,6-*t*Bu_3Ph	88	26
4	**2.12c**	4-NO_2-2,6-Cl_2Ph	34	53
5	**2.12d**	4-NO_2-2,6-Br_2Ph	92	52
6	**2.12e**	4-CF_3-2,6-Br_2Ph	97	46
7	**2.12f**	2,6-$(NO_2)_2$Ph	71	12
8	**2.12g**	C_6F_5	49	54
9	**2.12h**	SO_2(4-NMe_2Ph)	93	59
10	**2.12i**	SO_2(2,4-MeO_2Ph)	82	44
11	**2.12j**	SO_2(4-MeOPh)	88	68
12	**2.12k**	Ts	73	48
13	**2.12l**	SO_2Mes	98	62
14	**2.9**	SO_2Trisyl	97	66
15	**2.12m**	SO_2(3,5-Me_2Ph)	86	44
16	**2.12n**	SO_2(3,5-*t*Bu_2Ph)	99	60
17	**2.12o**	SO_2*t*Bu	94	66

[a]Reactions were performed with 5.0 mol % of catalyst loading at 0.1 M concentration of substrate with 2.0 equiv of thioacetic acid. [b]Conversion was determined by ^{1}H NMR analysis. [c]Enantiomeric excess was determined by chiral HPLC analysis.

Our studies to date therefore indicate that multiple factors contribute to asymmetric induction in sulfinyl urea catalysis, including the acidity, steric size, electronics, solubility and stereochemistry of the catalyst. Based on mechanistic work by Takemoto and Jacobsen with similar organocatalytic systems, the reaction presumably proceeds with bifunctional organocatalysis, where the urea hydrogens activate the nitroalkene via hydrogen bonding, while the pendant amine deprotonates thioacetic acid (Figure 2.4).[5, 6, 10, 11]

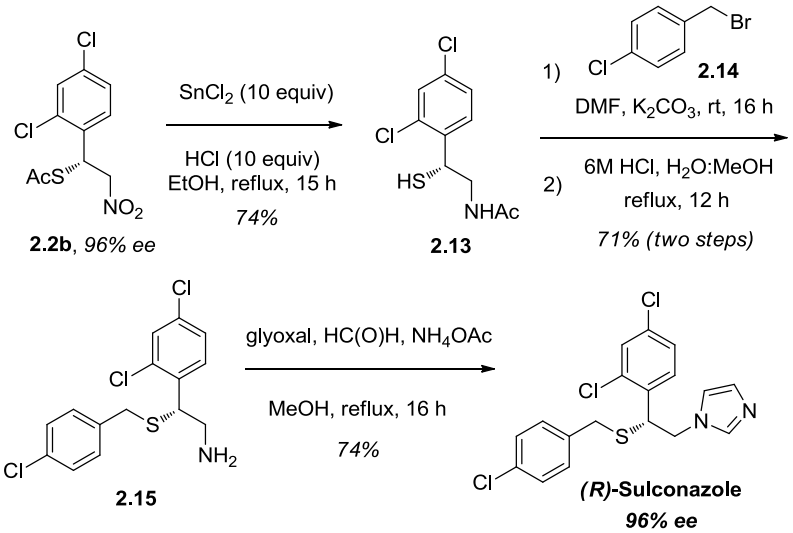
Figure 2.4. Mechanistic Rationale for Sulfinyl Urea-Catalyzed Thioacetic Acid Addition



IV. Application to the Asymmetric Synthesis of Sulconazole

The utility of this process for pharmaceutical applications was also demonstrated. Examination of the structures of a number of commercial drugs revealed that the backbone of the anti-fungal drug Sulconazole[7] bears a striking resemblance to our thioacetic acid addition product. Conceptually, Sulconazole is a derivative of our product in which the thioacid is converted into a benzyl thioester and the nitro group is converted into an imidazole moiety. Practically, these manipulations turned out to be quite feasible, enabling us to achieve the first asymmetric synthesis of Sulconazole from addition product **2.2b** in only four steps (Scheme 2.3). Reduction of the 1,2-nitrothiolate was unprecedented in the literature and is complicated by thiol poisoning of typical transition metal-catalysts employed in nitro reduction. However, by using excess tin(II) chloride and anhydrous hydrochloric acid, reduction of **2.2b** was achieved with concomitant acyl transfer to the amine, providing thiol amide **2.13** in 74% yield. Additionally, the nitro reduction was accomplished with complete preservation of enantiomeric purity, a concern that had been raised during initial isolation issues (*vide supra*) but was expected to be mitigated by the acid-stability of the product. Acetyl protection of the amine, which occurred spontaneously upon reduction, was a convenient strategy to ensure complete chemoselectivity in the alkylation of the newly unmasked thiol. Alkylation with benzyl bromide **2.14** followed by quantitative amide hydrolysis gave free amine **2.15** in 71% overall yield. Final condensation of

Scheme 2.3. Enantioselective Synthesis of (*R*)-Sulconazole



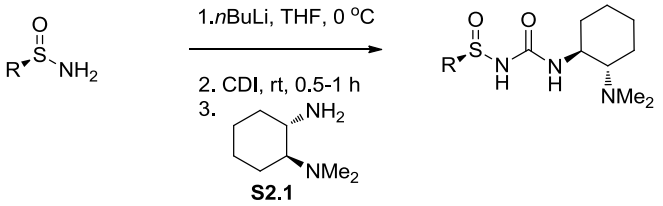
amine **2.15** with glyoxal and formaldehyde[12] afforded *R*-Sulconazole in 74% yield. The drug was synthesized in 32% overall yield for the five steps and with 96% ee from β-nitrostyrene **2.1b**.

Conclusion

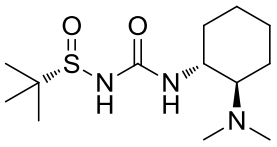
In conclusion, we have demonstrated that a sulfinyl urea organocatalyst promotes the first highly enantio- and diastereoselective addition of thioacetic acid to aromatic and aliphatic β-substituted nitroalkenes as well as a range of cyclic nitroalkenes to introduce two stereocenters. This reaction can serve as a general method for preparing chiral 1,2-aminothiols in compounds of pharmaceutical interest, as demonstrated by the expedient synthesis of *R*-Sulconazole in 96% ee and good overall yield. Furthermore, through an expansive structure-activity-relationship study of urea catalysts, we have shown that a sulfinyl group is a key component in the catalyst that enables high enantioselectivities. Current work is devoted to the further development of hydrogen-bonding catalysts that rely on *N*-sulfinyl urea motif to attain the optimal electronic, steric and stereochemical profile for efficient and selective catalysis.

Experimental Section

I. General Experimental. Unless otherwise noted, all reactions were carried out in flame dried glassware under inert atmosphere. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Tetrahydrofuran (THF), ether, methylene chloride (CH_2Cl_2) and dioxane were passed though columns of activated alumina under nitrogen pressure immediately prior to use. Ethanol was distilled over magnesium ethoxide under an atmosphere of nitrogen prior to use. Cyclopentyl methyl ether (CPME) was distilled over finely cut elemental sodium, re-distilled under inert atmosphere over benzophenone ketyl into an oven-dried Schlenk tube, then freeze-pump-thawed and stored in the glove box. All urea catalysts were dried under high vacuum over fresh P_2O_5 overnight prior to use. Thioacetic acid was distilled under inert atmosphere. Dry potassium hydride was stored and weighed under inert atmosphere in the glove box. Takemoto catalysts **2.3** and **2.4**,[11] diamine ***S*-2.1**,[13] triisopropylbenzene sulfonamide,[14] and triisopropylbenzene sulfinamide[2b,15,16] were prepared according to literature procedure. Reactions were monitored by thin layer chomatography (TLC) and visualized with ultraviolet light and ninhydrin or potassium permanganate stains. Unless otherwise noted, ^1H and $^{13}C\{^1H\}$ NMR chemical shifts are reported in ppm relative to either the residual solvent peak (^1H, ^{13}C) or TMS (^1H) as an internal standard. Enantiomeric excess was determined using an Agilent 1100 or 1200 series HPLC equipped with Chiralcel IA, IB, AS-H and AD-H columns and a multiwavelength detector. IR spectra were recorded on an FTIR spectrometer equipped with an attenuated total reflectance accessory as thin films on a KBr beamsplitter, and only partial data are listed. Mass spectra (HRMS) analysis was performed by the Yale Protein Expression Database facility on a 9.4T Bruker Qe FT-ICR MS.

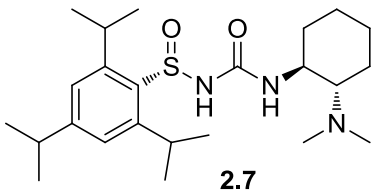


II. General Procedure for the Preparation of Sulfinyl Ureas from Sulfinamides (Procedure A). A solution of sulfinamide (1.0 equiv) in THF (0.1 M) was cooled in an ice-water bath. Butyllithium in hexanes (1.0 equiv) was added dropwise and the solution was stirred for 10 min. 1,1'-Carbonyldiimidazole (1.0 equiv) was dissolved in THF (0.20 M) in a separate flask and cooled in an ice-water bath. The sulfinamide solution was then added dropwise to the 1,1'-carbonyldiimidazole solution, and the mixture was stirred for 20 min. The ice-water bath was removed, and the reaction mixture was allowed to warm to ambient temperature and was stirred for an additional 2 h. A solution of diamine **S2.1** (1.0 equiv) in THF (1.0 M) was added dropwise, and the suspension was stirred at room temperature for 3-6 h. The reaction was quenched with a solution of acetic acid (1 equiv) in THF (1.0 M). The crude product was concentrated *in vacuo* and purified by column chromatography.



2.5

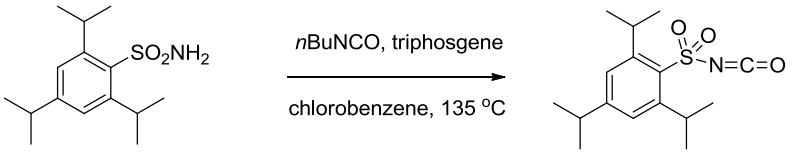
Urea 2.5. The general procedure (A) was followed using (*S*)-*tert*-butanesulfinamide (0.050 g, 0.41 mmol), butyllithium (0.26 mL, 0.41 mmol), 1,1'-carbonyldiimidazole (0.067 g, 0.41 mmol) and (*S*,*S*)-diamine **S2.1** (0.073 g, 0.46 mmol). Following silica gel chromatography (100% CH_2Cl_2, then 90:9:1 CH_2Cl_2:MeOH:NH_4OH, then 85:14:1 CH_2Cl_2:MeOH:NH_4OH) and reverse phase chromatography (5:95 CH_3CN:H_2O to 100% CH_3CN), urea **2.5** was isolated as a white powder (0.040 g, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (br s, 1H), 3.36-3.32 (m, 1H), 2.49-2.47 (m, 1H), 2.31-2.29 (m, 1H), 2.25 (s, 6H), 1.85-1.80 (m, 2H), 1.68-1.66 (m, 1H), 1.28 (s, 9H), 1.28-1.06 (m, 4H). ^{1}H NMR shifts correspond to the literature data.[6]



2.7

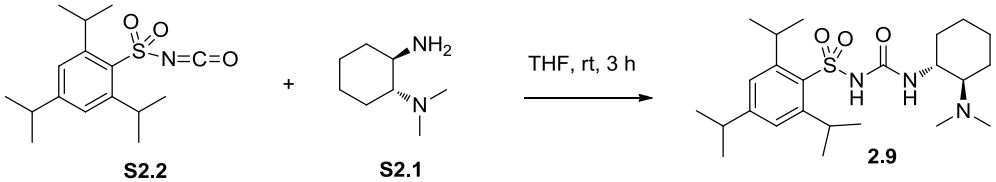
Urea 2.7. The general procedure (A) was followed using (*S*)-triisopropylbenzenesulfinamide (400 mg, 1.50 mmol), butyllithium (0.940 mL, 1.50 mmol), 1,1'-carbonyl-diimidazole (243 mg, 1.50 mmol), and (*S*,*S*)-diamine **S2.1** (235 mg, 1.65 mmol). Sulfinyl urea **2.7** was purified by silica gel chromatography (100% EtOAc, then flushed with 85:14:1 CH_2Cl_2:MeOH:NH_4OH), followed by reverse phase chomatography using a C18 column (95:5 H_2O:MeOH to 100% MeOH). Product **2.7** was isolated as a grainy sand-colored solid (345 mg, 53% yield), mp 157-158 °C. IR: 3308, 2962, 2932, 2862, 1639, 1598, 1552, 1462, 1403, 1102, 1017, 848 cm^{-1}. ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.13 (s, 2H), 6.22 (br s, 1H), 3.96 (br s, 2H), 3.42-3.37 (m, 1H), 2.95-2.88 (septet, *J* = 6.8 Hz, 1H), 2.53-2.50 (m, 1H), 2.35-2.31 (m, 1H), 2.22 (s, 6H), 1.88-1.83 (m, 2H), 1.72-1.70 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 6H), 1.28 (d, *J* = 6.8 Hz, 6H), 1.27 (d, *J* = 6.8 Hz, 6H), 1.28-1.12 (m, 4H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 154.7, 152.9, 148.1, 136.4, 123.2, 66.7, 52.5, 40.1, 34.4, 32.8, 28.7, 25.3, 24.6, 24.5, 24.1, 23.8, 21.5. HMS (ESI) calcd for $C_{24}H_{42}O_2N_3S$ $[MH]^+$ 436.2992; found 436.2995.



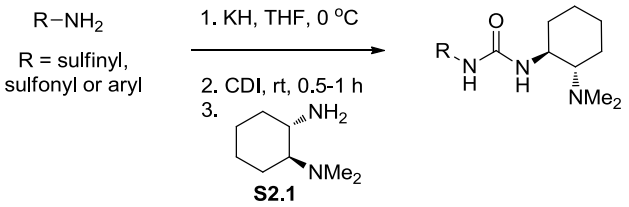
S2.2

IV. Procedure for Preparation of Sulfonyl Isocyanate S2.2.[17] A round bottom flask containing the aryl sulfonamide[3] (2.8 g, 9.9 mmol) was equipped with a stir bar and a short path vigreux column distillation head. Chlorobenzene (15 mL) was added to the flask, then 2 mL of the solvent was distilled off to azeotropically remove any trace water. The heating bath was then cooled to 135 °C. Next, *n*-butyl isocyanate (0.23 mL, 2.0 mmol) was added and the resulting mixture was stirred for 5 min at 135 °C. Triphosgene (1.8 g, 6.0 mmol) was dissolved in 4 mL of chlorobenzene, and the resulting solution was added dropwise to the reaction mixture. The reaction mixture was stirred at 135 °C for 18 h. Additional *n*-butyl isocyanate (0.23 mL, 2.0 mmol) was added, and stirring was continued for 3 h at 130 °C. Next, 2 mL of solvent was distilled off, then additional nBu isocyanate (0.60 mL, 5.3 mmol) and triphosgene (1.8 g, 6.0 mmol) were added, and heating and stirring were continued for 1 h. The solvent was then removed by distillation, affording crude sulfonyl isocyanate **S2.2** (1.9 g, 65% yield) as a white solid, which was subsequently used without further purification.

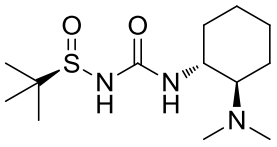


S2.2 **S2.1** **2.9**

III. Procedure for Preparation of Sulfonyl Urea 2.9. To a solution of sulfonyl isocyanate **S2.2** (619 mg, 2.00 mmol) in 2.0 mL THF was added diamine **S2.1** (284 mg, 2.00 mmol). The reaction mixture was stirred at room temperature for 3 h. The crude product was purified by silica gel chromatography (90:9:1 DCM:MeOH:NH_4OH) to afford sulfonyl urea **2.9** (687 mg, 76% yield) as a white powder, mp 119-120 °C. IR: 3044, 2948, 2866, 1706, 1596, 1463, 1449, 1380, 1329, 1240, 1225, 1128, 1112, 1056, 877, 660 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.13 (s, 2H), 6.04 (br s, 1H), 4.35 (br s, 2H), 2.91-2.83 (septet, 1H, *J* = 6.8 Hz), 2.35 (br s, 1H), 2.23 (br s, 6H), 1.94 (m, 1H), 1.78 (br s, 1H), 1.69 (br s, 1H), 1.53 (br s, 1H), 1.23-0.98 (m, 5H), 1.21-1.19 (d, 6H, *J* = 6.8 Hz), 1.17-1.15 (d, 12H, *J* = 6.8 Hz). $^{13}C\{^1H\}$ NMR (600 MHz, DMSO-d_6) (sample was dilute due to low solubility in DMSO and all other solvents tested): 151.5, 149.9, 123.3, 70.3, 50.7, 33.8, 33.1, 28.8, 25.0, 24.7, 24.5, 24.0, 22.2. HMS (ESI) calcd for $C_{24}H_{42}O_3N_3S$ $[M]^+$ 452.2932; found 452.2941.

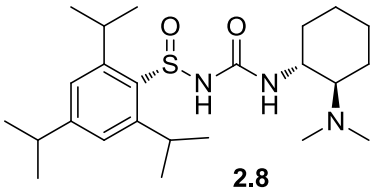


V. General Procedure for the Preparation of Ureas from Sulfinamides, Sulfonamides or Anilines (Procedure B). A suspension of potassium hydride (3 equiv) in THF (0.6 M) was cooled in an ice-water bath. A solution of sulfonamide, sulfonamide or aniline (1.0 equiv) in THF (0.20 M) was added dropwise, and the suspension was stirred for 15 min. 1,1'-Carbonyldiimidazole (1.0 equiv) was dissolved in 1:1 THF:dioxane (0.20 M) and added dropwise to the reaction mixture, resulting in the formation of a white precipitate. The ice-water bath was removed, and the reaction mixture was allowed to warm to ambient temperature and was stirred for 2 h. A solution of diamine **S2.1** (1.0 equiv) in THF (1.0 M) was added dropwise, and the suspension was stirred at room temperature for 20 h. The reaction was quenched with a solution of acetic acid (3 equiv) in THF (1.0 M). The crude product was concentrated *in vacuo* and purified by silica gel chromatography.



2.6

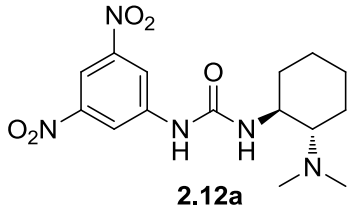
Urea 2.6. The general procedure (B) was followed using (*R*)-*tert*-butanesulfinamide (242 mg, 2.00 mmol), potassium hydride (240 mg, 6.00 mmol), 1,1'-carbonyldiimidazole (324 mg, 2.00 mmol), and (*R*,*R*)-diamine **S2.1** (284 mg, 2.00 mmol). Following silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH), reverse phase chromatography (5:95 MeOH:H_2O to 100% MeOH), and drying under high vacuum over phosphorous pentoxide, urea **2.6** was isolated as a white crystalline solid (0.400 g, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.26 (br s, 1H), 3.33-3.29 (m, 1H), 2.47-2.44 (m, 1H), 2.30-2.26 (m, 1H), 2.22 (s, 6H), 1.83-1.78 (m, 2H), 1.67-1.63 (m, 1H), 1.26 (s, 9H), 1.20-1.02 (m, 4H). ^{1}H NMR shifts correspond to the literature data.[6]



2.8

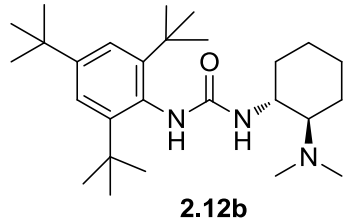
Urea 2.8. The general procedure (B) was followed using (*S*)-triisopropylbenzenesulfinamide (615 mg, 2.30 mmol), potassium hydride (276 mg, 6.90 mmol), 1,1'-carbonyldiimidazole (373 mg, 2.30 mmol), and (*R*,*R*)-diamine **S2.1** (327 mg, 2.30 mmol). Sulfinyl urea **2.8** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.8** was isolated as a white fluffy solid (730 mg, 73% yield), mp 156-157 °C. IR: 3350, 3136, 2962, 2922, 2857, 2763, 1665, 1627, 1538, 1400, 1085 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 2H), 5.96 (s, 1H), 3.94 (br s, 2H), 3.35-3.31 (m, 1H), 2.90-2.83 (septet, *J* = 6.8 Hz, 1H), 2.54-2.51 (m, 1H),

2.28-2.24 (m, 1H), 2.17 (s, 6H), 1.83-1.78 (m, 2H), 1.67-1.64 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.21 (d, *J* = 6.8 Hz, 6H), 1.22-1.03 (m, 4H). $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$): δ 155.2, 152.8, 148.4, 136.7, 123.3, 66.4, 52.3, 39.8, 34.4, 32.7, 28.5, 25.3, 24.6, 24.5, 24.1, 23.8, 21.2. HMS (ESI) calcd for $C_{24}H_{42}O_2N_3S$ $[MH]^+$ 436.2992; found 436.2990.



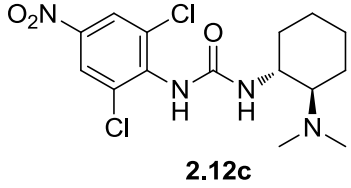
2.12a

Urea 2.12a. The general procedure (B) was followed using 3,5-dinitroaniline (183 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*S*,*S*)-diamine **S2.1** (142 mg, 1.00 mmol). Urea **2.12a** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12a** was isolated as a yellow powder (265 mg, 75% yield), mp 109 °C. IR: 2936, 2863, 1674, 1532, 1472, 1335, 1260, 1207, 1067, 892, 726 cm^{-1}. ^{1}H NMR (500 MHz, MeOD) δ 8.70 (d, *J* = 2.0 Hz, 2H), 8.53 (t, *J* = 2.0 Hz, 1H), 3.61 (td, *J* = 10.7, 4.0 Hz, 1H), 2.53 – 2.40 (m, 1H), 2.34 (s, 6H), 2.26 (m, 1H), 1.96 (m, 1H), 1.87 (m, 1H), 1.79 – 1.71 (m, 1H), 1.41 – 1.24 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.2, 150.6, 144.6, 118.7, 111.9, 68.2, 52.7, 40.9, 35.2, 26.6, 26.4, 23.7. HRMS (ESI) calcd for $C_{15}H_{21}N_5O_5$ $[MH]^+$ 352.16155; found 352.16150.



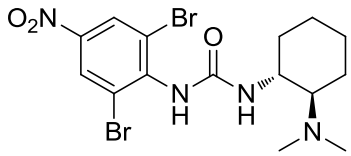
2.12b

Urea 2.12b. The general procedure (B) was followed using 2,4,6-tri-*tert*-butylaniline (120 mg, 0.460 mmol), potassium hydride (56 mg, 1.4 mmol), 1,1'-carbonyldiimidazole (74 mg, 0.46 mmol), and (*R*,*R*)-diamine **S2.1** (65 mg, 0.46 mmol). Urea **2.12b** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12b** was isolated as a white powder (47 mg, 24% yield), mp 190 °C. IR: 3178, 2930, 2863, 2781, 1661, 1510, 1477, 1362, 1341, 1267, 1241, 811, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 2H), 5.60 (br s, 1H), 4.67 (br s, 1H), 3.19 (m, 1H), 2.71 (m, 1H), 2.05 – 1.79 (s, 6H), 1.78 – 1.65 (m, 2H), 1.59 (m, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.34 (s, 9H), 1.25 (m, 2H), 1.16 – 1.03 (m, 2H), 0.94 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 149.5, 131.0, 123.3, 122.9, 66.7, 51.3, 40.1, 36.8, 36.6, 35.0, 32.7, 32.2, 32.0, 31.9, 31.5, 25.4, 24.4, 21.3. HRMS (ESI) calcd for $C_{27}H_{47}N_3O$ $[MH]^+$ 430.37919; found 430.37780.



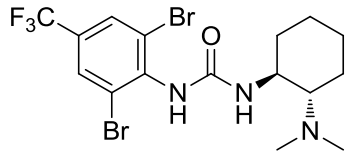
2.12c

Urea 2.12c. The general procedure (B) was followed using 2,6-dichloro-4-nitroaniline (140 mg, 0.676 mmol), potassium hydride (79 mg, 2.0 mmol), 1,1'-carbonyldiimidazole (110 mg, 0.679 mmol), and (*R*,*R*)-diamine **S2.1** (96 mg, 0.676 mmol). Urea **2.12c** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12c** was isolated as a yellow powder (180 mg, 73% yield), mp 160 ^oC. IR: 2932, 2859, 2784, 1651, 1530, 1456, 1386, 1340, 1253, 1232, 811, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2H), 5.66 (s, 1H), 3.49 – 3.25 (m, 1H), 2.32 – 2.12 (m, 2H), 2.22 (s, 6H), 1.89 – 1.78 (m, 1H), 1.78 – 1.69 (m, 1H), 1.64 (m, 1H), 1.27 – 1.01 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.0, 146.8, 142.0, 135.0, 125.1, 68.1, 53.2, 41.1, 35.4, 26.7, 26.4, 24.6. HRMS (ESI) calcd for $C_{15}H_{20}Cl_2N_4O_3$ $[MH]^+$ 375.09852; found 375.09817.



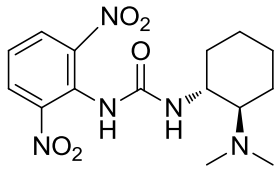
2.12d

Urea 2.12d. The general procedure (B) was followed using 2,6-dibromo-4-nitroaniline (296 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine **S2.1** (142 mg, 1.00 mmol). Urea **2.12d** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12d** was isolated as a yellow powder (373 mg, 80% yield), mp 104 ^oC. IR: 2931, 2858, 2783, 1650, 1523, 1449, 1376, 1340, 1233, 738 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 8.49 (s, 2H), 3.70 – 3.48 (m, 1H), 2.43 (m, 1H), 2.38 (s, 6H), 2.23 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.72 (m, 1H), 1.38 – 1.22 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.0, 147.4, 144.5, 128.8, 125.1, 68.0, 53.2, 41.2, 35.5, 26.7, 26.4, 24.9. HRMS (ESI) calcd for $C_{15}H_{20}Br_2N_4O_3$ $[MH]^+$ 464.99553; found 464.99497.



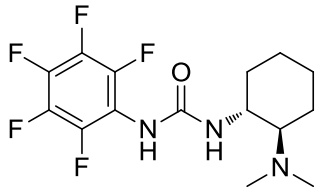
2.12e

Urea 2.12e. The general procedure (B) was followed using 2,6-dibromo-4-(trifluoromethyl)aniline (319 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*S*,*S*)-diamine **S2.1** (156 mg, 1.10 mmol). Urea **2.12e** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12e** was isolated as a white powder (360 mg, 74% yield), mp 180 ^oC. IR: 2933, 2859, 1645, 1538, 1392, 1312, 1267, 1234, 1163, 1127, 1096, 880, 738 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.94 (s, 2H), 3.57 (td, J = 10.3, 3.8 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.34 (s, 6H), 2.27 – 2.18 (m, 1H), 1.89 (m, 1H), 1.82 (m, 1H), 1.69 (m, 1H), 1.35 – 1.20 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.5, 142.1, 131.8 (q, J = 135 Hz), 130.7 (q, J = 15 Hz), 126.4, 124.3 (q, J = 1085 Hz), 68.02, 53.13, 41.21, 35.60, 26.76, 26.42, 25.12. HRMS (ESI) calcd for $C_{16}H_{20}Br_2F_3N_3O$ $[MH]^+$ 487.99783; found 487.99633.



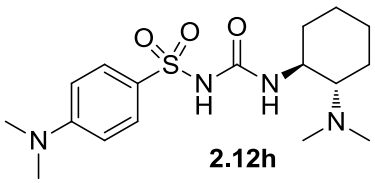
2.12f

Urea 2.12f. The general procedure (B) was followed using 2,6-dinitroaniline (183 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine **S2.1** (142 mg, 1.00 mmol). Urea **2.12f** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12f** was isolated as an orange powder (257 mg, 81% yield), mp 110 ^oC. IR: 2934, 2860, 2787, 1668, 1532, 1478, 1344, 1298, 1236, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 2H), 7.10 (t, *J* = 8.3 Hz, 1H), 6.08 (br s, 1H), 3.25 (td, *J* = 10.5, 3.0 Hz, 1H), 2.33 – 2.17 (m, 2H), 2.14 (s, 6H), 1.78 – 1.61 (m, 2H), 1.51 (m, 1H), 1.07 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 156.0, 145.6, 131.4, 130.1, 124.3, 68.1, 52.9, 41.1, 35.6, 26.6, 26.5, 24.4. HRMS (ESI) calcd for $C_{15}H_{21}N_5O_5$ $[MH]^+$ 352.16155; found 352.16147.



2.12g

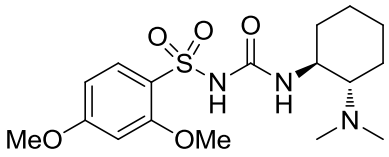
Urea 2.12g. The general procedure (B) was followed using pentafluoroaniline (147 mg, 0.803 mmol), potassium hydride (97 mg, 2.4 mmol), 1,1'-carbonyldiimidazole (131 mg, 0.808 mmol), and (*R*,*R*)-diamine **S2.1** (115 mg, 0.810 mmol). Urea **2.12g** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12g** was isolated as a yellow powder (229 mg, 65% yield), mp 147 ^oC. IR: 2935, 2862, 1648, 1551, 1518, 1267, 1233, 1003, 975, 874, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (br s, 1H), 3.43 (m, 1H), 2.39 (td, *J* = 10.9, 3.3 Hz, 1H), 2.28 (s, 6H), 2.18 – 2.16 (m, 1H), 1.84 (m, 1H), 1.81 – 1.70 (m, 1H), 1.65 (m, 1H), 1.27 – 1.03 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 162.9 (m), 157.8, 145.3 (dm, *J* = 1000 Hz), 141.1 (dm, *J* = 1000 Hz), 139.5 (dm, *J* = 1000 Hz), 117.3 (m), 115.3 (m), 69.9, 51.4, 43.1, 38.1, 34.5, 25.9, 25.5, 24.6. HRMS (ESI) calcd for $C_{15}H_{18}F_5N_3O$ $[MH]^+$ 352.14428; found 352.14410.



2.12h

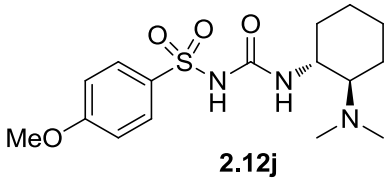
Urea 2.12h. The general procedure (B) was followed using 4-(*N*,*N*-dimethyl)benzenesulfonamide (46 mg, 0.23 mmol), potassium hydride (28 mg, 0.69 mmol), 1,1'-carbonyldiimidazole (37 mg, 0.23 mmol), and (*S*,*S*)-diamine **S2.1** (33 mg, 0.23 mmol). Urea **2.12h** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12h** was isolated as a white powder (22 mg, 26% yield), mp 134 ^oC. IR: 2936, 2860, 1596,

1512, 1446, 1319, 1235, 1115, 1086, 867, 652 cm^{-1}. ^{1}H NMR (500 MHz, MeOD) δ 7.63 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 9.0 Hz, 2H), 3.53 (m, 1H), 2.90 (s, 6H), 2.89 (m, 1H), 2.61 (s, 6H), 1.92 (m, 1H), 1.81 (m, 1H), 1.77 (m, 1H), 1.61 (m, 1H), 1.33 (m, 1H), 1.20 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 152.7, 130.7, 128.3, 128.3, 110.7, 69.3, 39.3, 33.0, 29.7, 29.6, 24.5, 24.2, 22.9. HRMS (ESI) calcd for $C_{17}H_{28}N_4O_3S$ $[MH]^+$ 369.19549; found 369.19533.



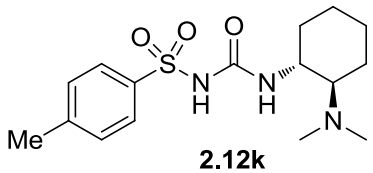
2.12i

Urea 2.12i. The general procedure (B) was followed using 2,4-dimethoxybenzenesulfonamide (217 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*S*,*S*)-diamine **S2.1** (142 mg, 1.00 mmol). Urea **2.12i** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12i** was isolated as a white solid (165 mg, 43% yield), mp 113 ^{o}C. IR: 3053, 2939, 2861, 1702, 1593, 1578, 1466, 1314, 1254, 1212, 1163, 1076, 1026, 732 cm^{-1}. ^{1}H NMR (400 MHz, MeOD) δ 7.86 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 1H), 6.61 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.73 (s, 1H), 3.11 (td, *J* = 11.8, 3.5 Hz, 1H), 2.78 (s, 6H), 2.06 (m, 1H), 1.90 (m, 2H), 1.74 (m, 1H), 1.46 (m, 1H), 1.35 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 165.8, 160.1, 159.7, 132.8, 124.0, 105.4, 100.2, 69.9, 56.7, 56.2, 54.8, 40.3, 34.1, 25.5, 25.2, 24.0. HRMS (ESI) calcd for $C_{17}H_{27}N_3O_5S$ $[MH]^+$ 386.17442; found 386.17427.



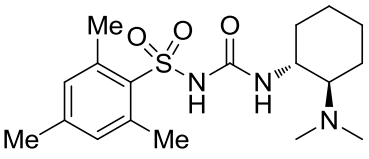
2.12j

Urea 2.12j. The general procedure (B) was followed using 4-methoxybenzenesulfonamide (207 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine **S2.1** (142 mg, 1.00 mmol). Urea **2.12j** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12j** was isolated as a white solid (220 mg, 58% yield), mp 114 ^{o}C. IR: 2941, 2863, 1595, 1497, 1383, 1242, 1123, 1082, 1025, 729, 666 cm^{-1}. ^{1}H NMR (500 MHz, MeOD) δ 7.82 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.63 (m, 1H), 3.12 (td, *J* = 11.9, 3.4 Hz, 1H), 2.72 (s, 6H), 1.99 (m, 1H), 1.81 (m, 2H), 1.65 (m, 1H), 1.45 – 1.21 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 163.2, 138.2, 129.8, 129.7, 114.5, 69.8, 56.1, 50.8, 40.3, 34.1, 25.6, 25.2, 24.1. HRMS (ESI) calcd for $C_{16}H_{25}N_3O_4S$ $[MH]^+$ 356.16385; found 356.16400.



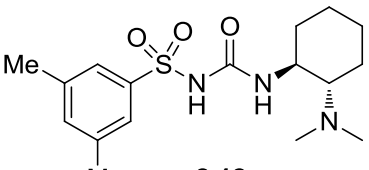
2.12k

Urea 2.12k. The general procedure (B) was followed using *p*-toluenesulfonamide (187 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine **S2.1** (142 mg, 1.00 mmol). Urea **2.12k** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12k** was isolated as a white solid (107 mg, 30% yield), mp 81 ^oC. IR: 2939, 2864, 1597, 1437, 1249, 1119, 1070, 869, 813, 729 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 3.81 (td, *J* = 11.1, 4.3 Hz, 1H), 3.29 – 3.23 (m, 1H), 2.88 (s, 3H), 2.78 (s, 3H), 2.46 (s, 3H), 2.11 (m, 1H), 1.91 (m, 1H), 1.85 – 1.78 (m, 1H), 1.75 (m, 1H), 1.56 – 1.47 (m, 1H), 1.37 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 154.5, 146.4, 139.0, 131.1, 129.2, 69.7, 50.9, 43.3, 38.2, 34.3, 25.8, 25.4, 24.4, 21.9. HRMS (ESI) calcd for $C_{16}H_{25}N_3O_3S$ $[MH]^+$ 340.16894; found 340.16900.



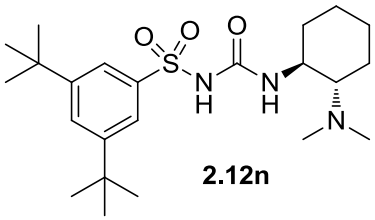
2.12l

Urea 2.12l. The general procedure (B) was followed using mesitylenesulfonamide (199 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine **S2.1** (142 mg, 1.00 mmol). Urea **2.12l** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12l** was isolated as a white solid (92 mg, 25% yield), mp 108 ^oC. IR: 2936, 2861, 1702, 1601, 1450, 1379, 1339, 1236, 1112, 851, 658 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 6.92 (s, 2H), 3.62 (m, 1H), 3.00 (td, *J* = 11.7, 2.8 Hz, 1H), 2.78 (s, 6H), 2.69 (s, 6H), 2.27 (s, 3H), 2.05 (m, 1H), 1.90 (m, 2H), 1.73 (m, 1H), 1.49 – 1.25 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 162.9, 141.6, 141.6, 139.8, 132.2, 71.6, 70.5, 50.9, 40.4, 34.1, 25.6, 25.2, 24.0, 23.3, 20.9. HRMS (ESI) calcd for $C_{18}H_{29}N_3O_3S$ $[MH]^+$ 368.20024; found 368.20020.



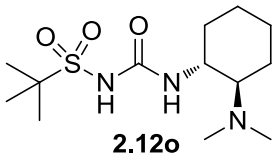
2.12m

Urea 2.12m. The general procedure (B) was followed using 3,5-dimethylbenzenesulfonamide (93 mg, 0.50 mmol), potassium hydride (60 mg, 1.5 mmol), 1,1'-carbonyldiimidazole (81 mg, 0.50 mmol), and (*S*,*S*)-diamine **S2.1** (85 mg, 0.60 mmol). Urea **2.12m** was purified by reverse phase chromatography using a 43 g C18 column (95:5 H_2O:MeCN to 100% MeCN, 40 mL/min, λ = 254, 210 nm). Product **2.12m** was isolated as a white powder (144 mg, 81% yield), mp 114-115 ^oC. IR: 3047, 2937, 2862, 1602, 1513, 1468, 1450, 1381, 1321, 1274, 1243, 1126, 1096, 886, 786 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.54 (s, 2H), 7.14 (s, 1H), 3.67 (m, 1H), 3.19 (td, *J* = 12.0, 3.5 Hz, 1H), 2.78 (s, 6H), 2.36 (s, 6H), 2.09 – 2.01 (m, 1H), 1.88 (m, 2H), 1.72 (m, 1H), 1.54 – 1.26 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 163.7, 146.6, 139.7, 133.8, 125.8, 70.3, 51.2, 40.7, 34.6, 26.1, 25.6, 24.5, 21.8. HRMS (ESI) calcd for $C_{17}H_{27}O_3N_3S$ $[MH]^+$ 354.18459; found 354.18397.



2.12n

Urea 2.12n. The general procedure (B) was followed using 3,5-di(*tert*-butyl)benzenesulfonamide (135 mg, 0.500 mmol), potassium hydride (60 mg, 1.5 mmol), 1,1'-carbonyldiimidazole (81 mg, 0.50 mmol), and (*S*,*S*)-diamine **S2.1** (78 mg, 0.55 mmol). Urea **2.12n** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12n** was isolated as a white solid (106 mg, 48% yield), mp 132 ^oC. IR: 2955, 2865, 1702, 1595, 1517, 1476, 1394, 1364, 1322, 1245, 1097, 882, 734 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 7.82 (s, 2H), 7.60 (s, 1H), 3.71 (m, 1H), 3.19 (td, *J* = 11.9, 3.4 Hz, 1H), 2.80 (s, 6H), 2.06 (m, 1H), 1.89 (m, 2H), 1.73 (m, 1H), 1.48 – 1.28 (m, 4H), 1.42 (s, 18H). ^{13}C NMR (126 MHz, MeOD) δ 163.3, 152.3, 145.6, 126.1, 121.9, 69.9, 50.8, 40.2, 36.0, 34.2, 31.8, 25.6, 25.2, 24.0. HRMS (ESI) calcd for $C_{23}H_{39}N_3O_3S$ $[MH]^+$ 438.27849; found 438.27807.



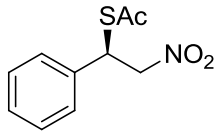
2.12o

Urea 2.12o. The general procedure (B) was followed using *tert*-butanesulfonamide (126 mg, 0.920 mmol), potassium hydride (110 mg, 2.80 mmol), 1,1'-carbonyldiimidazole (149 mg, 0.920 mmol), and (*R*,*R*)-diamine **S2.1** (131 mg, 0.923 mmol). Urea **2.12o** was purified by silica gel chromatography (90:9:1 CH_2Cl_2:MeOH:NH_4OH). Product **2.12o** was isolated as a white solid (211 mg, 75% yield), mp 189 ^oC. IR: 2933, 2862, 1705, 1585, 1514, 1478, 1450, 1388, 1324, 1282, 1216, 1132, 1091, 1066, 864 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 3.85 – 3.66 (m, 1H), 3.05 (m, 1H), 2.80 (s, 6H), 2.07 (m, 2H), 1.92 (m, 1H), 1.78 (m, 1H), 1.55 – 1.45 (m, 1H), 1.44 – 1.39 (s, 9H), 1.33 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 162.3, 70.6, 60.2, 51.8, 40.7, 34.5, 26.1, 25.7, 25.5, 24.4. HRMS (ESI) calcd for $C_{13}H_{27}N_3O_3S$ $[MH]^+$ 306.18459; found 306.18450.

VI. Representative Procedure for Racemic Addition of Thioacetic Acid to *trans*-β-Nitrostyrene. To a solution of *trans*-β-nitrostyrene (30 mg, 0.20 mmol) in diethyl ether (1.0 mL) was added one drop of triethylamine. The solution was cooled to -15 ^oC. Thioacetic acid (0.029 mL, 0.40 mmol) was added. The reaction mixture was stirred at -15 ^oC for 4 h, then quenched at that temperature by addition of saturated $NaHCO_{3(aq)}$ (1 mL). The mixture was then diluted with ether (2 mL) and washed with saturated $NaHCO_{3(aq)}$ (2 x 2 mL). The crude product was purified by silica gel chomatography (9:1 hexanes:EtOAc).

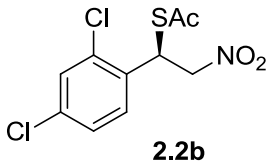
VII. Representative Procedure for Enantioselective Addition of Thioacetic Acid to *trans*-β-Nitrostyrenes. A mixture of *trans*-β-nitrostyrene (30 mg, 0.20 mmol) and sulfinyl urea catalyst (0.010 mmol) in cyclopentyl methyl ether (2.0 mL) was cooled to -78 ^oC. Thioacetic acid (0.029 mL, 0.40 mmol) was added. The reaction mixture was stirred at -78 ^oC for 48 h, then quenched at that temperature by addition of saturated $NaHCO_{3(aq)}$ (1 mL). The mixture was then diluted with diethyl ether (1 mL) and allowed to warm with shaking until the aqueous layer was

thawed. The layers were separated and the organic layer was washed quickly with saturated $NaHCO_{3(aq)}$ (3 x 1 mL). The crude ether solution was eluted immediately through a silica gel plug with diethyl ether. The resulting solution was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (90:9:1 hexanes:EtOAc:AcOH). Enantiomeric excess was determined by chiral HPLC analysis.



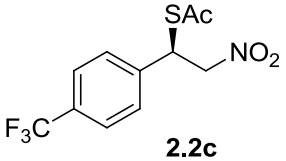
2.2a

1-Thioacetyl-1-phenyl-2-nitroethane 2.2a. The general procedure was followed using *trans*-β-nitrostyrene (30 mg, 0.20 mmol), catalyst **2.8** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2a** (33 mg, 73% yield) as a white solid, mp 131-132 ^{o}C. IR: 3032, 2964, 2919, 2855, 1683, 1548, 1494, 1453, 1377, 1138, 1109, 953, 638 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.35 (m, 5H), 5.35-5.31 (t, 1H, *J* = 7.6 Hz), 4.90-4.88 (d, 2H, *J* = 7.6 Hz), 2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$): δ 193.3, 135.7, 129.2, 128.8, 127.8, 78.0, 44.5, 30.4. Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.25; H, 4.87; N, 5.92; S, 14.11. $[\alpha]^{23}_{D}$ = -237.8^{o} (*c* = 1.0, $CHCl_3$). The ee was determined to be 90% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2a** major) = 13.1 min, t_R (**2.2a** minor) = 15.8 min.



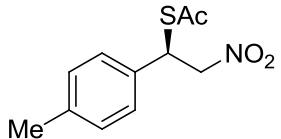
2.2b

1-Thioacetyl-1-(2,4-dichlorophenyl)-2-nitroethane 2.2b. The general procedure was followed using 2,4-dichloro-*trans*-β-nitrostyrene (0.44 g, 2.0 mmol), catalyst **2.8** (44 mg, 0.10 mmol) and thioacetic acid (0.29 mL, 4.0 mmol) to afford product **2.2b** (0.49 g, 84% yield) as a colorless viscous oil. IR: 3091, 3025, 2919, 1698, 1554, 1475, 1427, 1374, 1129, 1103, 953, 828, 619 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 1H, *J* = 2.0 Hz), 7.34-7.32 (d, 1H, *J* = 8.4 Hz), 7.27-7.24 (dd, 1H, *J* = 2.0 Hz, 8.4 Hz), 5.67-5.63 (dd, 1H, *J* = 6.0 Hz, 4.8 Hz), 5.01-4.95 (dd, 1H, *J* = 9.2 Hz, 4.8 Hz), 4.88-4.83 (dd, 1H, *J* = 6.0 Hz, 9.2 Hz), 2.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$): δ 192.2, 135.3, 134.5, 131.9, 130.4, 130.3, 127.7, 77.3, 41.4, 30.2. Anal. Calcd. for $C_{10}H_9Cl_2NO_3S$: C, 40.83; H, 3.08; N, 4.76; S, 10.90. Found: C, 40.78; H, 3.22; N, 4.63; S, 10.87. $[\alpha]^{23}_{D}$ = -183.9^{o} (*c* = 1.0, $CHCl_3$). The ee was determined to be 96% by chiral HPLC analysis (Chiralcel AS-H, hexane/isopropanol 95/5, 1.0 mL/min, λ = 210 nm): t_R (**2.2b** minor) = 16.0 min, t_R (**2.2b** major) = 23.5 min.



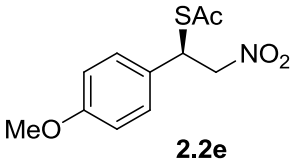
2.2c

1-Thioacetyl-1-(4-trifluoromethylphenyl)-2-nitroethane 2.2c. The general procedure was followed using 4-trifluoromethyl-*trans*-β-nitrostyrene (44 mg, 0.20 mmol), catalyst **2.8** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2c** (51 mg, 88% yield) as a white solid, mp 35-36 ^{o}C. IR: 3036, 2969, 2927, 2853, 1694, 1558, 1421, 1380, 1327, 1161, 1125, 1113, 1071, 950, 860, 621 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (d, 2H, *J* = 8.0 Hz), 7.51-7.49 (d, 2H, *J* = 8.0 Hz), 5.40-5.36 (t, 1H, *J* = 8.0 Hz), 4.91-4.89 (d, 2H, *J* = 8.0 Hz), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$): δ 192.7, 140.0, 131.2, 130.8, 128.3, 126.2, 126.1, 125.1, 122.4, 77.5, 43.9, 30.4. ^{19}F{^{1}H} NMR (400 MHz, $CDCl_3$): δ -62.1. Anal. Calcd. for $C_{11}H_{10}F_3NO_3S$: C, 45.05; H, 3.44; N, 4.78; S, 10.93. Found: C, 45.15; H, 3.42; N, 4.63; S, 10.91. $[\alpha]^{23}_D$ = -165.6^{o} (*c* = 1.2, $CHCl_3$). The ee was determined to be 85% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2c** major) = 11.8 min, t_R (**2.2c** minor) = 13.2 min.



2.2d

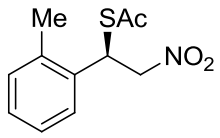
1-Thioacetyl-1-(4-methylphenyl)-2-nitroethane 2.2d. The general procedure was followed using 4-methyl-*trans*-β-nitrostyrene (33 mg, 0.20 mmol), catalyst **2.8** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2d** (31 mg, 65% yield) as a white solid, mp 91-92 ^{o}C. IR: 3034, 2922, 2853, 1687, 1553, 1514, 1441, 1377, 1131, 949, 632 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.23 (d, 2H, *J* = 8.4 Hz), 7.20-7.18 (d, 2H, *J* = 8.4 Hz), 5.32-5.28 (t, 1H, *J* = 8.0 Hz), 4.88-4.85 (d, 2H, *J* = 8.0 Hz), 2.39 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$): δ 193.5, 138.8, 132.5, 129.9, 127.6, 78.1, 44.3, 30.4, 21.2. Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.11; H, 5.25; N, 5.67; S, 13.25. $[\alpha]^{23}_D$ = -159.1^{o} (*c* = 1.0, $CHCl_3$). The ee was determined to be 91% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2d** major) = 9.8 min, t_R (**2.2d** minor) = 11.3 min.



2.2e

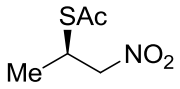
1-Thioacetyl-1-(4-methoxyphenyl)-2-nitroethane 2.2e. The general procedure was followed using 4-methoxy-*trans*-β-nitrostyrene (36 mg, 0.20 mmol), catalyst **2.8** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2e** (33 mg, 65% yield) as a white solid, mp 105-106 ^{o}C. IR: 3040, 2924, 2856, 1697, 1551, 1449, 1453, 1377, 1114, 970, 617 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.26 (d, 2H, *J* = 8.4 Hz), 6.92-6.89 (d, 2H, *J* = 8.4 Hz), 5.29-5.26 (m, 1H), 4.90-4.80 (m, 2H), 3.83 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$): δ 193.6, 159.8, 129.0, 127.4, 114.6, 78.2, 55.3, 44.1, 30.4. Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.60; H, 5.02; N, 5.26; S, 12.25. $[\alpha]^{23}_D$ = -234.3^{o} (*c* = 1.0, $CHCl_3$). The ee was determined to be 93% by chiral HPLC analysis

(Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2e** major) = 15.1 min, t_R (**2.2e** minor) = 18.6 min.



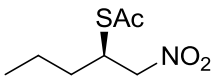
2.2f

1-Thioacetyl-1-(2-methylphenyl)-2-nitroethane 2.2f. The general procedure was followed using 2-methyl-*trans*-β-nitrostyrene (33 mg, 0.20 mmol), catalyst **2.8** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2f** (30 mg, 63% yield) as a colorless oil. IR: 3029, 2974, 2920, 1693, 1553, 1492, 1428, 1375, 1125, 952, 622 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.21 (m, 4H), 5.63-5.57 (m, 1H), 4.98-4.85 (m, 2H), 2.50 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 193.8, 136.6, 133.4, 131.3, 128.7, 126.8, 126.6, 77.4, 40.5, 30.3, 19.4. Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.07; H, 5.37; N, 5.69; S, 13.67. $[\alpha]^{23}_D$ = -118.3° (*c* = 1.3, $CHCl_3$). The ee was determined to be 94% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2f** major) = 7.6 min, t_R (**2.2f** minor) = 9.0 min.



2.2g

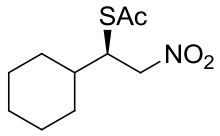
1-Thioacetyl-1-methyl-2-nitroethane 2.2g. The general procedure was followed using *trans*-1-nitro-1-propene (17 mg, 0.20 mmol), catalyst **2.8** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2g** (21 mg, 64% yield) as a colorless oil. IR: 3032, 2964, 2919, 2855, 1683, 1548, 1494, 1453, 1377, 1138, 1109, 953, 638 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.63-4.60 (dd, 1H, *J* = 5.0 Hz, *J* = 13 Hz), 4.46-4.42 (dd, 1H, *J* = 8.0 Hz, *J* = 13 Hz), 4.18-4.11 (m, 1H), 2.35 (s, 3H), 1.43-1.41 (d, 3H, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR (500 MHz, $CDCl_3$): δ 194.2, 79.2, 35.9, 30.5, 17.7. Anal. Calcd. for $C_5H_9NO_3S$: C, 36.80; H, 5.56; N, 8.58; S, 19.65. Found: C, 36.66; H, 5.38; N, 8.23; S, 19.84. $[\alpha]^{23}_D$ = +5.4° (*c* = 1.0, $CHCl_3$). The ee was determined to be 78% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2g** major) = 8.0 min, t_R (**2.2g** minor) = 10.9 min.



2.2h

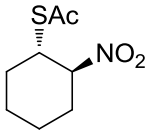
1-Thioacetyl-1-*n*-propyl-2-nitroethane 2.2h. The general procedure was followed using *trans*-1-nitro-1-pentene (23 mg, 0.20 mmol), catalyst **2.8** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2h** (31 mg, 82% yield) as a colorless oil. IR: 2963, 2934, 2875, 1694, 1552, 1427, 1376, 1114, 953, 625 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.67-4.62 (dd, 1H, *J* = 6.0 Hz, *J* = 13 Hz), 4.57-4.52 (dd, 1H, *J* = 7.2 Hz, *J* = 13 Hz), 4.16-4.09 (m,

1H), 2.40 (s, 3H), 1.78-1.60 (m, 2H), 1.57-1.40 (m, 2H), 0.99-0.96 (t, 3H, *J* = 7.6 Hz). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 194.4, 78.3, 41.0, 33.4, 30.7, 19.9, 13.6. Anal. Calcd. for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32; S, 16.77. Found: C, 43.77; H, 6.72; N, 7.17; S, 17.16. $[\alpha]^{23}_D$ = +3.7° (*c* = 0.5, $CHCl_3$). The ee was determined to be 80% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2h** major) = 8.1 min, t_R (**2.2h** minor) = 9.9 min.



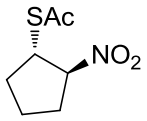
2.2i

1-Thioacetyl-1-cyclohexyl-2-nitroethane 2.2i. The general procedure was followed using *trans*-1-cyclohexyl-2-nitroethylene (31 mg, 0.20 mmol), catalyst **2.7** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product **2.2i** (44 mg, 95% yield) as a white solid, mp 42-44 °C. IR: 3040, 2924, 2856, 1698, 1551, 1449, 1378, 1116, 970, 619 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.61-4.57 (dd, 1H, *J* = 7.5 Hz, *J* = 13 Hz), 4.56-4.52 (dd, 1H, *J* = 7.5 Hz, *J* = 13 Hz), 4.14-4.10 (m, 1H), 2.36 (s, 3H), 1.81-1.65 (m, 6H), 1.30-1.07 (m, 4H), 1.02-0.95 (m, 1H). $^{13}C\{^1H\}$ NMR (500 MHz, $CDCl_3$): δ 193.9, 77.2, 46.7, 39.0, 30.7, 30.5, 29.2, 25.9. Anal. Calcd. for $C_{10}H_{17}NO_3S$: C, 51.92; H, 7.41; N, 6.06; S, 13.86. Found: C, 51.98; H, 7.39; N, 5.96; S, 13.49. $[\alpha]^{23}_D$ = -5.7° (*c* = 0.9, $CHCl_3$). The ee was determined to be 84% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.2i** major) = 9.2 min, t_R (**2.2i** minor) = 14.7 min.



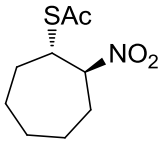
2.11a

***trans*-1-Thioacetyl-2-nitro-cyclohexane 2.11a.** The general procedure was followed using *trans*-1-nitrocyclohexene (13 mg, 0.10 mmol), catalyst **2.7** (2.2 mg, 0.0050 mmol) and thioacetic acid (14 μL, 0.20 mmol) in cyclopentyl methyl ether (1 mL) to afford product **2.11a** (19 mg, 95% yield) with >99% diastereomeric purity as a colorless oil. IR: 2943, 2862, 1693, 1543, 1448, 1373, 1353, 1301, 1269, 1244, 1112, 999, 953, 911, 859, 758, 625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (dt, *J* = 7.9, 4.1 Hz, 1H), 4.25 (s, 1H), 2.33 (s, 3H), 2.09 (dd, *J* = 8.4, 5.1 Hz, 3H), 1.88 – 1.79 (m, 1H), 1.74 – 1.56 (m, 3H), 1.52 – 1.42 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9, 85.2, 42.9, 30.6, 29.9, 28.8, 23.3, 21.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_8H_{13}NO_3S$, 226.05084; found, 226.05033. $[\alpha]^{20}_D$ = -52.2° (*c* = 1.0, $CHCl_3$). The ee was determined to be 94% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.11a** major) = 11.1 min, t_R (**2.11a** minor) = 8.0 min.



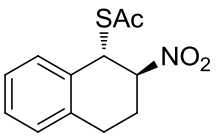
2.11b

1-Thioacetyl-2-nitro-cyclopentane 2.2l. The general procedure was followed using *trans*-1-nitrocyclopentene (11 mg, 0.10 mmol), catalyst **2.7** (2.2 mg, 0.0050 mmol) and thioacetic acid (21 μL, 0.30 mmol) in cyclopentyl methyl ether (2.5 mL) to afford a 65:35 diastereomeric mixture of product **2.11b** (15 mg, 80% yield) as a colorless oil. IR: 2960, 1694, 1548, 1449, 1369, 1355, 1324, 1272, 1128, 955, 628 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (only peaks corresponding the the major isomer are listed) 5.12 (dd, *J* = 9.0, 4.5 Hz, 1H), 4.81 – 4.77 (m, 1H), 4.28 (dd, *J* = 12.5, 7.5 Hz, 1H), 3.90 (dt, *J* = 14.0, 7.1 Hz, 1H), 2.41 – 2.22 (m, 6H), 2.13 – 2.06 (m, 1H), 2.01 (d, *J* = 11.9 Hz, 1H), 1.84 – 1.68 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (peaks corresponding to both the major and minor diastereomers are listed) 195.1, 194.6, 91.6, 89.3, 46.6, 45.1, 32.5, 31.8, 31.3, 30.4, 30.4, 29.6, 24.2, 22.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_7H_{11}NO_3S$, 212.03519; found, 212.03510**.** The ee for the major diastereomer was determined to be 93% by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.11b** major) = 16.3 min, t_R (**2.11b** minor) = 9.8 min.



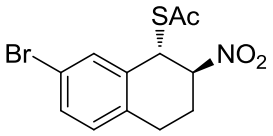
2.11c

1-Thioacetyl-2-nitro-cycloheptane 2.11c. The general procedure was followed using *trans*-1-nitrocycloheptene (14 mg, 0.10 mmol), catalyst **2.7** (2.2 mg, 0.0050 mmol) and thioacetic acid (14 μL, 0.20 mmol) in cyclopentyl methyl ether (1 mL) to afford a 80:20 diastereomeric mixture of product **2.11c** (18 mg, 82% yield) as a colorless oil. IR: 2933, 2862, 1691, 1545, 1457, 1374, 1354, 1297, 1107, 953, 854, 771, 628 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (only peaks corresponding the the major isomer are listed) 4.89 – 4.78 (m, 1H), 4.72 (dd, *J* = 11.8, 7.7 Hz, 1H), 4.25 (t, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.26 – 2.15 (m, 2H), 1.92 (dd, *J* = 16.3, 6.7 Hz, 1H), 1.82 – 1.68 (m, 3H), 1.67 – 1.56 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (peaks corresponding to both the major and minor diastereomers are listed) 194.2, 91.2, 89.1, 46.3, 45.3, 32.7, 32.5, 31.6, 30.9, 30.5, 28.3, 27.1, 26.6, 26.4, 23.5, 23.1. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_9H_{15}NO_3S$, 218.08454; found, 218.08447**.** The ee of the major diastereomer was determined to be 86% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 99/1, 1.0 mL/min, λ = 210 nm): t_R (**2.11c** major) = 17.3 min, t_R (**2.11c** minor) = 10.5 min.



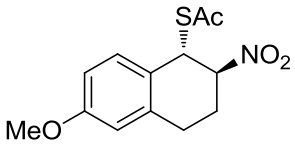
2.11d

***trans*-1-Thioacetyl-2-nitro-3,4-dihydronaphthalene 2.11d.** The general procedure was followed using *trans*-2-nitro-3,4-dihydronaphthalene (18 mg, 0.10 mmol), catalyst **2.7** (2.2 mg, 0.0050 mmol) and thioacetic acid (14 μL, 0.20 mmol) in cyclopentyl methyl ether (0.25 mL) to afford a 96:4 diastereomeric mixture of product **2.11d** (24 mg, 96% yield) as a colorless oil. IR: 2934, 2333, 1697, 1548, 1489, 1453, 1436, 1374, 1355, 1265, 1127, 952, 909, 729, 626 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H), 7.23 (t, *J* = 3.5 Hz, 2H), 7.16 – 7.07 (m, 1H), 5.66 (d, *J* = 4.3 Hz, 1H), 5.50 (t, *J* = 5.8 Hz, 1H), 5.04 (ddd, *J* = 10.7, 4.6, 3.2 Hz, 1H), 4.98 – 4.89 (m, 1H), 3.14 – 3.01 (m, 1H), 3.01 – 2.91 (m, 1H), 2.61 – 2.50 (m, 1H), 2.40 (s, 3H), 2.40 – 2.37 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 134.4, 134.3, 129.7, 129.2, 128.5, 127.6, 84.2, 44.9, 30.7, 27.2, 25.1. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{12}H_{13}NO_3S$, 252.06889; found, 252.06870**.** The ee of the major diastereomer was determined to be 90% by chiral HPLC analysis (Chiralcel AS-H, hexane/isopropanol 95/5, 1.0 mL/min, λ = 210 nm): t_R (**2.11d** major) = 25.4 min, t_R (**2.11d** minor) = 17.6 min.



2.11e

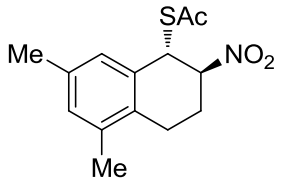
***trans*-1-Thioacetyl-2-nitro-3,4-dihydro-7-bromonaphthalene 2.11e.** The general procedure was followed using *trans*-2-nitro-3,4-dihydro-7-bromonaphthalene (51 mg, 0.20 mmol), catalyst **2.7** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) in cyclopentyl methyl ether (0.5 mL) to afford a 95:5 diastereomeric mixture of product **2.11e** (64 mg, 98% yield) as a colorless oil. IR: 2939, 2326, 2084, 1695, 1591, 1546, 1480, 1435, 1373, 1354, 1265, 1149, 1125, 951, 733, 625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 5.51 (d, *J* = 4.2 Hz, 1H), 5.05 – 4.89 (m, 1H), 2.94 (dt, *J* = 17.3, 5.6 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.49 (s, 1H), 2.41 – 2.28 (m, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 136.4, 133.5, 132.2, 131.5, 130.8, 121.0, 84.0, 44.1, 30.8, 26.5, 25.2. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{12}H_{12}BrNO_3S$, 329.97940; found, 329.97937**.** The ee of the major diastereomer was determined to be 89% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 95/5, 1.0 mL/min, λ = 210 nm): t_R (**2.11e** major) = 14.8 min, t_R (**2.11e** minor) = 11.1 min.



2.11f

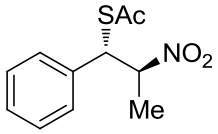
***trans*-1-Thioacetyl-2-nitro-3,4-dihydro-6-methoxynaphthalene 2.11f.** The general procedure was followed using *trans*-2-nitro-3,4-dihydro-6-methoxynaphthalene (21 mg, 0.10 mmol), catalyst **7** (2.2 mg, 0.0050 mmol) and thioacetic acid (36 μL, 0.50 mmol) in cyclopentyl methyl ether (1 mL) to afford a 97:3 diastereomeric mixture of product **2.11f** (27 mg, 97% yield) as a yellow oil. IR: 2944, 2838, 2341, 1696, 1607, 1549, 1500, 1463, 1432, 1374, 1318, 1272, 1244, 1159, 1127, 1035, 951, 625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 1H), 6.78

(d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H), 5.63 (d, *J* = 4.1 Hz, 1H), 5.45 (m, 1H), 5.00 (dd, *J* = 7.4, 3.7 Hz, 1H), 4.91 (s, 1H), 3.79 (s, 3H), 3.09 – 2.98 (m, 1H), 2.98 – 2.81 (m, 1H), 2.52 (dd, *J* = 21.4, 15.3 Hz, 1H), 2.41 – 2.29 (m, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 159.2, 135.4, 130.6, 126.0, 113.8, 113.0, 83.9, 55.3, 44.3, 30.4, 27.2, 24.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{15}NO_3S$, 304.06140; found, 304.06163**.** The ee of the major diastereomer was determined to be 85% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 95/5, 1.0 mL/min, λ = 210 nm): t_R (**2.11f** major) = 17.9 min, t_R (**2.11f** minor) = 13.9 min.



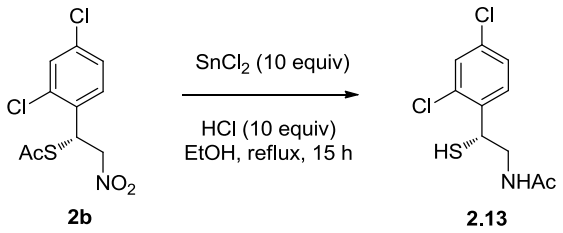
2.11g

***trans*-1-Thioacetyl-2-nitro-3,4-dihydro-5,7-dimethylnaphthalene 2.11g.** The general procedure was followed using *trans*-2-nitro-3,4-dihydro-5,7-dimethylnaphthalene (41 mg, 0.20 mmol), catalyst **7** (4.4 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) in cyclopentyl methyl ether (0.5 mL) to afford a 96:4 diastereomeric mixture of product **2.11g** (50 mg, 90% yield) as a colorless oil. IR: 1698, 1549, 1482, 1432, 1375, 1355, 1265, 1125, 953, 908, 731, 702 655, 624 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.90 (s, 1H), 5.60 (d, *J* = 2.7 Hz, 1H), 5.03 – 4.88 (m, 1H), 4 2.87 (m, 1H), 2.73 – 2.60 (m, 1H), 2.60 – 2.52 (m, 1H), 2.34 (s, 3H), 2.30-2.24 (m, 1H), 2.24 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 137.1, 136.8, 134.3, 131.1, 129.9, 127.8, 83.9, 45.4, 30.8, 25.0, 24.8, 21.2, 19.9. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{17}NO_3S$, 280.10019; found, 280.10010**.** The ee of the major diastereomer was determined to be 90% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ = 210 nm): t_R (**2.11g** major) = 12.1 min, t_R (**2.11g** minor) = 8.9 min.



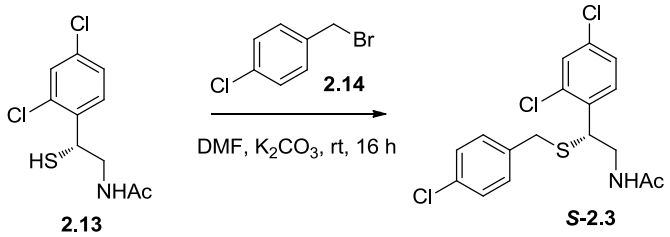
2.11h

1-Thioacetyl-1-phenyl-2-nitropropane 2.11h. The general procedure was followed using *trans*-β-methyl-β-nitrostyrene (16 mg, 0.10 mmol), catalyst **2.7** (2.2 mg, 0.0050 mmol) and thioacetic acid (21 μL, 0.30 mmol) in cyclopentyl methyl ether (2.5 mL) to afford a 67:33 diastereomeric mixture of product **2.11h** (23 mg, 96% yield) as a colorless oil. IR: 2941, 1696, 1549, 1492, 1451, 1386, 1356, 1293, 1124, 1094, 953, 864, 747, 698, 624 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (peaks listed for both diastereomers) 7.34 (m, 5H), 5.17 (d, *J* = 9.2 Hz, 0.67H), 5.14 (d, *J* = 9.1 Hz, 0.33H), 5.05 – 4.95 (m, 1H), 2.40 (s, 2H), 2.35 (s, 1H), 1.71 (d, *J* = 6.7 Hz, 2H), 1.51 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (peaks listed for both diastereomers) 192.4, 137.0, 129.1, 129.0, 128.6, 128.3, 128.0, 86.6, 86.1, 50.4, 50.3, 30.5, 30.5, 18.0, 17.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{13}NO_3S$, 262.05084; found, 262.05073**.** The ee of the major diastereomer was determined to be 94% by chiral HPLC analysis (Chiralcel AS-H, hexane/ethanol 98/2, 1.0 mL/min, λ = 210 nm): t_R (**2.11h** major) = 9.6 min, t_R (**2.11h** minor) = 10.4 min.



2b **2.13**

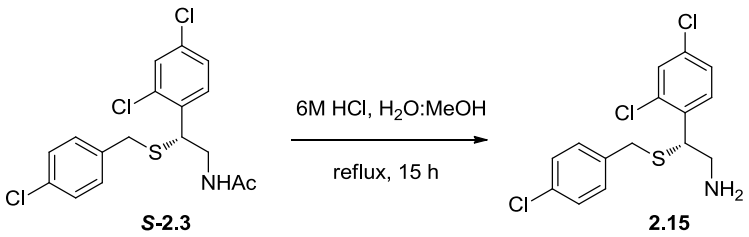
Procedure for Tin(II) Chloride Reduction of Nitrothioacetate 2.2b. An oven-dried 50-mL round-bottomed flask was equipped with a stir bar, N_2 inlet and septum, and charged with 2.3 g (12 mmol) of anhydrous tin(II) chloride. To a separate 25-mL round-bottomed flask, equipped with a stir bar, septum and N_2 inlet, was added 12 mL of dry ethanol, followed by dropwise addition of 0.85 mL (12 mmol) of acetyl chloride. After 10 minutes of stirring, 9 mL of the ethanolic hydrochloric acid solution was transferred to a vial containing 0.35 g (1.2 mmol) of 1-thioacetyl-1-(2,4-dichlorophenyl)-2-nitroethane **2.2b**. Once dissolved, the starting material solution was transferred to the flask containing tin(II) chloride. The vial was rinsed with the remaining 3 mL of the ethanolic hydrochloric acid solution, and the rinse solution was then transferred to the reaction flask. The flask was fitted with a reflux condenser and heated to 90 ^oC with vigorous stirring. The reaction mixture was stirred at 90 ^oC for 15 h and then cooled to room temperature. The crude product solution was concentrated to dryness and purified by reverse phase chromatography on a C18 column (5-100% methanol in water with 0.1% TFA). The purified product was concentrated *in vacuo* in a 34 ^oC water bath. The remaining wet product was dissolved in ethyl acetate and filtered through a plug of silica gel (100% EtOAc). Thiol amide **2.13** was isolated as a viscous, odorous oil (231 mg, 74% yield). IR: 3078, 3004, 2930, 2535, 1652, 1555, 1473, 1432, 1373, 1287, 1104, 820, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.42 (m, 2H), 7.32-7.29 (m, 1H), 5.95 (br s, 1H), 4.65-4.59 (dd, 1H, *J* = 7.6 Hz, *J* = 14.8 Hz), 3.80-3.65 (m, 2H), 2.08-2.06 (d, 1H, *J* = 7.6 Hz), 2.00 (s, 3H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 170.5, 137.5, 134.0, 133.9, 129.6, 128.8, 127.8, 45.9, 38.9, 23.1. HMS (ESI) calcd for $C_{10}H_{11}ONCl_2NaS$ $[M+Na]^+$ 285.9831; found 285.9833. $[\alpha]^{23}_D = +4.7^o$ (*c* = 1.4, $CHCl_3$). The ee was determined to be 96% by chiral HPLC analysis (Chiralcel AS-H, hexane/isopropanol 70/30, 0.8 mL/min, λ = 210 nm): t_R (**2.13** minor) = 16.4 min, t_R (**2.13** major) = 20.1 min.



2.13 ***S*-2.3**

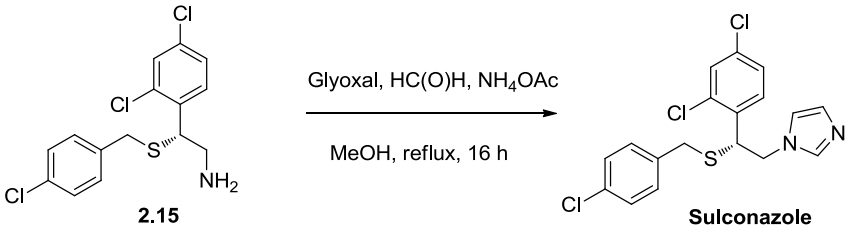
Procedure for Alkylation of Thiol Amide. Thiol amide **2.13** (28 mg, 0.11 mmol) was dissolved in 0.60 mL of deoxygenated DMF in a 4-mL vial containing a stir bar, septum and N_2 inlet. Then 4-chlorobenzyl bromide **2.14** (27 mg, 0.13 mmol) was added, and the reaction vial was evacuated and backfilled with N_2 (3x). Potassium carbonate (24 mg, 0.17 mmol) was quickly added, and the reaction vial was evacuated and backfilled with N_2. The reaction mixture was stirred vigorously at room temperature for 16 h. The reaction mixture was quenched with 1 mL of H_2O. The layers were separated and the aqueous layer was extracted with 2 mL 1:1 hexanes:EtOAc (3x). The combined organic layers were concentrated *in vacuo*. The crude oil

was purified by silica gel chromatography (1:1 hexanes:EtOAc). The product thioether amide ***S*-2.3** was isolated as a clear, colorless oil (29 mg, 72% yield). IR: 3660, 3075, 2926, 2851, 1652, 1554, 1489, 1471, 1431, 1373, 1287, 1090, 821, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.51–7.49 (d, 1H, *J* = 8.4 Hz), 7.40 (d, 1H, *J* = 1.6 Hz), 7.30-7.26 (m, 3H), 7.19-7.17 (d, 2H, *J* = 8.4 Hz), 5.65 (br s, 1H), 4.42-4.38 (t, 1H, *J* = 7.6 Hz), 3.70-3.53 (m, 4H), 1.93 (s, 3H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 170.1, 136.1, 134.7, 133.9, 133.1, 130.3, 130.0, 129.5, 128.7, 127.8, 44.7, 43.4, 35.3, 23.2. LRMS (EI) *m/z* 389 (M^+). $[\alpha]^{23}_D$ = -119° (*c* = 0.9, $CHCl_3$).



***S*-2.3** **2.15**

Procedure for Amide Hydrolysis. Thioether amide ***S*-2.3** (0.15 g, 0.39 mmol) was dissolved in 2.0 mL of distilled methanol in a round-bottomed flask containing a stir bar, septum and N_2 inlet. Aqueous hydrochloric acid (2.0 mL, 6.0 M) was added. The reaction flask was fitted with a reflux condenser and heated to 100 °C. The reaction mixture was stirred at reflux overnight. After cooling to room temperature, methanol was removed *in vacuo* and the residual aqueous mixture was made basic by addition of aqueous NaOH (15 mL, 1M) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford thioether amine **2.15** (0.14 g, 99% yield) as a yellow oil. IR: 3378, 3027, 2922, 2853, 1587, 1489, 1468, 1382, 1092, 1015, 815, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59–7.56 (d, 1H, *J* = 8.4 Hz), 7.41 (d, 1H, *J* = 2.0 Hz), 7.32-7.26 (m, 3H), 7.17-7.15 (d, 2H, *J* = 8.4 Hz), 4.30-4.26 (t, 1H, *J* = 6.8 Hz), 3.65-3.61 (m, 2H), 3.55-3.52 (d, 1H, *J* = 13.6 Hz), 3.00-2.98 (d, 2H, *J* = 6.8 Hz), 1.27 (br s, 2H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 136.8, 136.3, 134.7, 133.5, 133.0, 130.3, 130.2, 129.3, 128.7, 127.7, 48.9, 46.9, 35.1. HMS (ESI) calcd for $C_{15}H_{14}NCl_3S$ $[M]^+$ 345.9985; found 345.9975. $[\alpha]^{23}_D$ = -197° (*c* = 0.9, $CHCl_3$).



2.15 **Sulconazole**

Procedure for Imidazole Formation from Thioether Amine. Thioether amine **2.15** (85 mg, 0.25 mmol) was dissolved in 1.2 mL of distilled methanol in a round-bottomed flask containing a stir bar, septum and N_2 inlet. Glyoxal (71 μL, 40 wt%, 0.49 mmol), formaldehyde (41 μL, 36 wt%, 0.49 mmol) and ammonium acetate (38 mg, 0.49 mmol) were added to the reaction mixture. The reaction flask was fitted with a reflux condenser and heated to 95 °C. The reaction mixture was stirred at reflux for 16 h. After cooling to room temperature, the crude mixture was concentrated to dryness and made basic by addition of aqueous potassium hydroxide (8 mL, 2M) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was

purified by silica gel chromatography (99:1:0.1 DCM:MeOH:NH_4OH) to afford (*R*)-sulconazole as a pale yellow oil (70 mg, 74% yield). IR: 3109, 3062, 2924, 1587, 1502, 1489, 1472, 1441, 1383, 1284, 1230, 1091, 819, 732, 660 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37−7.36 (m, 2H), 7.26-7.23 (m, 4H), 7.06-7.05 (d, 2H, *J* = 8.5 Hz), 6.99 (s, 1H), 6.72 (s, 1H), 4.44-4.42 (t, 1H, *J* = 6.5 Hz), 4.23-4.14 (m, 2H), 3.51-3.48 (d, 1H, *J* = 13.5 Hz), 3.43-3.40 (d, 1H, *J* = 13.5 Hz). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 137.6, 135.3, 134.7, 134.5, 134.4, 133.3, 130.2, 129.6, 128.8, 128.0, 119.4, 51.2, 46.0, 35.7. HMS (ESI) calcd for $C_{17}H_{16}ONCl_3NaS$ $[M]^+$ 397.0094; found 397.0089. $[\alpha]^{23}_D$ = -163° (*c* = 1.0, $CHCl_3$). The ee was determined to be 96% by chiral HPLC analysis (Chiralcel AS-H, hexane/ethanol/DEA 85/15/0.1, 1.0 mL/min, λ = 230 nm): t_R (**sulconazole** minor) = 8.7 min, t_R (**sulconazole** major) = 11.8 min.

References

(1) For reviews of H-bonding organocatalysis, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (e) Terada, M. *Synthesis* **2010**, *12*, 1929. (f) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem. Eur. J.* **2010**, *16*, 9350.

(2) For examples of *N*-sulfinyl urea catalysis, see: (a) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (b) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754. (c) Kimmel, K. L.; Weaver, J. W.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121.

(3) For other examples of organocatalysts containing sulfinamide, see: (a) Beck, E. M.; Hyde, A. M.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 4260. (b) Tan, K. L.; Jacobsen, E. N.; *Angew. Chem., Int. Ed.* **2007**, *46*, 1315. (c) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913. (d) Wang, C.; Wu, X.; Zhou, L.; Sun, J. *Chem.- Eur. J.* **2008**, *14*, 8789. (e) Pei, D.; Zhang, Y.; Wei, S.; Wang, M.; Sun, J. *Adv. Synth. Catal.* **2008**, *350*, 619.

(4) For a review on asymmetric Michael additions of thiols, see: Enders, D.; Luettgen, K.; Narine, A. A. *Synthesis* **2007**, *7*, 959. For organocatalytic enantioselective Michael additions of sulfur nucleophiles to α,β-unsaturated carbonyl compounds, see: (a) Dai, L.; Yang, H.; Niu, J.; Chen, F-E. *Synlett* **2012**, *23*, 314. (b) Dong, X-Q.; Fang, X.; Wang, C-J. *Org. Lett.* **2011**, *13*, 4426. (c) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418. (d) Marigo, M.; Schulte, T.; Franzen, J.; Jorgensen, K. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (e) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (f) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth Catal.* **2008**, *350*, 49. For metal-catalyzed enantioselective Michael additions of sulfur nucleophiles to α,β-unsaturated carbonyl compounds, see: (g) Abe, A. M.; Sauerland, S. J.; Koskinen, A. M. *J. Org. Chem.* **2007**, *72*, 5411. (h) Nishamura, K.; Tomioka, K. *J. Org. Chem.* **2002**, *67*, 431. (i) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589. (j) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675. (k) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (l) Dong, X-Q.; Fang, X.; Wang, C.-J. *Org. Lett.* **2011**, *13*, 4426. (m) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089. (n) Hui, Y.-H.;

Jiang, J.; Wang, W.-T.; Chen, W.-L.; Cai, Y.-F.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4290.

(5) For Michael additions of sulfur nucleophiles to nitroalkenes, see: (a) see ref. 2b (b) Li, H.; Wang, J.; Zu, L.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 2585. (c) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823 To obtain a reasonable ee (58%), stoichiometric cinchona alkaloid catalyst was required. Several publications have appeared on asymmetric sulfa-Michael additions to nitroalkenes since the initial publication of our method. See: (d) Palacio, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849. (e) Lu, H-H.; Zhang, F-G.; Meng, X-G.; Duan, S-W.; Xiao, W-J. *Org. Lett.* **2009**, *11*, 3946.

(6) (a) Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (b) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (c) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, *1*, 137.

(7) Fromtling, R. A. *Clinical Microbiology Reviews* **1988**, *1*, 187. Azole antifungals such as sulconazole are known to act by inhibition of the fungal cell CYP51 lanosterol demethylase. Though inhibitory activity data for the enantiomers of sulconazole is not available, *in vitro* studies of very similar azole antifungals have demonstrated that the *R*-enantiomer can be up to 60-fold more active than the *S*-enantiomer. For biological data on azole enantiomers, see: (a) Mangas-Sanchez, J.; Busto, E.; Gotor-Fernandez, V.; Malpartida, F.; Gotor, V. *J. Org. Chem.* **2010**, *76*, 2115. (b) Quaglia, M. G., Donati, E., Desideri, N., Fanali, S., D'Auria, F. D., Tecca, M. *Chirality* **2002**, *14*, 449. (c) Lamb, D. C., Kelly, D. E., Baldwin, B. C., Gozzo, F., Boscott, P., Richards, W. G., Kelly, S. L. *FEMS Microbiology Letters* **1997**, *149*, 25. (d) Foguet, R.; Ramentol, J.; Guglietta, A.; Palacin, C.; Anglada, L. (Ferrer Internacional S.A., Spain) PCT Appl. WO 03/068770, February 4, 2003. (e) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Mueller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807.

(8) The products of thioacetic acid addition to nitroalkenes have been taken on (racemically) to synthesize a variety of biologically relevant taurine derivatives. See: Chen, N.; Xu, J. *Tetrahedron* **2012**, *68*, 2513.

(9) Cyclopentyl methyl ether (CPME) was employed because it provided the highest selectivity in an initial solvent screen. For leading references on the properties of CPME that have made it an increasingly popular industrial solvent, see: (a) Antonucci, V.; Coleman, J.; Ferry, J. B.; Johnson, N.; Mathe, M.; Scott, J. P.; Xu, J. *Org. Process Res. Dev.* **2011**, *15*, 939. (b) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251–258.

(10) For relevant mechanistic studies of H-bonding organocatalysis, see: Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

(11) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *127*, 119.

(12) Matsuoka, Y.; Ishida, Y.; Sasaki, D.; Saigo, K. *Tetrahedron* **2006**, *62*, 8199.

(13) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431.

(14) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125.

(15) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880.

(16) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93.

(17) Ulrich, H.; Sayigh, A. A. *Angew. Chem., Int. Ed.* **1966**, *5*, 704-712.

Chapter 3: Enantio- and Diastereoselective Addition of Cyclohexyl Meldrum's Acid to β- and α,β-Disubstituted Nitroalkenes via *N*-Sulfinyl Urea Catalysis

*Using N-sulfinyl urea catalysis, a method has been developed for the asymmetric synthesis of biologically important γ-amino acids with a high level of efficiency, practicality and unprecedented control of multiple stereocenters. This method is based upon the highly enantio- and diastereoselective addition of cyclohexyl Meldrum's acid as an easily deprotectable monocarboxylic acid equivalent. The addition to both β-substituted and α,β-disubstituted nitroalkenes using N-sulfinyl urea organocatalyst **3.8** is described. The utility of this new method toward drug production is demonstrated by the mole scale preparation of a key precursor to the commercial drug Lyrica using catalyst **3.8** at only 0.2 mol % loading. Moroever, α,β-disubstituted nitroalkene addition products are efficiently converted to γ-amino acid derivatives without epimerization of either stereocenter. This work is published in an article (Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. Chem. Sci. **2012**, 3, 121).*

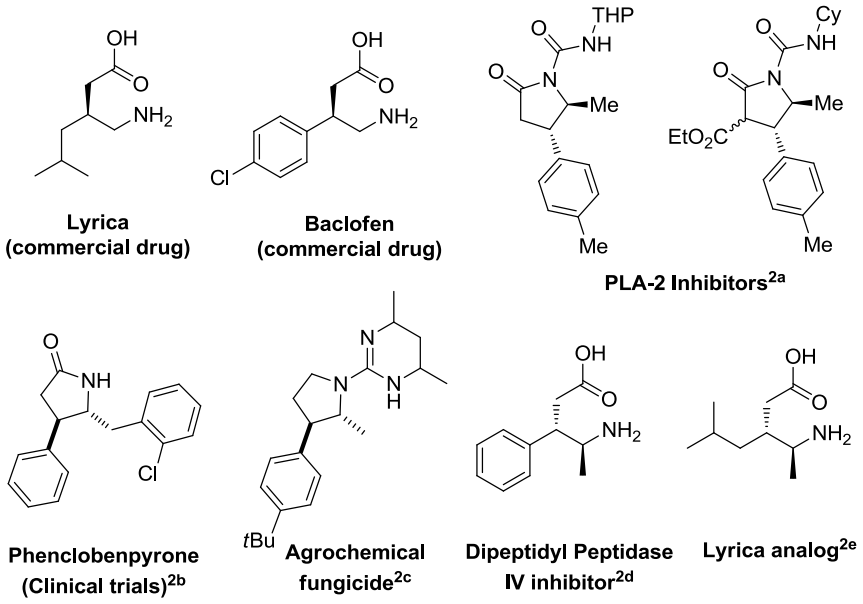
Authorship

The work on enantio- and diastereoselective addition of cyclohexyl Meldrum's acid to nitroalkenes was conducted in collaboration with Dr. Jimmie Weaver.

Introduction

γ-Amino acids are present in numerous drugs, drug candidates and bioactive natural products (Figure 3.1).[1,2] Moreover, this structure can readily be transformed into pyrrolidinones and pyrrolidines, which are also present in a large number of bioactive compounds.

Figure 3.1. Representative Examples of Bioactive γ-Amino Acid Derivatives

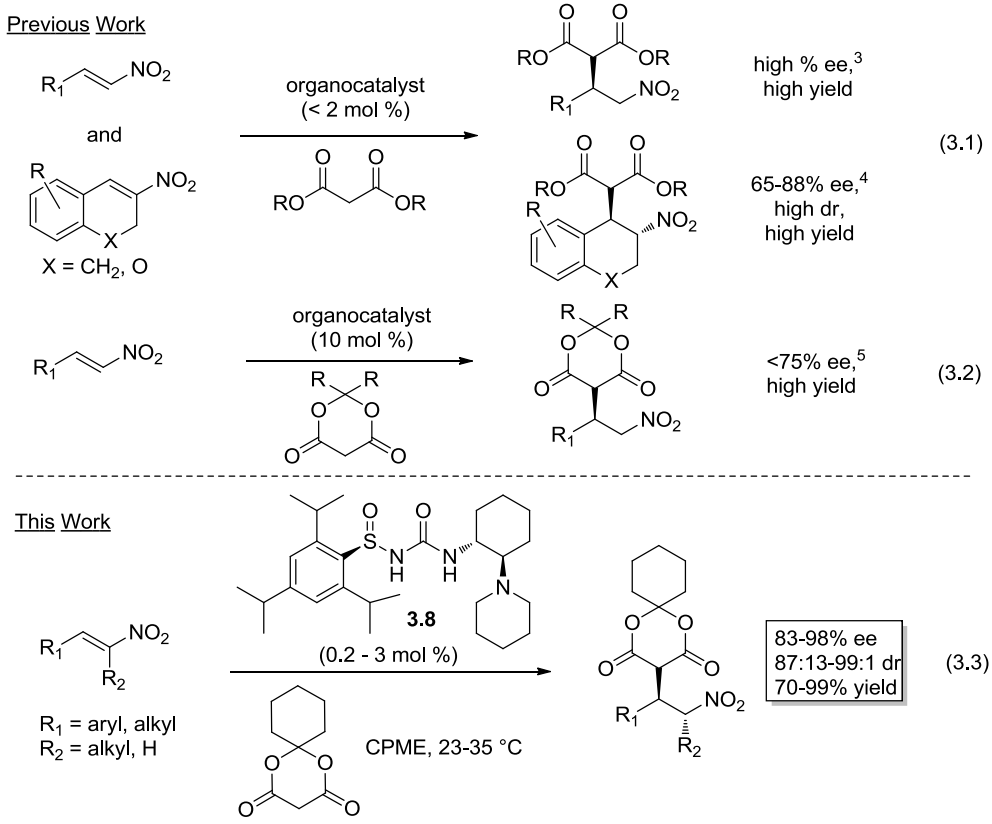


Highly effective organocatalytic methods have consequently been developed for the asymmetric addition of malonates to β-substituted nitroalkenes at low catalyst loading to provide efficient and practical access to γ-amino acid derivatives (eq 3.1).[3] In contrast, only a narrow set of cyclic substrates have been reported for additions to α,β-disubstituted nitroalkenes.[4] Moreover, despite considerable effort, only moderate enantioselectivity has been achieved for the organocatalytic addition of Meldrum's acid derivatives to nitroalkenes (eq 3.2).[5] For each of the reported examples, high catalyst loading was also used.

The successful asymmetric addition of Meldrum's acid with high selectivity and catalyst efficiency is a worthwhile and important goal due to two distinctive properties of the Meldrum's acid structure. First, Meldrum's acid derivatives are more acid labile than malonates due to their acetal framework, thereby enabling a mild and convenient single step, acid catalyzed process for tandem deprotection/decarboxylation to form the corresponding γ-amino acids.[6] Second, Meldrum's acid derivatives (pK_a in DMSO = 7-8)[7] are considerably more acidic than malonates (pK_a in DMSO = 16-17) [7] resulting in new opportunities for reactivity and selectivity. In particular, the previously reported addition of malonates to cyclic nitroalkenes (eq 3.1), presumably provides the more stable *trans*-disubstituted products through thermodynamic control as a consequence of the comparable acidity of the nitroalkane product (pK_a in DMSO =

16-17)[7] and the malonate nucleophile. Unfortunately, only a very modest thermodynamic ratio of tran-/cis-isomers for *acyclic* nitroalkene addition products with α- and β-stereocenters is likely to be observed (vide infra). The much greater acidity of Meldrum's acids relative to both malonates and nitroalkanes should enable efficient *kinetic* control and potentially high selectivity for additions to α,β-disubstituted nitroalkenes.[8]

Figure 3.2. Literature Precedent for Enantioselective Additions of Malonates to Nitroalkenes

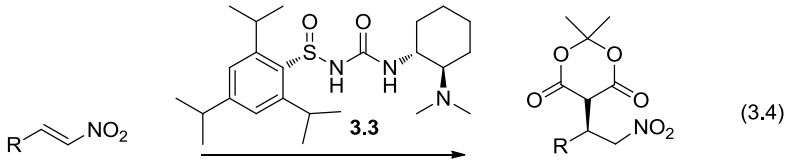


Herein, we report that *N*-sulfinyl urea[9,10] catalyst **3.8** at low catalyst loadings (0.2 – 3 mol %) provides the first highly enantio- and diastereoselective organocatalytic addition of Meldrum's acid derivatives to nitroalkenes (eq 3.3). This work also provides the first example of the organocatalytic addition of any carbon nucleophile to acyclic α,β-disubstituted nitroalkenes to set both the α- and β-stereocenters in acyclic products with high enantio- and diastereoselectivity.[11] Significantly, the Meldrum's acid addition products undergo facile hydrolysis and decarboxylation under acidic conditions followed by reduction to directly afford enantioenriched γ-amino acids with preserved stereochemistry. A representative addition product of Meldrum's acid to an α,β-disubstituted nitroalkene has also been converted to a variety of useful, biologically active γ-amino acid-derived structures[2] without epimerization. The practicality of our method is further demonstrated by the mole scale addition of cyclohexyl Meldrum's acid to nitroalkene **3.1b** at only 0.2 mol % of organocatalyst loading followed by one-step hydrolysis/decarboxylation to provide a known precursor to the drug *S*-Pregabalin (Lyrica),[12] which is used extensively for the treatment of neuropathic pain as well as other disorders.[1b,c]

Results and Discussion

I. Reaction Development

N-Sulfinyl ureas have emerged as promising enantioselective organocatalysts with the sulfinyl group serving as both a chiral directing group and electron withdrawing substituent[10a] and have proven to be particularly effective for the addition of the acidic thioacetic acid pronucleophile.[10b] The previously reported *N*-sulfinyl urea catalyst **3.3**[10b] was used for initial screening in the enantioselective addition of Meldrum's acid to nitroalkenes **3.1**. In cyclopentyl methyl ether (CPME), which has seen increasing use as a solvent for large scale industrial applications,[13] the addition to *trans*-β-nitrostyrene **3.1a** proceeded at rt with 95% ee, while the alkyl nitroalkene **3.1b**, which notably leads to the drug Lyrica,[12] provided the addition product **3.2b** in 87% ee (eq 3.4). With the goal of ultimately applying the method to the synthesis of Lyrica, we focused subsequent optimization studies on substrate **3.1b**.

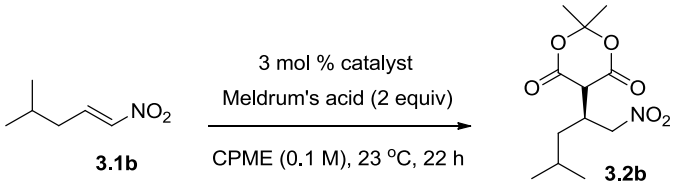


(3.4)

Recent reports for other urea catalysts have shown dramatic differences in selectivity and activity arising from different tertiary amine moieties.[14] On this basis, several new sulfinyl ureas were synthesized and tested in the enantioselective addition of Meldrum's acid to aliphatic nitroalkene **3.1b** (Table 3.1, Figure 3.3). Catalysts **3.4**, **3.5** and **3.6**, all bearing acyclic tertiary amines, reduced the enantioselectivity (entries 2-4). Cyclic tertiary amine catalysts, such as pyrrolidine **3.7** and piperidine **3.8**, showed more promise, with catalyst **3.8** propelling the reaction to 91% conversion and 92% ee (entry 6). Free amine catalyst **3.9** exhibited poor solubility and poor conversion (entry 7). Interestingly, diastereomeric catalyst **3.10** gave drastically reduced selectivity, indicating a substantial matched-mismatched effect arising from the relative configurations of the sulfinyl and 1,2-diamine stereocenters (entry 8). *tert*-Butanesulfinyl urea **3.11** was also tested, but was found to be less selective than the corresponding trisyl sulfinyl urea **3.3** (entry 9).[15]

Low catalyst loading was sought to enhance the practical utility of this transformation. However, the reaction rate was limited by the low solubility of Meldrum's acid in CPME and other nonpolar solvents (more polar solvents result in diminished enantioselectivities). We postulated that using a more hydrophobic Meldrum's acid derivative might circumvent this problem. Indeed, cyclohexyl Meldrum's acid exhibited enhanced (~4-fold, at 23 °C) solubility in CPME. The resulting increase in effective concentration allowed the catalyst loading to be reduced to 1 mol % at room temperature. Additionally, a slight increase in enantioselectivity was observed upon switching to cyclohexyl Meldrum's acid (Table 3.2, entry 2).

Table 3.1. Identification of the Optimal Catalyst

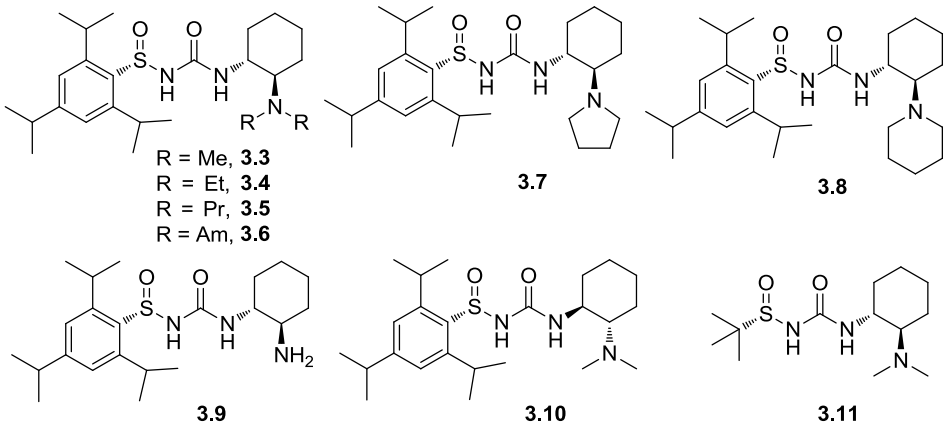


3.1b **3.2b**

entry	catalyst	conv[a] (%)	ee[b] (%)
1	**3.3**	76	87
2	**3.4**	62	80
3	**3.5**	71	77
4	**3.6**	82	81
5	**3.7**	83	91
6	**3.8**	91	92
7	**3.9**	29	70
8	**3.10**	73	-64
9	**3.11**	70	79

[a]Conversion was determined by ^{1}H NMR analysis of the ratio of product to starting material. [b]Enantiomeric excess was determined by chiral HPLC analysis. [c]Absolute stereochemistry was determined by correlation of the optical rotation of product **3.2b** to the literature value.[9b]

Figure 3.3. Catalysts Tested in the Addition of Meldrum's Acid to Nitroalkenes

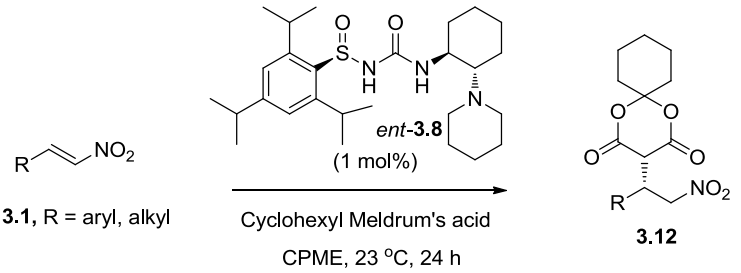


II. Synthetic Scope

The substrate scope was explored for the addition of cyclohexyl Meldrum's acid to various aromatic and aliphatic nitroalkenes **3.1** using 1 mol % of catalyst *ent*-**3.8** (the enantiomer of catalyst **3.8**) (Table 3.2). *trans*-β-Nitrostyrene **3.1a** underwent addition in 95% yield and 98% ee (entry 1), and the aliphatic Lyrica precursor **3.1b** gave the product **3.12b** in 90% yield and 94% ee (entry 2). Substitution around the aromatic ring was well tolerated, giving up to 99% yield and 98% ee over a range of aromatic substrates (entries 3-7). The enantioselectivity was also excellent for both electron-deficient and -rich derivatives (entries 5 and 6, respectively). 2,4-Dichlorophenyl substrate **3.1g** reacted more slowly, but increasing the amount of cyclohexyl

Meldrum's acid afforded the product in 95% yield and 96% ee (entry 7). Moreover, both linear (entry 8) and branched (entries 2 and 9) β-alkyl substituted nitroalkenes provided addition products in good yields and with high selectivities (≥94% ee).

Table 3.2. Catalytic Enantioselective Addition of Cyclohexyl Meldrum's Acid to β-Substituted Nitroalkenes



entry	R	product[a]	yield[b] (%)	ee[c] (%)
1	C_6H_5	**3.12a**	95	98
2	*i*-Bu	**3.12b**	90	94
3	*o*-MeC_6H_4	**3.12c**	94	96
4	*p*-MeC_6H_4	**3.12d**	99	98
5	*p*-$CF_3C_6H_4$	**3.12e**	82	98
6	*p*-$MeOC_6H_4$	**3.12f**	99	96
7	*o,p*-$Cl_2C_6H_3$	**3.12g**[d]	95	96
8	*n*-Pr	**3.12h**	94	94
9	*c*-Hex	**3.12i**	73	96

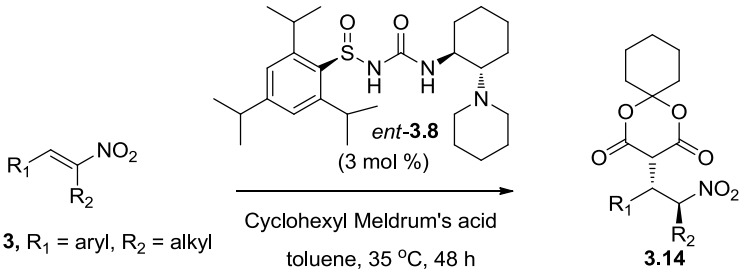
[a]Reactions were performed with 1.0 mol % catalyst loading at 0.3 M concentration of substrate with 1.5 equiv of cyclohexyl Meldrum's acid. [b]Isolated yield of analytically pure material after chromatography. [c]Enantiomeric excess was determined by chiral HPLC. [d]Reaction was run using 3.0 equiv of cyclohexyl Meldrum's acid.

Additions to the more complex α,β-disubstituted nitroalkenes **3.13** generate products **3.14** (Table 3.3) with two stereocenters that are of notable importance for biological applications. However, additions to the α,β-disubstituted nitroalkenes introduce several challenges. Firstly, under basic conditions, the acidity of the α-nitro proton of **3.14** can cause epimerization of that stereocenter, leading to a thermodynamic ratio of diastereomers. Secondly, for acyclic trisubstituted nitroalkenes, the thermodynamic product ratio is close to 1:1.[16] Finally, the more substituted nitroalkenes **3.13** were expected to undergo addition at much slower rates. Nevertheless, we were pleased to find that using catalyst *ent*-**3.8**, α,β-disubstituted nitroalkene **3.13a** afforded addition product **3.14a** with almost perfect diastereoselectivity (Table 3.3, entry 1). An X-ray crystal structure of product **3.14a** revealed that the relative stereochemistry is consistent with delivery of the nucleophile and proton to the same face of the nitroalkene.

We investigated the substrate scope for the enantioselective addition of cyclohexyl Meldrum's acid to a number of cyclic and acyclic α,β-disubstituted nitroalkenes **3.13** (Table 3.3). Despite the lower reactivity of these more challenging substrates, only 3 mol % of catalyst *ent*-**3.8** was necessary for efficient conversion to addition products **3.14**. Parent substrate **3.13a** afforded the product in 97:3 dr, 93% ee, and after chromatography, a 90% isolated yield of a single diastereomer. Variation of the aromatic ring shows a high tolerance for both electron-rich and -

poor derivatives, as well as various para-substituents (entries 2-5). The substituent alpha to the nitro group can also be varied from a simple methyl group to other groups such as benzyl (entry 6) or butyl (entry 7) groups. The less challenging cyclic α,β-disubstituted nitroalkenes are also effective substrates, affording products **3.14h**-**3.14j** with high selectivities and yields. In fact, these cyclic substrates required only 1 mol % catalyst loading.

Table 3.3. Catalytic Enantio- and Diastereoselective Addition of Cyclohexyl Meldrum's Acid to α,β-Disubstituted Nitroalkenes



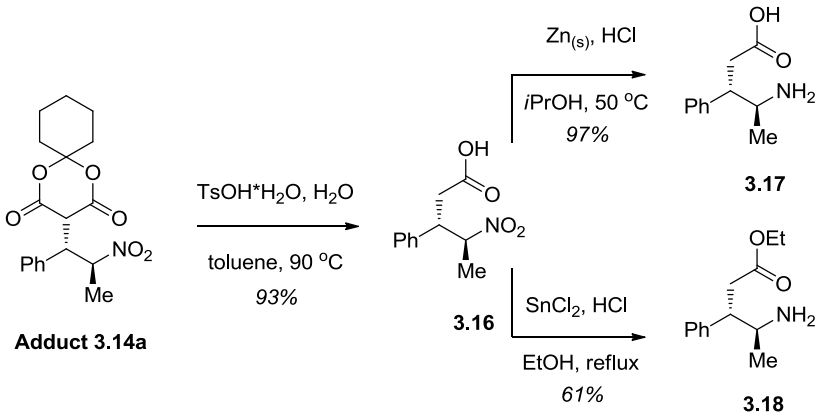
entry	R_1	R_2	product[a]	yield[b] (%)	crude dr[c]	ee[d] (%)
1	C_6H_5	Me	**3.14a**[e]	90	97:3	93
2	*p*-$CF_3C_6H_4$	Me	**3.14b**	71	95:5	94
3	*p*-$MeOC_6H_4$	Me	**3.14c**	91	96:4	92
4	*p*-ClC_6H_4	Me	**3.14d**	77	96:4	91
5	*p*-MeC_6H_4	Me	**3.14e**	91	97:3	92
6	C_6H_5	Bn	**3.14f**	74	98:2	90
7	C_6H_5	*n*-Bu	**3.14g**	70	99:1	83
8	-$(CH_2)_4$-	-$(CH_2)_4$-	**3.14h**[f,g]	78	87:13	91
9	-$(CH_2)_3$-	-$(CH_2)_3$-	**3.14i**[f,g]	93	98:2	97
10	-$(CH_2)_5$-	-$(CH_2)_5$-	**3.14j**[f,h]	92	>99:1	98

[a]Reactions were performed with 3.0 mol % catalyst loading at 0.6 M concentration of substrate and with 3.0 equiv of cyclohexyl Meldrum's acid. [b]Isolated yield of analytically pure single diastereomers after chromatography. [c]Crude diastereomeric ratios were determined by ^{1}H NMR analysis. [d]Enantiomeric excess was determined by chiral HPLC analysis. [e]Absolute and relative stereochemistry was determined from an X-ray crystal structure. [f]Reaction was performed using 1.0 mol % of catalyst. [g]Reaction was performed at 0.05 M concentration. [h]Reaction was performed at 0.3 M concentration using 1.5 equiv of cyclohexyl Meldrum's acid.

III. Applications to the Synthesis of γ-Amino Acid Derivatives

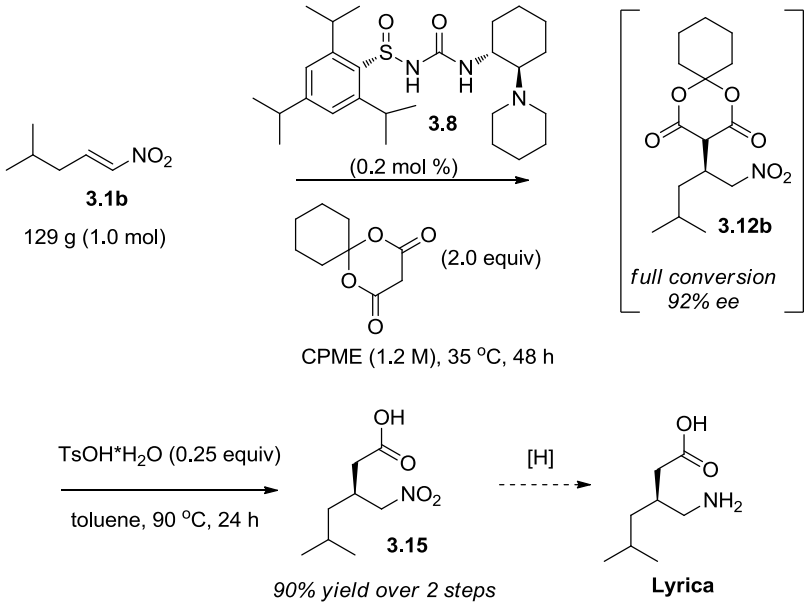
We then sought to demonstrate the utility of these addition products for the construction of biologically relevant γ-amino acid derivatives. Importantly, adduct **3.14a** with two stereocenters can be readily converted to γ-amino acid derivatives[2] with retention of stereochemical information (Scheme 1). TsOH catalyzed one-pot hydrolysis/decarboxylation[12] of **3.14a** affords monoacid **3.16** in 93% yield and in diastereomerically and analytically pure form after simple extractive isolation. Monoacid **3.16** can then either be reduced using Zn dust and HCl to give diastereomerically pure γ-amino acid **3.17**[2d] in 97% yield or by $SnCl_2$ reduction/esterification conditions to provide the amino ethyl ester **3.18** in 61% overall yield also in diastereomerically pure form.

Scheme 3.1. Synthesis of γ-Amino Acid Scaffolds from Adduct **3.14a**



Finally, we sought to demonstrate the utility of our method for drug production with the mole scale synthesis of Lyrica precursor **3.15** (Scheme 3.2). Though 1 mol % catalyst loading is sufficient for laboratory scale chemistry, further reduction of the catalyst loading is desirable for large scale drug production. With mild heating to 35 °C, complete conversion can be achieved with only 0.2 mol % of catalyst **3.8** and with only a very slight reduction in enantioselectivity. The crude addition product can be taken on directly to a one-pot hydrolysis/decarboxylation step, allowing for a telescoped overall process. Key Lyrica intermediate **3.15** was synthesized by this route on a one mole scale in 90% overall yield from nitroalkene **3.1b**. One-step conversion of intermediate **3.15** to Lyrica via hydrogenation has been reported in the literature.[12]

Scheme 3.2. Large-scale Production of Key Lyrica Intermediate



Conclusion

In summary, we have introduced a practical method for constructing optically active γ-amino acids that utilizes cyclohexyl Meldrum's acid as a versatile monocarboxylic acid equivalent and piperidinyl sulfinyl urea **3.8** as a highly selective and efficient organocatalyst. Decarboxylation and nitro reduction can be performed to provide γ-amino acid derivatives without any loss of stereochemistry even for α,β-disubstituted nitroalkene inputs. The viability of this method toward drug production was demonstrated with the mole scale synthesis of Lyrica precursor **3.15** using only 0.2 mol % of catalyst **3.8**. This method is not only the first example of the highly enantioselective addition of Meldrum's acid derivatives to nitroalkenes, but also provides the first example of the organocatalytic addition of any type of carbon nucleophile to acyclic α,β-disubstituted nitroalkenes to set both the α- and β-stereocenters in acyclic products with high enantio- and diastereoselectivity. The reaction is believed to proceed through a transition state similar to that proposed in Chapter 2 for the addition of thioacetic acid to nitroalkenes (Figure 2.4). The key in this case to obtaining high diastereoselectivity is the acidic nature of Meldrum's acid versus the more traditional malonate esters. We believe that Meldrum's acid will be similarly advantageous for a variety of transformations that are currently under investigation.

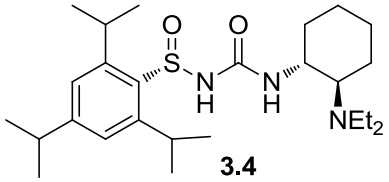
Experimental Section

I. General Experimental. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Cyclopentyl methyl ether (CPME), tetrahydrofuran (THF), diethyl ether, methylene chloride (CH_2Cl_2) and dioxane were passed though columns of activated alumina under nitrogen pressure immediately prior to use. Cyclopentyl methyl ether was additionally distilled prior to passage through alumina to remove BHT stabilizer. All urea catalysts were dried under high vacuum over fresh P_2O_5 overnight prior to use. Dry potassium hydride was stored and weighed under inert atmosphere in the glove box. Diamine ***S*-3.1**[17] and triisopropylbenzenesulfinamide[18,19] were prepared according to literature procedures. Reactions were monitored by thin layer chromatography (TLC) and visualized with ultraviolet light and potassium permanganate stain. Flash column chromatography was carried out with Merck 60 230-240 mesh silica gel. NMR spectra were obtained on a Bruker AVB-400, Bruker AVB-500 or Varian 400 spectrometer, and unless otherwise noted, ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to either the residual solvent peak (^1H, ^{13}C) or TMS (^1H) as an internal standard. Enantiomeric excess was determined using an Agilent 1100 or 1200 series HPLC equipped with a Chiralcel IA column and a multiwavelength detector. IR spectra were recorded on a Nicolet 6700 FTIR spectrometer equipped with an attenuated total reflectance accessory as thin films on a KBr beamsplitter, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. Specific rotations were determined using a Perkin-Elmer 341 polarimeter with a sodium lamp, and concentrations are reported in g/dL. Mass spectra (HRMS) analysis was performed by the Yale Protein Expression Database facility on a 9.4T Bruker Qe FT-ICR MS.

II. General Procedure for the Preparation of Sulfinyl Ureas (Procedure A). To an oven-dried round-bottomed flask equipped with a magnetic stir bar and N_2 inlet was added potassium hydride (3 equiv) and sulfinamide (1.0 equiv). The reaction flask was cooled in an ice-water bath, and THF (0.6 M) was added. The suspension was stirred at 0 ^oC until bubbling ceased. The ice-water bath was removed, and the reaction mixture was allowed to warm to ambient

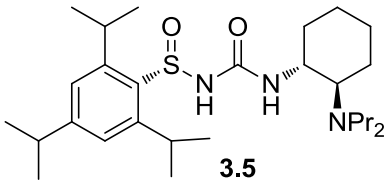
temperature. 1,1'-Carbonyldiimidazole (1.0 equiv) was dissolved in 1,4-dioxane (1.0 M) and added to the reaction mixture, resulting in the formation of a white precipitate, and the reaction mixture was stirred for 1 h. A solution of diamine (1.2 equiv) in THF (1.0 M) was added, and the suspension was stirred at room temperature for 15-24 h. The reaction was quenched with a solution of acetic acid (3 equiv) in THF (1.0 M). The crude product was concentrated *in vacuo* and purified by chromatography or recrystallization.

III. General Procedure for the Preparation of Sulfinyl Ureas (Procedure B).[14a] To a solution of sulfinyl urea **9** in acetonitrile (0.2 M) was added the appropriate aldehyde (5 equiv). After the reaction mixture was stirred for 15 min, $NaBH_3CN$ (2.1 equiv), and 15 min later, acetic acid (5 equiv) were added. The reaction mixture was stirred 3-12 h, then quenched by addition of 1 N $NaOH_{(aq)}$. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with 1 N NaOH. The crude product was concentrated *in vacuo* and purified by reverse phase chromatography.



3.4

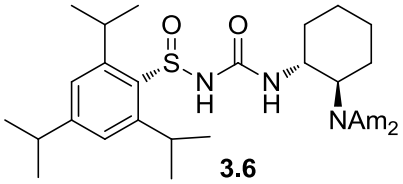
Urea 3.4. The general procedure (B) was followed using urea **3.7** (50 mg, 0.12 mmol), acetaldehyde (70 μL, 0.62 mmol), $NaBH_3CN$ (17 mg, 0.25 mmol), and acetic acid (35 μL, 0.62 mmol). Sulfinyl urea **3.4** was purified by reverse phase chromatography (1:1 MeOH:H_2O to 100% MeOH), to yield 30 mg (53% yield) of a white solid, mp 170 ^oC. IR: 2965, 2931, 1735, 1666, 1628, 1535, 1385, 1265, 1088 cm^{-1}. ^1H NMR (400 MHz, MeOH-d_4) δ 7.12 (s, 2H), 4.05 – 3.61 (br s, 2H), 3.61 – 3.36 (m, 1H), 2.96 – 2.68 (septet, J = 6.9 Hz, 1H,), 2.68 – 2.42 (m, 2H), 2.42 – 2.12 (m, 4H), 1.92 – 1.74 (m, 1H), 1.73 – 1.65 (m, 1H), 1.65 – 1.52 (m, 1H), 1.28 (d, J = 6.9 Hz, 6H), 1.18 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 6.9 Hz, 6H), 1.22-1.13 (m, 4H), 0.88 (t, J = 7.1 Hz, 6H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.07, 152.83, 148.22, 136.62, 123.19, 77.20, 62.71, 52.08, 42.90, 34.33, 32.58, 28.47, 25.74, 24.54, 24.45, 23.99, 23.70, 23.68, 23.33, 14.66. HRMS (ESI) calcd for $C_{26}H_{45}O_2N_3S$ $[M+H]^+$ 464.33053; found 464.32943.



3.5

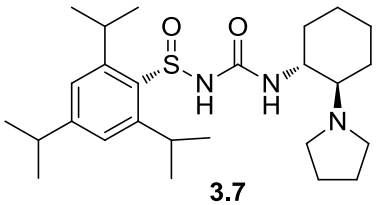
Urea 3.5. The general procedure (B) was followed using urea **3.7** (50 mg, 0.12 mmol), propionaldehyde (44 μL, 0.62 mmol), $NaBH_3CN$ (17 mg, 0.25 mmol), and acetic acid (35 μL, 0.62 mmol). Sulfinyl urea **3.5** was purified by reverse phase chromatography (1:1 MeOH:H_2O to 100% MeOH), to yield 33 mg (55% yield) of a white solid, mp 156-157 ^oC. IR: 3264, 2958, 2930, 2869, 1656, 1597, 1534, 1461, 1383, 1264, 1074, 877 cm^{-1}. ^1H NMR (400 MHz, MeOH-d_4) δ 7.22 (s, 2H), 3.89 (br s, 2H), 3.54 (td, J = 10.8, 4.0 Hz, 1H), 2.94 (septet, J = 6.9 Hz, 1H), 2.53 – 2.22 (m, 5H), 1.97 – 1.86 (m, 1H), 1.86 – 1.77 (m, 1H), 1.71 (m, 1H), 1.38 (d, J = 6.8 Hz,

6H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.49 – 1.12 (m, 7H), 0.96 – 0.93 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.11, 152.85, 148.15, 136.82, 123.16, 77.19, 73.93, 63.30, 52.14, 51.60, 34.34, 32.60, 28.46, 25.74, 24.54, 24.44, 24.00, 23.69, 23.14, 22.26, 11.84. HRMS (ESI) calcd for $C_{28}H_{49}O_2N_3S$ $[M+H]^+$ 492.36183; found 492.36060.



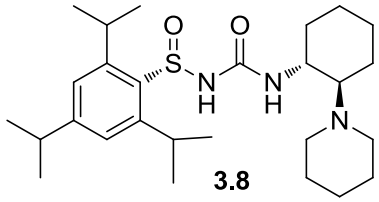
3.6

Urea 3.6. The general procedure (B) was followed using urea **3.7** (50 mg, 0.12 mmol), valeraldehyde (66 μL, 0.62 mmol), $NaBH_3CN$ (17 mg, 0.25 mmol), and acetic acid (35 μL, 0.62 mmol). Sulfinyl urea **3.6** was purified by reverse phase chromatography (1:1 MeOH:H_2O to 100% MeOH), to yield 48 mg (72% yield) of a white solid, mp 166-167 °C. IR: 2959, 2930, 2860, 1669, 1597, 1486, 1384, 1264, 1095 cm^{-1}. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.22 (s, 2H), 3.92 (br s, 2H), 3.55 (m, 1H), 2.99 – 2.89 (septet, *J* = 6.8 Hz, 1H), 2.60 – 2.21 (m, 6H), 1.89 (m, 1H), 1.84, (m, 1H), 1.72 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 6H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 6H), 1.47 – 1.12 (m, 16H), 0.87 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.10, 152.77, 148.17, 136.95, 123.24, 63.15, 52.16, 49.54, 34.35, 32.49, 29.61, 28.80, 28.47, 25.75, 24.55, 24.42, 24.02, 23.71, 23.11, 22.58, 14.00. HRMS (ESI) calcd for $C_{32}H_{57}O_2N_3S$ $[M+H]^+$ 548.42443; found 548.42200.



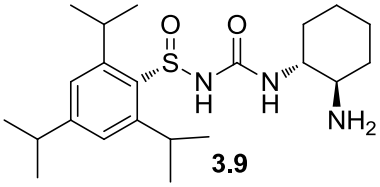
3.7

Urea 3.7. The general procedure (B) was followed using urea **3.7** (50 mg, 0.12 mmol), succinaldehyde$_{(aq)}$[20] (0.41 mL, 1.5 M), $NaBH_3CN$ (17 mg, 0.25 mmol), and acetic acid (35 μL, 0.62 mmol). Sulfinyl urea **3.7** was purified by reverse phase chromatography (1:1 MeOH:H_2O to 100% MeOH), to yield 27 mg (47% yield) of a white solid, mp 114-115 °C. IR: 2964, 2935, 2868, 1666, 1597, 1540, 1384, 1264, 1075, 906 cm^{-1}. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.23 (s, 2H), 3.94 (br s, 2H), 3.68 – 3.59 (m, 1H), 3.00 – 2.91 (septet, *J* = 6.8 Hz, 1H), 2.77 – 2.56 (m, 4H), 2.50 (m, 1H), 2.22 (m, 1H), 1.89-1.80 (m, 2H), 1.78-1.66 (m, 5H), 1.45-1.30 (m, 4H), 1.39 (d, *J* = 6.8 Hz, 6H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.51, 153.27, 148.77, 137.05, 123.65, 77.63, 62.41, 53.84, 47.59, 34.79, 32.70, 28.89, 25.32, 24.97, 24.72, 24.47, 24.15, 22.66. HRMS (ESI) calcd for $C_{26}H_{43}O_2N_3S$ $[M+H]^+$ 462.31488; found 462.31407.



3.8

Urea 3.8. The general procedure (A) was followed using (*S*)-triisopropylbenzenesulfinamide (4.0 g, 15 mmol), potassium hydride (1.8 g, 45 mmol), 1,1'-carbonyldiimidazole (2.4 g, 15 mmol), and (*R*,*R*)-*trans*-1-piperidyl-2-aminocyclohexane (3.3 g, 18 mmol). Sulfinyl urea **3.8** was purified by trituration with methanol/water, then recrystallization from 0.4 L of warm methanol, to yield 4.1 g (59% yield) of a white solid, mp 169 ^{o}C. IR: 3325, 2959, 2929, 2855, 2799, 1655, 1597, 1535, 1384, 1206, 1076, 839 cm^{-1}. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.11 (s, 2H), 3.81 (br s, 2H), 3.48 – 3.40 (m, 1H), 2.83 (septet, J = 6.9 Hz, 1H), 2.53 (m, 2H), 2.27 – 2.10 (m, 4H), 1.79 (m, 1H), 1.69 (m, 1H), 1.59 (m, 1H), 1.43 – 0.98 (m, 10H), 1.27 (d, J = 6.8 Hz, 6H), 1.16 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.49, 152.94, 148.62, 136.73, 123.34, 67.99, 51.77, 50.51, 49.41, 34.55, 33.08, 28.70, 26.75, 25.80, 25.07, 24.79, 24.20, 23.96, 23.91, 23.30. HRMS (ESI) calcd for $C_{27}H_{45}O_2N_3S$ $[M+H]^+$ 476.33053; found 476.32973.



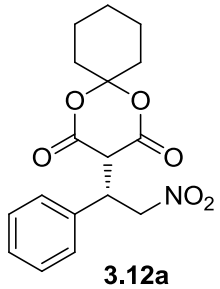
3.9

Urea 3.9. The general procedure (A) was followed using (*S*)-triisopropylbenzenesulfinamide (0.27 g, 1.0 mmol), potassium hydride (0.12 g, 3.0 mmol), 1,1'-carbonyldiimidazole (0.16 g, 1.0 mmol), and (1*R*,2*R*)-(-)-*trans*-1,2-cyclohexanediamine (0.34 g, 3.0 mmol). Sulfinyl urea **3.9** was purified by reverse phase chromatography (5:95 MeOH:H_2O to 100% MeOH), to yield 0.27 g (65% yield) of a white solid, mp 205 ^{o}C. IR: 3301, 2960, 2928, 2864, 1664, 1597, 1543, 1384, 1057, 877 cm^{-1}. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.22 (s, 2H), 3.95 (br s, 2H), 3.45 – 3.36 (m, 1H), 3.01 – 2.84 (septet, J = 6.8 Hz, 1H), 2.46 (m, 1H), 2.11 – 1.89 (m, 2H), 1.76-1.70 (m, 2H), 1.42 – 1.22 (m, 4H), 1.38 (d, J = 6.8 Hz, 6H), 1.28 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 6H). ^{13}C NMR (500 MHz, MeOH-d_4) δ 158.84, 154.63, 150.56, 137.47, 124.67, 57.83, 56.24, 36.08, 35.06, 33.90, 30.29, 26.58, 26.25, 25.56, 24.72. HRMS (ESI) calcd for $C_{22}H_{37}O_2N_3S$ $[M+H]^+$ 408.26793; found 408.26610.

IV. Representative Procedure for Racemic Addition of Cyclohexyl Meldrum's Acid to *trans*-β-Nitrostyrene. To a solution of *trans*-β-nitrostyrene (15 mg, 0.10 mmol) in dichloromethane (1.0 mL) was added a few drops of triethylamine. Cyclohexyl Meldrum's acid (36 mg, 0.20 mmol) was added, and the reaction mixture was stirred for 18 h. The triethylamine was then removed by eluting the reaction mixture through a plug of silica gel with dichloromethane.

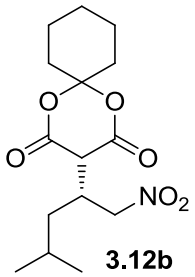
V. Representative Procedure for Enantio- and Diastereoselective Addition of Cyclohexyl Meldrum's Acid to *trans*-β-Nitrostyrenes. A mixture of *trans*-β-nitrostyrene (45 mg, 0.30 mmol) and sulfinyl urea catalyst *ent*-**8** (1.4 mg, 0.003 mmol) was dissolved in cyclopentyl

methyl ether (1.0 mL). Cyclohexyl Meldrum's acid (83 mg, 0.45 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, then eluted through a plug of silica with dichloromethane to remove the catalyst and then concentrated *in vacuo*. The crude product was purified by silica gel chromatography. Enantiomeric excess was determined by chiral HPLC analysis.



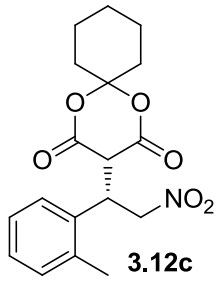
3.12a

3.12a: (*R*)-3-(2-Nitro-1-phenylethyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 95 mg (95% yield) of a viscous colorless oil was isolated by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 98% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 12.2 min, t_R (major) = 13.5 min) $[\alpha]_D^{20}$ = -8.5 (*c* 1.0, $CHCl_3$): IR (neat): 2943, 1778, 1737, 1551, 1496, 1453, 1368, 1299, 1265, 1064, 986, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H), 5.45 (dd, *J* = 14.0, 9.1 Hz, 1H), 5.04 (dd, *J* = 14.0, 6.5 Hz, 1H), 4.68 (ddd, *J* = 9.1, 6.5, 3.1 Hz, 1H), 4.05 (d, *J* = 3.1 Hz, 1H), 1.96 – 1.87 (m, 2H), 1.74 – 1.66 (m, 2H), 1.60 (m, 2H), 1.54 – 1.40 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.53, 164.05, 135.19, 129.20, 128.92, 128.80, 106.71, 76.02, 48.89, 41.98, 36.82, 36.64, 23.81, 22.29, 21.70. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{19}NO_6$, 334.12851; found, 334.12830**.**



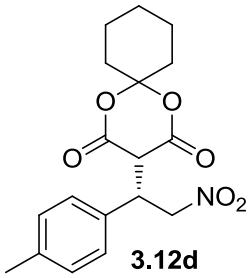
3.12b

3.12b: (*R*)-3-(4-Methyl-1-nitropentan-2-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 85 mg (90% yield) of a viscous colorless oil was isolated by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 94% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 7.6 min, t_R (major) = 7.2 min) $[\alpha]_D^{20}$ = -1.3 (*c* 1.0, $CHCl_3$): IR (neat): 2956, 2871, 1778, 1739, 1550, 1466, 1452, 1369, 1307, 1274, 1064, 981, 853 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.93 (dd, *J* = 13.3, 10.3 Hz, 1H), 4.46 (dd, *J* = 13.3, 4.2 Hz, 1H), 3.83 (d, *J* = 2.5 Hz, 1H), 3.33 – 3.19 (m, 1H), 1.91 (m, 4H), 1.76 – 1.68 (m, 2H), 1.67 – 1.60 (m, 2H), 1.57 – 1.42 (m, 4H), 1.17 – 1.10 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.19, 163.95, 106.34, 75.77, 47.32, 38.11, 36.61, 36.05, 34.45, 25.64, 23.98, 23.13, 22.59, 21.66, 21.42. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{15}H_{23}NO_6$, 314.15981; found, 314.15973**.**



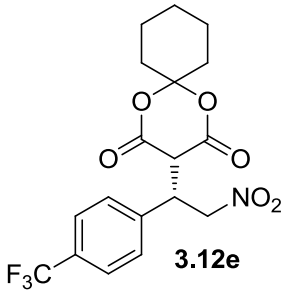
3.12c

3.12c: (*R*)-3-(-2-Nitro-1-o-tolylethyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 98 mg (94% yield) of a colorless oil was isolated by flash column chromatography using 70:30:1 hexanes:CPME:AcOH as eluent: 96% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 11.3 min, t_R (major) = 13.7 min) $[\alpha]_D^{20}$ = -88.9 (*c* 0.44, $CHCl_3$): IR (neat): 3023, 2944, 1775, 1738, 1552, 1493, 1452, 1368, 1304, 1272, 1065, 985, 853 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 1H), 7.20 – 7.13 (m, 3H), 5.28 (dd, *J* = 13.7, 9.0 Hz, 1H), 4.96 – 4.89 (ddd, *J* = 9.0, 6.6, 3.1 Hz, 1H), 4.83 (dd, *J* = 13.7, 6.6 Hz, 1H), 3.90 (d, *J* = 3.1 Hz, 1H), 2.43 (s, 3H), 1.93 – 1.85 (m, 2H), 1.71 – 1.57 (m, 6H), 1.43 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.16, 164.22, 137.05, 134.97, 131.66, 128.70, 127.24, 127.19, 106.94, 75.61, 48.66, 37.09, 37.06, 36.74, 24.10, 22.58, 21.98, 19.79. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{21}NO_6$, 348.14416; found, 348.14433**.**



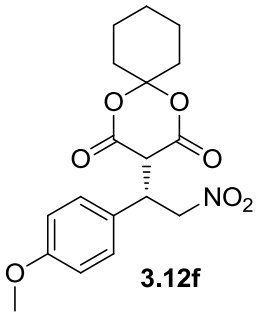
3.12d

3.12d: (*R*)-3-(2-Nitro-1-p-tolylethyl)-1,5-dioxaspiro[5.5]un decane-2,4-dione: 103 mg (99% yield) of a viscous colorless oil was isolated by flash column chromatography using 70:30:1 hexanes:CPME:AcOH as eluent: 98% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 12.0 min, t_R (major) = 13.9 min) $[\alpha]_D^{20}$ = -19.4 (*c* 0.77, $CHCl_3$): IR (neat): 2945, 1776, 1738, 1552, 1516, 1452, 1368, 1300, 1272, 1068, 988, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 5.32 (dd, *J* = 13.9, 9.0 Hz, 1H), 4.92 (dd, *J* = 13.9, 6.6 Hz, 1H), 4.53 (ddd, *J* = 9.0, 6.6, 3.1 Hz, 1H), 3.94 (d, *J* = 3.1 Hz, 1H), 2.24 (s, 3H), 1.86 – 1.77 (m, 2H), 1.64 – 1.30 (m, 8H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.04, 164.58, 139.10, 132.55, 130.23, 129.21, 107.09, 76.65, 49.41, 42.11, 37.24, 37.05, 24.27, 22.73, 22.15, 21.45. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{21}NO_6$, 348.14416; found, 348.14317**.**



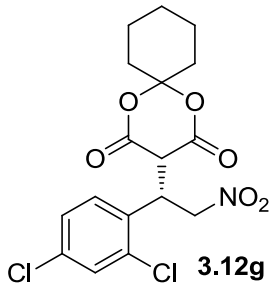
3.12e

3.12e: (*R*)-3-(2-Nitro-1-(4-(trifluoromethyl)phenyl)ethyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 99 mg (82% yield) of a viscous colorless oil was isolated by flash column chromatography using 50:50:1 hexanes:DCM:AcOH as eluent: 98% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 1 mL/min, 210 nm, t_R (minor) = 14.3 min, t_R (major) = 18.2 min) $[\alpha]_D^{20}$ = -13.0 (*c* 0.93, $CHCl_3$): IR (neat): 3024, 2949, 1779, 1740, 1622, 1555, 1453, 1369, 1324, 1275, 1069, 1001, 844 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.13 (d, *J* = 8.0 Hz, 2H), 5.29 (dd, *J* = 13.7, 9.0 Hz, 1H), 5.00 (dd, *J* = 13.7, 6.6 Hz, 1H), 4.65 (ddd, *J* = 9.0, 6.6, 3.1 Hz, 1H), 4.03 (d, *J* = 3.1 Hz, 1H), 1.87 – 1.84 (m, 2H), 1.61 – 1.59 (m, 6H), 1.39-1.38 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.16, 163.59, 139.19, 130.94 (dd, *J* = 65.3, 32.5 Hz), 129.69, 126.00 (q, *J* = 3.7 Hz), 123.69 (q, *J* = 272.4 Hz), 106.91, 75.71, 48.84, 41.25, 36.59, 36.36, 23.78, 22.38, 21.60. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{18}F_3NO_6$, 402.11590; found, 402.11613**.**



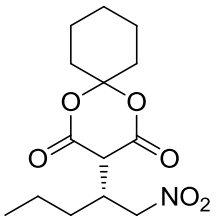
3.12f

3.12f: (*R*)-3-(1-(4-Methoxyphenyl)-2-nitroethyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 108 mg (99% yield) of a viscous colorless oil was isolated by flash column chromatography using 50:50:1 hexanes:DCM:AcOH as eluent: 96% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 16.7 min, t_R (major) = 18.7 min) $[\alpha]_D^{20}$ = -20.6 (*c* 0.73, $CHCl_3$): IR (neat): 2959, 1781, 1736, 1553, 1514, 1452, 1368, 1300, 1251, 1068, 986, 834 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.38 (dd, *J* = 13.9, 8.8 Hz, 1H), 5.02 (dd, *J* = 13.9, 6.8 Hz, 1H), 4.67 – 4.54 (ddd, *J* = 8.8, 6.8, 3.1 Hz, 1H), 4.03 (d, *J* = 3.1 Hz, 1H), 3.79 (s, 3H), 1.96 – 1.84 (m, 2H), 1.71 – 1.40 (m, 8H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.06, 164.63, 160.19, 130.61, 127.38, 114.87, 107.07, 76.84, 55.68, 49.49, 41.85, 37.23, 37.09, 24.26, 22.73, 22.15. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{21}NO_7$, 364.13908; found, 364.13880**.**



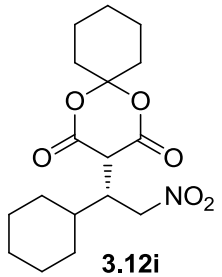
3.12g

3.12g: (*R*)-3-(1-(2,4-Dichlorophenyl)-2-nitroethyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 114 mg (95% yield) of a viscous colorless oil was isolated by flash column chromatography using 50:50:1 hexanes:DCM:AcOH as eluent: 96% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 12.6 min, t_R (major) = 15.5 min) $[\alpha]_D^{20}$ = -2.5 (*c* 0.73, $CHCl_3$): IR (neat): 2944, 1784, 1739, 1553, 1475, 1452, 1368, 1302, 1274, 1063, 974, 852 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 8.5, 2.2 Hz, 1H), 5.12 – 5.05 (td, *J* = 7.4, 2.8 Hz, 1H), 5.00 (d, *J* = 7.4 Hz, 2H), 4.06 (d, *J* = 2.8 Hz, 1H), 1.95 (m, 4H), 1.80 – 1.71 (m, 2H), 1.66 (m, 2H), 1.53 – 1.43 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 163.90, 163.40, 135.39, 135.11, 132.94, 130.48, 130.37, 128.25, 107.32, 73.53, 48.35, 37.23, 36.79, 36.03, 24.37, 23.02, 22.15. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{17}Cl_2NO_6$, 402.05057; found, 402.05040**.**



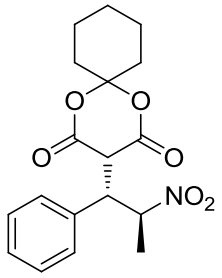
3.12h

3.12h: (*R*)-3-(1-Nitropentan-2-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 84 mg (94% yield) of a viscous colorless oil was isolated by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 94% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 1 mL/min, 210 nm, t_R (minor) = 11.4 min, t_R (major) = 13.5 min) $[\alpha]_D^{20}$ = +11.2 (*c* 0.50, $CHCl_3$): IR (neat): 2945, 2874, 1780, 1739, 1551, 1453, 1369, 1305, 1274, 1066, 976, 854 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (dd, *J* = 13.4, 10.0 Hz, 1H), 4.58 (dd, *J* = 13.4, 4.5 Hz, 1H), 3.93 (d, *J* = 2.5 Hz, 1H), 3.30 (tddd, *J* = 12.2, 10.0, 4.5, 2.5 Hz, 1H), 2.09 – 1.93 (m, 4H), 1.80 (dt, *J* = 12.2, 6.3 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.64 – 1.33 (m, 6H), 0.96 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.56, 106.79, 76.38, 47.60, 37.06, 36.70, 36.42, 31.83, 24.41, 23.01, 22.11, 20.98, 14.14. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{21}NO_6$, 300.14416; found, 300.14400**.**



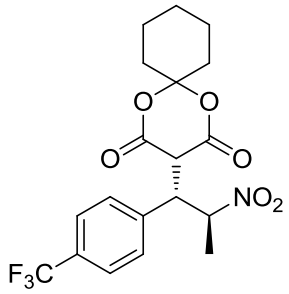
3.12i

3.12i:(*R*)-3-(1-Cyclohexyl-2-nitroethyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 74 mg (73% yield) of a viscous colorless oil was isolated by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 96% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 7.8 min, t_R (major) = 8.2 min) $[\alpha]_D^{20}$ = -0.6 (*c* 0.48, $CHCl_3$): IR (neat): 2928, 2855, 1780, 1740, 1552, 1451, 1369, 1305, 1265, 1067, 963, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (dd, *J* = 13.2, 10.2 Hz, 1H), 4.67 (dd, *J* = 13.2, 3.8 Hz, 1H), 3.85 (d, *J* = 2.1 Hz, 1H), 3.24 – 3.12 (m, 1H), 2.08 – 1.95 (m, 4H), 1.82 (m, 4H), 1.78 – 1.62 (m, 5H), 1.55 (m, 2H), 1.47 (m, 1H), 1.25 – 1.05 (m, 5H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.61, 106.35, 75.75, 45.37, 41.90, 37.74, 36.56, 36.15, 31.33, 30.87, 26.29, 26.04, 25.81, 23.99, 22.57, 21.68. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{25}NO_6$, 340.17546; found, 340.17550**.**



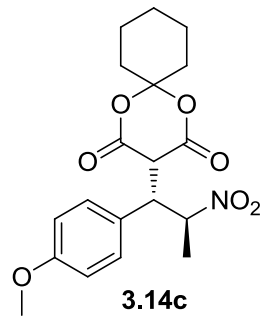
3.14a

3.14a: 3-((1*R*,2*S*)-(2-Nitro-1-phenylpropyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 94 mg (90% yield) of a single diastereomer, crude dr = 97:3, was isolated as a white solid, mp= 111 °C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 93% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 1 mL/min, 210 nm, t_R (minor) = 12.4 min, t_R (major) = 10.6 min) $[\alpha]_D^{20}$ = +22.1 (*c* 0.53, $CHCl_3$): IR (neat): 3021, 2946, 2870, 1776, 1741, 1549, 1497, 1452, 1368, 1297, 1274, 1070, 998, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.90 (dq, *J* = 13.4, 6.7 Hz, 1H), 4.28 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.81 (d, *J* = 3.1 Hz, 1H), 1.92 – 1.78 (m, 2H), 1.71 – 1.63 (m, 2H), 1.62 – 1.55 (m, 2H), 1.47-1.42 (m, 4H), 1.44 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (500 MHz, $CDCl_3$) δ 164.51, 164.19, 134.91, 129.74, 129.25, 128.75, 106.45, 83.31, 48.85, 48.53, 36.79, 36.69, 23.81, 22.25, 21.67, 19.31. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{21}NO_6$, 348.14416; found, 348.14377**.**



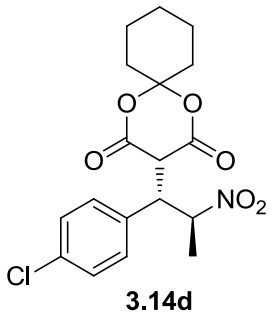
3.14b

3.14b: 3-((1*R*,2*S*)-(2-Nitro-1-phenylhexyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 88 mg (71% yield) of a single diastereomer, crude dr = 95:5, was isolated as a white solid, mp 66-67 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 94% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 1 mL/min, 210 nm, t_R (minor) = 11.8 min, t_R (major) = 12.9 min) $[\alpha]_D^{20}$ = -4.0 (*c* 1.0, $CHCl_3$): IR (neat): 3024, 2947, 1777, 1742, 1621, 1552, 1453, 1369, 1325, 1276, 1069, 1001, 846 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 5.93 (dq, *J* = 11.5, 6.7 Hz, 1H), 4.35 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.85 (d, *J* = 3.0 Hz, 1H), 1.98 – 1.84 (m, 2H), 1.67 (m, 6H), 1.55 – 1.42 (m, 2H), 1.44 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 164.59, 164.13, 139.39, 131.42 (dd, *J* = 65.6, 32.9 Hz), 130.96, 126.52 (q, *J* = 3.5 Hz), 124.11 (q, *J* = 271.9 Hz), 107.07, 83.35, 48.77, 48.65, 37.00, 36.93, 24.24, 22.79, 22.02, 19.69. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{19}H_{20}F_3NO_6$, 416.13155; found, 416.13137**.**



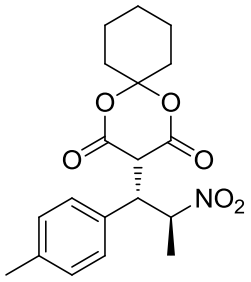
3.14c

3.14c: 3-((1*R*,2*S*)-(1-(4-methoxyphenyl)-2-nitropropyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 103 mg (91% yield) of a single diastereomer, crude dr = 96:4, was isolated as a pale yellow solid, mp 124-125 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 92% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 1 mL/min, 210 nm, t_R (minor) = 19.9 min, t_R (major) = 14.1 min) $[\alpha]_D^{20}$ = -11.9 (*c* 1.0, $CHCl_3$): IR (neat): 2945, 1776, 1741, 1610, 1549, 1513, 1452, 1368, 1296, 1265, 1070, 998, 835 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.14 (dt, *J* = 8.5, 3.5 Hz, 2H), 6.87 – 6.74 (dt, *J* = 8.5, 3.5 Hz, 2H), 5.80 (dq, *J* = 11.7, 6.7 Hz, 1H), 4.16 (dd, *J* = 11.5, 3.1 Hz, 1H), 3.75 (s, 3H), 3.73 (d, *J* = 3.1 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.60 (m, 2H), 1.54 (m, 2H), 1.46 (m, 2H), 1.43 – 1.36 (m, 2H), 1.36 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (500 MHz, $CDCl_3$) δ 164.58, 164.30, 159.69, 130.94, 126.53, 114.50, 106.38, 83.59, 55.23, 48.56, 48.19, 36.82, 36.65, 23.82, 22.27, 21.67, 19.32. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{19}H_{23}NO_7$, 378.15473; found, 378.15460**.**



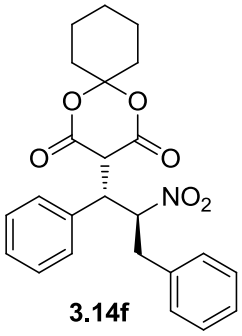
3.14d

3.14d: 3-((1*R*,2*S*)-(1-(4-chlorophenyl)-2-nitropropyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 87 mg (77% yield) of a single diastereomer, crude dr = 96:4, was isolated as a white solid, mp 123-124 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 91% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 0.8 mL/min, 210 nm, t_R (minor) = 18.4 min, t_R (major) = 16.3 min) $[\alpha]_D^{20}$ = -13.5 (*c* 2.0, $CHCl_3$): IR (neat): 2943, 2868, 1778, 1742, 1551, 1493, 1452, 1368, 1299, 1275, 1071 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 4H), 5.82 (dq, *J* = 11.6, 6.7 Hz, 1H), 4.20 (dd, *J* = 11.5, 3.1 Hz, 1H), 3.76 (d, *J* = 3.1 Hz, 1H), 1.88 – 1.78 (m, 2H), 1.62 (m, 6H), 1.39 (m, 2H), 1.38 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.28, 163.87, 134.81, 133.31, 131.34, 129.36, 106.50, 83.15, 48.37, 48.01, 36.65, 36.54, 23.82, 22.34, 21.61, 19.26. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{20}ClNO_6$, 382.10519; found, 382.10497**.**



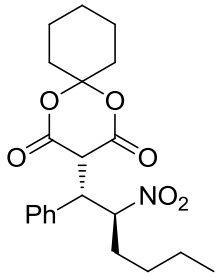
3.14e

3.14e:3-((1*R*,2*S*)-(1-(4-methylphenyl)-2-nitropropyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 98 mg (91% yield) of a single diastereomer, crude dr = 97:3, was isolated as a white solid, mp 142-143 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 92% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 0.8 mL/min, 210 nm, t_R (minor) = 14.7 min, t_R (major) = 13.0 min) $[\alpha]_D^{20}$ = -12.4 (*c* 2.0, $CHCl_3$): IR (neat): 2942, 2867, 1777, 1742, 1549, 1515, 1452, 1368, 1298, 1274, 1069 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.83 (dq, *J* = 11.6, 6.7 Hz, 1H), 4.18 (dd, *J* = 11.6, 3.1 Hz, 1H), 3.73 (d, *J* = 3.1 Hz, 1H), 2.29 (s, 3H), 1.85 – 1.77 (m, 2H), 1.61 (m, 2H), 1.55 (m, 2H), 1.46 – 1.37 (m, 4H), 1.38 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.55, 164.24, 138.60, 131.77, 129.86, 129.59, 106.36, 83.44, 48.56, 36.79, 36.68, 23.82, 22.25, 21.68, 20.98, 19.29. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{19}H_{23}NO_6$, 362.15981; found, 362.16030**.**



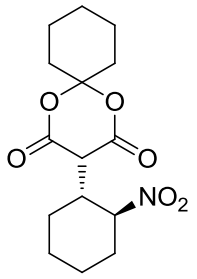
3.14f

3.14f: 3-((1*R*,2*S*)-(3-Phenyl-2-nitro-1-phenylpropyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 94 mg (74% yield) of a single diastereomer, crude dr = 98:2, was isolated as a white solid, mp 123-124 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 90% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 1 mL/min, 210 nm, t_R (minor) = 14.7 min, t_R (major) = 13.8 min) $[\alpha]_D^{20}$ = -18.3 (*c* 0.82, $CHCl_3$): IR (neat): 3026, 2943, 1778, 1743, 1552, 1495, 1455, 1368, 1299, 1267, 1072, 993, 859 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.31 (m, 5H), 7.26 (d, *J* = 3.0 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.07 – 6.92 (m, 2H), 6.02 (ddd, *J* = 11.8, 9.6, 4.1 Hz, 1H), 4.35 (dd, *J* = 11.8, 3.1 Hz, 1H), 3.66 (d, *J* = 3.1 Hz, 1H), 3.04 – 2.84 (m, 2H), 1.86 – 1.74 (m, 2H), 1.61 (m, 2H), 1.55 – 1.48 (m, 2H), 1.44 – 1.31 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.56, 135.45, 134.81, 130.42, 129.88, 129.43, 129.16, 129.09, 127.95, 106.95, 90.76, 77.22, 48.98, 48.49, 39.44, 37.21, 24.23, 22.67, 22.11. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{24}H_{25}NO_6$, 424.17546; found, 424.17557**.**



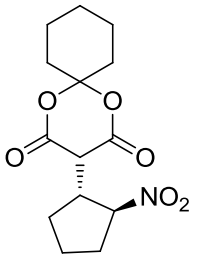
3.14g

3.14g: 3-((1*R*,2*S*)-(2-Nitro-1-phenylhexyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 82 mg (70% yield) of a single diastereomer, crude dr = 99:1, was isolated as a white solid, mp 95-96 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 83% ee (Chiralcel IA, 92 (1% TFA):8 hexanes:EtOH, 1 mL/min, 210 nm, t_R (minor) = 8.4 min, t_R (major) = 8.0 min) $[\alpha]_D^{20}$ = -12.2 (*c* 0.59, $CHCl_3$): IR (neat): 2959, 2873, 1777, 1745, 1550, 1496, 1453, 1368, 1299, 1264, 1077, 992, 853 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 5H), 5.82 (ddd, *J* = 11.7, 10.4, 3.0 Hz, 1H), 4.31 (dd, *J* = 11.7, 3.2 Hz, 1H), 3.67 (d, *J* = 3.2 Hz, 1H), 1.83 (m, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.56 (m, 3H), 1.41 (m, 4H), 1.34 – 1.25 (m, 3H), 1.24 – 1.14 (m, 1H), 0.81 (t, *J* = 7.0 Hz, 3H).^{13}C NMR (500 MHz, $CDCl_3$) δ 164.33, 164.21, 134.56, 129.76, 129.24, 128.77, 106.44, 88.76, 48.49, 48.15, 36.91, 36.70, 32.48, 27.41, 23.79, 22.21, 21.75, 21.66, 13.56. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{21}H_{27}NO_6$, 390.19111; found, 390.19107**.**



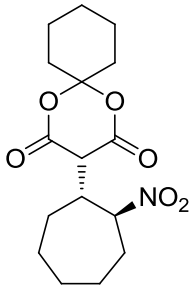
3.14h

3.14h: 3-((1*R*,2*S*)-(2-Nitrocyclohexyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 73 mg (78% yield) of a single diastereomer, crude dr = 87:13, was isolated as a white solid, mp 149 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 91% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 8.9 min, t_R (major) = 9.9 min) $[\alpha]_D^{20}$ = -15.4 (*c* 0.57, $CHCl_3$): IR (neat): 2946, 2867, 1778, 1743, 1547, 1453, 1369, 1295, 1265, 1056, 1000, 850 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (td, *J* = 11.6, 4.0 Hz, 1H), 3.59 (d, *J* = 2.5 Hz, 1H), 3.10 – 2.89 (tdd, *J* = 11.6, 4.0, 2.5 Hz, 1H), 2.47 – 2.29 (m, 1H), 1.99 – 1.83 (m, 6H), 1.83-1.74 (m, 4H), 1.72 – 1.65 (m, 2H), 1.64-1.56 (m, 1H), 1.53-1.46 (m, 2H), 1.44-1.33 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.14, 163.82, 106.20, 85.75, 47.02, 40.40, 36.61, 35.98, 32.04, 26.60, 24.78, 24.13, 23.96, 22.52, 21.67. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{15}H_{21}NO_6$, 312.14416; found, 312.14390**.**



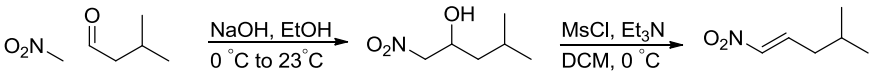
3.14i

3.14i:3-((1*R*,2*S*)-(2-Nitrocyclopentyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 46 mg (52% yield) of a single diastereomer, crude dr = 90:10, was isolated as a white solid, mp 148 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 97% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 8.8 min, t_R (major) = 10.1 min) $[\alpha]_D^{20}$ = +21.3 (*c* 0.69, $CHCl_3$): IR (neat): 2946, 1782, 1742, 1644, 1546, 1452, 1369, 1307, 1265, 1064, 1001, 854 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (td, *J* = 8.1, 5.3 Hz, 1H), 4.10 (d, *J* = 3.1 Hz, 1H), 3.27 (tdd, *J* = 8.1, 5.3, 3.1 Hz, 1H), 2.38 – 2.19 (m, 2H), 2.04 (m, 1H), 2.01 – 1.95 (m, 2H), 1.94 – 1.87 (m, 2H), 1.86 – 1.76 (m, 2H), 1.72 (m, 2H), 1.65 (m, 2H), 1.45 (m, 3H). **^{13}C** NMR (500 MHz, $CDCl_3$) δ 164.55, 164.51, 106.86, 88.06, 47.96, 44.06, 37.21, 36.05, 31.72, 28.50, 24.42, 24.35, 23.04, 22.15. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{19}NO_6$, 298.12851; found, 298.12850**.**



3.14j

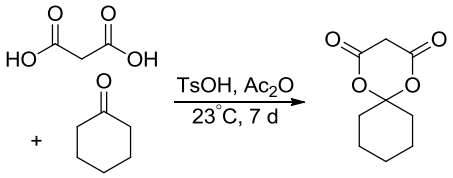
3.14j: 3-((1*R*,2*S*)-(2-Nitrocycloheptyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione: 90 mg (92% yield) of a single diastereomer, crude dr = >99:1, was isolated as a white solid, mp 122 ^{o}C, by flash column chromatography using 80:19:1 hexanes:EA:AcOH as eluent: 98% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 8.5 min, t_R (major) = 9.0 min) $[\alpha]_D^{20}$ = +20.0 (*c* 0.88, $CHCl_3$): IR (neat): 2939, 2860, 1781, 1743, 1545, 1453, 1369, 1303, 1265, 1067, 974, 859 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (td, *J* = 5.2, 4.8 Hz, 1H), 3.72 (d, *J* = 2.4 Hz, 1H), 3.30 (tdd, *J* = 11.2, 4.8, 2.4 Hz, 1H), 2.50 – 2.28 (m, 1H), 2.25 – 2.08 (m, 1H), 1.99 – 1.63 (m, 13H), 1.64 – 1.46 (m, 3H), 1.46 – 1.30 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.30, 164.01, 106.26, 88.72, 49.70, 41.80, 36.68, 35.77, 32.63, 29.09, 28.72, 28.34, 23.98, 22.56, 21.67. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{23}NO_6$, 326.15981; found, 326.15983**.**



VI. Large scale synthesis of *trans*-1-nitro-4-methyl-pent-1-ene. The following is a modified version of the procedure described by Bassas et al.[5b] In a 3-L, 2 neck roundbottom flask with 5 cm oval stirbar and an internal temperature probe was added isovaleraldehyde (241 mL, 2.25 mol), nitromethane (124 mL, 2.30 mol) and ethanol (1 L). The flask was then submerged in an ice-water bath and stirred until the temperature was 8 °C at which point the flask was fitted with an additional funnel and a 10 M solution of NaOH (90 g, 2.25 mol) was added dropwise such that the internal temperature remained between 10-15 °C. After ~150 mL of the NaOH solution had been added, a white slurry formed. Eventually the flask required swirling by hand for the remaining addition. Once the addition is complete the flask is allowed to warm to room temperature (12 h). The reaction is then quenched by the addition of AcOH (129 mL, 2.26 mol) all at once. The contents of the flask are transferred to a 6-L separatory funnel and the product is extracted with 4 L of Et_2O. The Et_2O layer is washed with H_2O (4X ~500 mL) then washed with a saturated solution of $NaHCO_3$ (1 X 500 mL) and finally a brine solution (1 X 500 mL). The Et_2O layer is then dried over magnesium sulfate and concentrated. The concentrated product was then placed on a Kugelrohr distillation apparatus and gently rocked and warmed (35-45 °C) for 3 h. This was found to be necessary to remove trace ethanol. The crude nitro alcohol, 4-methyl-1-nitropentan-2-ol, was sufficiently pure for the next step (290.3 g, 87.8%).

In a 5-L, 4 neck round bottom flask equipped with a mechanical stirrer, nitrogen inlet, stopper and addition funnel was placed the nitroalcohol (292.32 g, 1.97 mol), DCM (1.97 L) and MsCl (167.3 mL, 2.17 mol), and the flask was placed in an ice bath and allowed to stir for 20 min. Then Et_3N (589 mL, 4.24 mol) was placed in the addition funnel and added over 1 h. The

reaction becomes heterogeneous after ~2/3 of the amine has been added. The reaction was given an additional 30 minutes after all the Et_3N had been added. The reaction mixture is transferred to a 6-L separatory funnel and washed with H_2O (2 X 1 L) then 1 M HCl (1 X 0.3 L) and dried over MgSO4. The solvent is removed *in vacuo* and then the crude nitroalkene is purified by short path distillation (85 °C, 5 mmHg) affording *trans*-1-nitro-4-methyl-pent-1-ene (213.8 g, 84%).

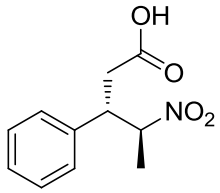


VII. Large scale synthesis of cyclohexyl Meldrum's acid. In a procedure adapted from that of Velikorodov[21] a 3-L, 3-neck round bottom flask equipped with a 5 cm oval stir bar was fitted with rubber stoppers. Within the flask was placed malonic acid (500 g, 4.81 mol), TsOH*H_2O (15.5 g, 0.0818 mol), cyclohexanone (497 mL, 4.81 mol) and then Ac_2O (776 mL). The heterogeneous mixture was stirred until it became a homogenous black solution (~ 5 h), and then the stirring was discontinued. After 7 d, 2.38 L of H_2O was added, and the resulting mixture was stirred until the product precipitated. The flask was moved to an ice bath and allowed to cool. Then the product was filtered on a Buchner funnel and washed with hot hexanes. The product was dried on the filter and then recrystallized using 5 mL/g of hot 5:2 hexanes: EtOH (200 proof). The crystals were then filtered and washed with hot hexanes to remove any remaining color to afford pure cyclohexyl Meldrum's acid (445 g, 50%). This procedure has been performed on 20 mol scale with similar results and ^{1}H NMR data match literature data.[21]

VIII. Procedure for Large Scale Enantioselective Addition of Cyclohexyl Meldrum's Acid to *trans*-1-nitro-4-methyl-pent-1-ene. To a 3-neck, 3-L Morton type round bottom flask equipped with stir bar (1.5 inch, oval) was added *trans*-1-nitro-4-methyl-pent-1-ene (129 g, 1.00 mol), sulfinyl urea catalyst **3.8** (0.95 g, 2.00 mmol), cyclohexyl Meldrum's acid (368 g, 2.00 mol), and cyclopentyl methyl ether (0.83 L). The reaction flask was stoppered, and the heterogeneous reaction mixture was stirred at 35 ^{o}C (oil bath) for 48 h. The reaction mixture became homogeneous within ~1.5 h. The reaction progress was monitored by the disappearance of the nitroalkene by TLC (R_f = 0.8, 8:2 Hex:EA). Upon complete reaction conversion (48 h), the CPME was removed *in vacuo,* and the crude reaction mixture was diluted with 400 mL of toluene and then concentrated to remove trace CPME (dilution and concentration was repeated a 2nd time). The unpurified product was then used directly in the next step without further purification. A small sample of the product (< 5 mg) was taken aside for determination of enantiomeric excess: 92% ee (Chiralcel IA, 90 (1% TFA):10 hexanes:IPA, 1 mL/min, 210 nm, t_R (minor) = 7.2 min, t_R (major) = 7.6 min). By ^{1}H NMR analysis, the reaction was determined to have proceeded to complete conversion.

IX. Procedure for Large Scale One-Pot Hydrolysis and Decarboxylation of (*S*)-3-(4-methyl-1-nitropentan-2-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione. The procedure for hydrolysis and decarboxylation was adapted from U.S. Patent WO2008117305 for industrial Lyrica production.[12] To the flask containing the crude (*S*)-3-(4-methyl-1-nitropentan-2-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (313 g, 1.00 mol) was added toluene (0.83 L) and *p*-toluenesulfonic acid monohydrate (86.0 g, 0.500 mol). It should be noted that 0.25 equiv of *p*-toluenesulfonic acid was used with respect to the sum of the adduct and excess cyclohexyl

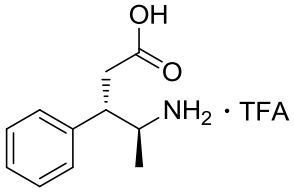
Meldrum's acid. Finally, H_2O (45 mL, 2.5 mol) was added and the flask was fitted with a condenser with an N_2 inlet at the top and with an internal temperature probe. The reaction mixture was heated in an oil bath such that the internal temperature was 90 ^oC for 24 h. An intermediate, which was presumably the diacid hydrolysis product, rapidly formed (<2 h) as determined by NMR analysis of an aliquot of the reaction mixture (vide infra). The reaction progress was monitored by taking an aliquot (5 μL) of the reaction mixture, blowing off the toluene, diluting the residue with $CDCl_3$, and monitoring by ^1H NMR for the disappearance of the diastereotopic α-CH_2 of the diacid intermediate: ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (dd, *J* = 13.6, 5.7 Hz, 1H). Once the reaction was determined to be complete, the reaction mixture was allowed to cool to room temperature. Then the reaction flask was placed in an ice bath, and with rapid stirring a ~30% solution of Na_2CO_3 was slowly added until the pH was 8. Then the biphasic mixture was transferred to a 6 L separatory funnel. The aqueous layer was separated, and the organic layer was extracted a second time with 30% Na_2CO_3 solution. The combined aqueous layers were washed with toluene (250 mL) and then transferred to a x 4 L Erlenmeyer flask fitted with 1.5 inch oval stir bar. The flask was placed in an ice bath, toluene was added (0.5 L), and the resulting mixture was allowed to cool to 0 ^oC with stirring. Then, with stirring, 3 M HCl was added until the aqueous layer reached pH <2. The biphasic mixture was transferred back to the separatory funnel, and an additional 250 mL of toluene was added. The layers were separated, and the acidic layer was extracted a second time with toluene (250 mL). The combined organic layers were washed with brine (2 X 200 mL) and then dried over magnesium sulfate, filtered and concentrated to afford monoacid **3.15** (170 g, 0.90 mol), which was obtained as a viscous oil in 90% overall yield from *trans*-1-nitro-4-methyl-pent-1-ene. ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, *J* = 12.4, 6.8 Hz, 1H), 4.46 (dd, *J* = 12.4, 5.8 Hz, 1H), 2.69 (dtd, *J* = 6.8, 6.4, 5.8 Hz, 1H), 2.52 (d, *J* = 6.4 Hz, 2H), 1.67 (septet, *J* = 6.8 Hz, 1H), 1.35 – 1.25 (m, 2H), 0.93 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 178.49, 78.90, 40.82, 36.16, 32.20, 25.44, 22.84, 22.63.



3.16

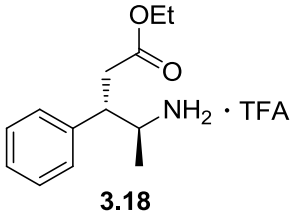
Intermediate 3.16: The procedure for hydrolysis and decarboxylation was adapted from U.S. Patent WO2008117305 for industrial Lyrica production.[12] To a vial containing adduct **3.14a** (104 mg, 0.3 mmol) was added toluene (0.25 mL), *p*-toluenesulfonic acid monohydrate (14 mg, 0.075 mmol), and water (6 μL). The reaction mixture was heated at 90 ^oC for 24 hr, then cooled to rt. The reaction mixture was diluted with toluene (1-2 mL) then washed with 2 x 1 mL 5% $Na_2CO_{3(aq)}$. The combined aqueous layers were washed with 1 mL toluene, and the toluene layers were discarded. The aqueous layer was acidifed to pH 2 with 1 N $HCl_{(aq)}$, then extracted with 3 x 3 mL toluene. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford nitro monoacid **3.16** as a single diastereomer (62 mg, 93% yield). Intermediate **3.16** was obtained as an oil, $[\alpha]_D^{20}$ = +13.3 (*c* 1.0, $CHCl_3$): IR (neat): 3064, 3032, 2993, 2946, 1712, 1549, 1496, 1454, 1389, 1360, 1261, 1082 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 3H), 7.11 – 7.06 (m, 2H), 4.81 – 4.54 (dq, *J* = 6.8, 6.4 Hz, 1H), 3.65 – 3.45

(ddd, *J* = 10.0, 4.8, 6.8 Hz, 1H), 2.74 – 2.68 (dd, *J* = 16.4, 10.0 Hz, 1H), 2.64-2.58 (dd, *J* = 16.4, 4.8 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.34, 134.14, 129.06, 128.12, 86.79, 45.87, 37.28, 17.65. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{13}NO_4$, 246.07368; found, 246.07377**.**



3.17

Amino Acid 3.17: The procedure for reduction was adapted from a literature procedure by Grenning et al.[22] To a 10 ml vial with stir bar was added nitro acid **3.16** (50 mg, 0.224 mmol), zinc dust (283 mg, 4.35 mmol) then isopropanol (0.1 ml) and HCl (2.24 ml, 1 M). The reaction was placed in an oil bath and heated to 50 °C for 2 h. The reaction was then filtered over a cotton plug to remove excess zinc metal, concentrated and then purified by reverse phase chromatography on a C18 column (5-100% methanol in water with 0.1% TFA) to provide the TFA salt of the amino acid as a single diastereomer (67mg, 97%). Product **3.17** was obtained as an oil, $[\alpha]_D^{20}$ = +0.6 (*c* 0.85, MeOH): IR (neat): 2924, 2854, 1663, 1456, 1180, 1137, 799, 757, 701 cm^{-1}. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.39 (m, 2H), 7.34 (m, 1H), 7.32 – 7.27 (m, 2H), 3.65 (dq, *J* = 7.0, 6.7 Hz, 1H), 3.38 – 3.36 (m, 1H), 2.92 (dd, *J* = 16.1, 5.7 Hz, 1H), 2.80 (dd, *J* = 16.1, 9.1 Hz, 1H), 1.15 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (500 MHz, MeOH-d_4) δ 174.73, 139.58, 129.98, 129.71, 128.92, 52.04, 46.89, 38.02, 16.51. ^{19}F NMR (400 MHz, MeOH-d_4) δ -77.04. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{11}H_{15}NO_2$, 194.11756; found, 194.11717**.**



3.18

Amino Ethyl Ester 3.18: The procedure for reduction was adapted from a literature procedure by Kimmel et al.[10] To a 4-mL vial with a stir bar and plastic cap was added anhydrous tin(II) chloride (378 mg, 2.0 mmol) and nitro monoacid **3.16** (45 mg, 0.2 mmol). In a separate vial, dry ethanol (2 mL) and acetyl chloride (0.14 mL, 2.0 mmol) were premixed and let sit until heat of mixing subsided, then added to reaction vial all at once. The reaction vial was placed in a 95^{o}C oil bath and stirred at reflux for 20 h, then allowed to cool to room temperature. The solvent was evaporated *in vacuo* and the crude residue was purified by reverse phase chromatography on a C18 column (5-100% methanol in water with 0.1% TFA) to provide the TFA salt of the amino ethyl ester as a single diastereomer (41 mg, 61%). Product **3.18** was obtained as an oil, $[\alpha]_D^{20}$ = +4.8 (*c* 1.0, MeOH): IR (neat): 2983, 1671, 1537, 1431, 1375, 1178, 1134, 1025, 907, 837, 721, 701 cm^{-1}. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.46 – 7.23 (m, 5H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.69 – 3.58 (m, 1H), 3.37 (m, 1H), 2.93 (dd, *J* = 15.7, 5.4 Hz, 1H), 2.82 (dd, *J* = 15.7, 9.8 Hz, 1H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (500

MHz, MeOH-d_4) δ 172.76, 139.31, 129.97, 129.72, 129.00, 61.76, 52.03, 47.13, 38.24, 16.60, 14.27. ^{19}F NMR (400 MHz, MeOH-d_4) δ -76.99. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{13}H_{19}NO_2$, 222.14886; found, 222.14820**.**

References

1) For a general review of GABA-related drugs, see: (a) Yogeeswari, P.; Ragavendran, J. V.; Sriram, D. *Recent Patents on CNS Drug Discovery.* **2006**, *1*, 113-118. For reviews of Pregabalin drug activity, see: (b) Beydoun, A.; Nasreddine, W.; Atweh, S. *Expert Review of Neurotherapeutics.* **2008**, *8*, 1013-1024. (c) Silverman, R. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3500-3504.
2) (a) Takagi, M.; Ishimitsu, K.; Nishibe, T. Preparation of Novel Hetereocyclic Compounds such as 2-Imidazolidinone, 2-Thiazolidinone and 2-Pyrrolidinone Derivatives as Anti-inflammatory Agents. Patent WO 2003031414(A1), April 17, 2003. (b) Cai, J.; Hao, X.; Wang, Y.; Xu, L.; Yang, X.; Wang, Y. Application of Phenclobenpyrone as Antidepressent. Patent CN 1759831(A), April 19, 2006. (c) Liebeschuetz, J. W.; Katz, R. B.; Duriatti, A. D.; Arnold, M. L. *Pesticide Science*. **1997**, *50*, 258-274. (d) Ansorge, S.; Bank, U.; Nordhoff, K.; Tager, M.; Striggow, F. Novel Dipeptidyl Peptidase IV Inhibitors used for Functionally Influencing Different Cells and Treating Immunological, Inflammatory, Neuronal, and other Diseases. Patent WO 2005037779(A2), April 28, 2005. (e) Belliotti, T. R.; Capiris, T.; Ekhato, I. V.; Kinsora, J. J.; Field, M. J.; Heffner, T. G.; Meltzer, L. T.; Schwarz, J. B.; Taylor, C. P.; Thorpe, A. J.; Vartanian, M. G.; Wise, L. D.; Ti, Z-S.; Weber, M. L.; Wustrow, D. J. *J. Med. Chem.* **2005**, *48*, 2294-2307. (f) Kalvins, I.; Lebedevs, A.; Cernobrovijs, A.; Dambrova, M.; Zvejniece, L.; Vorona, M.; Veinbergs, G. 4R,5S-Enantiomer of 2-(5-Methyl-2-Oxo-4-Phenyl-Pyrrolidin-1-yl)-Acetimide with Nootropic Activity. Patent WO 2011045888(A1), May 12, 2011.
3) Many examples of organocatalytic enantioselective additions to nitroalkenes have been accomplished using malonate esters. For select examples, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673. (b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481-4483. (c) Li, H.; Wang, L. T.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907. (d). Xu, F.; Corley, E.; Zacuto, M.; Conlon, D. A.; Pipik, B.; Humphrey, G.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2010**, *75*, 1343-1353.(e) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367-6370. (f) Zhang, L.; Lee, M-M.; Lee, S-M.; Lee, J.; Cheng, M.; Jeong, B-S.; Park, H-G.; Jew, S-S. *Adv. Synth. Catal.* **2009**, *351*, 3063-3066. For select examples of highly enantioselective metal-catalyzed additions of malonate esters to nitroalkenes, see: (g) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097-13105. (i) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958-9959.
4) (a) See ref. 3a (b) Chen, W-Y.; Li, P.; Xie, J-W.; Li, X-S. *Catal. Commun.* **2011**, *12*, 502-504.
5) For examples of Meldrum's acid additions that give low to modest enantioselectivity, see: (a) See ref. 3a. (b) Bassas, O.; Huuskenon, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340-1351. (c) Kleczkowska, E.; Sas, W. *Polish Journal of Chemistry* **2007**, *81*, 1457-1464.

6) Malonates typically require a two step process of basic saponification followed by acidification for decarboxylation, see: Xue, C-B.; Chen, L.; Cao, G.; Zhang, K.; Wang, A.; Meloni, D.; Glenn, J.; Anand, M. X.; Kong, L.; Huang, T.; Feng, H.; Zheng, C.; Li, M.; Galya, L.; Zhou, J.; Shin, N.; Baribaud, F.; Solomon, K.; Scherle, P.; Zhao, B.; Diamond, S.; Emm, T.; Keller, D.; Contel, N.; Yeleswaram, S.; Vaddi, K.; Hollis, G.; Newton, R.; Friedman, S.; Metcalf, B. *ACS Med. Chem. Lett.* **2010**, *1*, 483-487.

7) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.

8) Cojugate addition of diethyl malonate (3.0 equiv) to *trans*-β-nitro, β-methyl styrene (1.0 equiv) in CD_2Cl_2 using DBU (1.0 equiv) as the base resulted in complete consumption of the nitroalkene to afford a 1.8:1 ratio of diastereomers, determined by ^{1}H NMR spectroscopy of the reaction mixture and further confirmed by isolation of the product diastereomers using flash chromatography. In contrast, when cyclohexyl Meldrum's acid was employed under identical conditions, clean conversion (94%) to product with > 97:3 dr was observed in 13 h. Furthermore, attempts to add diethyl malonate to the same alkene, utilizing triethyl amine as the base, afforded ~5% (48 h) conversion to mix of diastereomers in low dr. When cyclohexyl Meldrum's acid was used under identical conditions full conversion (~24 h) and >20:1 dr was obtained.

9) For reviews of H-bonding organocatalysis, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520-1543. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299-4306. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743. (d) Akiyama, T. *Chem. Rev*. **2007**, *107*, 5744-5758. (e) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516-532. (f) Terada, M. *Synthesis* **2010**, *12*, 1929-1982. (g) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem. Eur. J.* **2010**, *16*, 9350-9365.

10) For examples of organocatalysts containing sulfinamides, see: (a) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110-15111. (b) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754-8755. (c) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N.; *Science* **2010**, *327*, 986-990. (d) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913-5915.

11) For examples of carbon nucleophile additions for which acyclic α,β-disubstituted nitroalkenes have been used in cyclization reactions, see: (a) Cao, C-L.; Zhou, Y-Y.; Sun, X-L.; Tang, Y.; Li, Y-X.; Li, G-Y.; Sun, J. *Chem. Eur. J.* **2009**, *15*, 11384-11389. (b) Chandrasekhar, S.; Mallikarjun, K.; Pavankumarreddy, G.; Rao, K. V.; Jagadeesh, B. *Chem. Commun.* **2009**, 4985-4987. (c) Rueping, M.; Kuenkel, A.; Frohlich, R. *Chem. Eur. J.* **2010**, *16*, 4173-4176. (d) Wang, Y.; Zhu, S.; Ma, D. *Org. Lett.* **2011**, *13*, 1602-1605.

12) After one pot hydrolysis and decarboxylation, the nitro monoacid is obtained. This compound has been carried onto Lyrica, see: Bobba, V. S. K.; Sanikommu, S. R.; More, B. M.; Metil, D. S.; Kulkarni, P. B.; Prabahar, K. J.; Khan, M., Novel Process for Preparing Pregabalin and its Acid Addition Salts. U.S. Patent WO2008117305(A2), October 2, 2008.

13) For leading references on CPME, see: (a) Antonucci, V.; Coleman, J.; Ferry, J. B.; Johnson, N.; Mathe, M.; Scott, J. P.; Xu, J. *Org. Process Res. Dev*. **2011**, ASAP. (b) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251–258.

14) (a) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964-8965. (b) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Mueller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807-811. (c) Berkessel, A.; Mukherjee, S.; Mueller, T. N.; Cleemann, F.;

Roland, K.; Brandenburg, M.; Neudoerfl, J-M.; Lex, J. *Org. & Biomol. Chem.* **2006**, *4*, 4319-4330. (d) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332-7335. (e) Li, L.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.*, **2008**, *130*, 12248–12249.
15) For the development and applications of triisopropylphenyl sulfinamide, see: Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. *Tetrahedron Lett.* **2003**, *44*, 4195-4197.
16) (a) The thermodynamic ratio of diastereomers **14a** was found to be 1.3:1. The ratio was determined by ^{1}H NMR after the α-nitro stereocenter of **14a** had been epimerized in the presence of excess triethylamine at 60 ^{o}C. (b) For an example of addition to acyclic α,β-disubstituted nitroalkenes in which low dr was observed, see: Ganesh, M.; Namboothiri, I. N. N. *Tetrahedron* **2007**, *63*, 11973-11983.
17) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153-156.
18) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880-7881.
19) Davis, F. A.; Ramachandra, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894-6898.
20) Costello, G. F.; James, R.; Shaw, J. S.; Slater, A. M.; Stutchbury, N. C. J. *J. Med. Chem.* **1991**, *34*, 181-189.
21) Velikorodov, A. V. *Russ. J. Org. Chem.* **2004**, *40*, 690-692.
22) Grenning, J. A.; Tunge, J. A. *Org. Lett.* **2010**, *12*, 740-742.

Appendix: Chapter 3. X-ray Crystal Data

Structure Determined by Dr. Christopher Incarvito

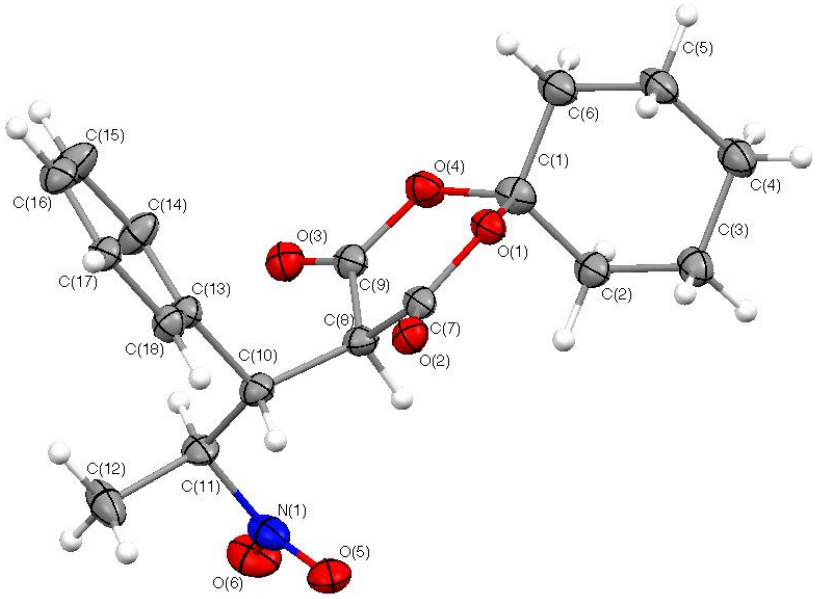

C(5)
C(6)
C(15)
O(4)
C(1)
C(4)
C(16)
C(14)
O(3)
O(1)
C(3)
C(17)
C(9)
C(13)
C(2)
C(8)
C(7)
C(18)
C(10)
O(2)
C(12)
C(11)
N(1)
O(5)
O(6)

Table 3.1. Crystal Data and structure refinement for ellman02

Empirical Formula	$O_6NC_{18}H_{21}$
Formula Weight	347.37
Temperature	93 K
Wavelength	1.54187 Å
Crystal System	triclinic
Lattice Type	Primitive
Space Group	P1 (#1)
Unit cell dimensions	a = 11.3125(2) Å α = 102.179(7)° b = 12.0218(2) Å β = 107.108(8)° c = 13.7304(10) Å γ = 93.227(7)°
Volume	1730.44(16) $Å^3$
Z value	4
Density (calculated)	1.333 g/cm^3
F_{000}	736.00
Crystal size	0.10 X 0.10 X 0.08 mm
Crystal Color, Habit	colorless, block
Theta max for data collection	65.9°
Reflections collected	11758
Independent reflections	7351 [$R_{(int)}$ = 0.0580]
Absorption correction	Multi-scan
Max and min transmission	0.613 and 0.935.
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7325 / 1 / 901
Goodness-of-fit on F^2	1.088
Final R indices [I>2sigma(I)]	R1 = 0.0562, wR2 = 0.1611
R indices (all data)	R1 = 0.0562, wR2 = 0.1611
Absolute structure parameter	0.04(20)
Largest diff. peak and hole	0.23 and -0.30 $e^-/Å^3$

Table 3.2. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	0.8156(3)	0.9023(2)	0.6085(2)	2.97(6)
O(2)	0.9302(3)	1.0559(3)	0.7212(3)	3.09(6)
O(3)	0.5203(4)	0.9520(3)	0.7067(3)	3.45(7)
O(4)	0.6077(3)	0.8495(3)	0.6017(3)	3.44(7)
O(5)	0.8365(5)	1.0374(3)	1.0000(3)	4.63(8)
O(6)	0.6498(4)	1.0104(3)	1.0100(3)	5.20(9)
O(7)	0.7485(3)	0.9164(2)	1.2823(2)	2.81(6)
O(8)	0.6086(3)	0.8108(3)	1.1400(3)	3.26(6)
O(9)	1.0358(4)	0.7836(3)	1.2152(3)	3.92(7)
O(10)	0.9636(3)	0.9119(2)	1.3146(2)	3.06(6)
O(11)	0.8417(3)	0.7863(3)	0.9175(3)	3.68(7)
O(12)	0.6439(4)	0.7909(3)	0.8525(3)	3.85(7)
O(13)	1.0747(3)	0.4311(3)	0.8037(3)	3.44(7)
O(14)	1.0302(4)	0.5501(3)	0.9297(3)	3.77(7)
O(15)	1.4246(3)	0.5801(3)	0.8864(3)	3.53(6)
O(16)	1.2711(3)	0.4513(2)	0.7794(2)	2.87(6)
O(17)	1.3680(4)	0.5914(3)	1.2035(3)	3.98(7)
O(18)	1.1711(4)	0.5526(3)	1.1729(3)	3.64(7)
O(19)	1.2242(3)	0.4632(2)	1.4685(2)	3.02(6)
O(20)	1.0996(3)	0.3241(3)	1.3448(3)	3.52(7)
O(21)	1.5225(4)	0.3985(3)	1.3803(3)	3.91(7)
O(22)	1.4365(3)	0.5059(3)	1.4846(2)	3.21(6)
O(23)	1.0758(6)	0.3064(4)	1.0368(4)	6.56(12)
O(24)	1.2755(5)	0.3402(4)	1.0859(3)	5.57(10)
N(1)	0.7262(5)	1.0497(3)	0.9741(3)	3.87(9)
N(2)	0.7321(4)	0.7558(3)	0.9083(3)	2.83(7)
N(3)	1.2612(4)	0.6071(3)	1.1649(3)	2.96(7)
N(4)	1.1771(6)	0.2938(4)	1.0902(4)	4.82(11)
C(1)	0.7181(5)	0.8072(4)	0.5835(4)	3.26(10)
C(2)	0.7624(5)	0.7214(4)	0.6482(4)	3.29(9)
C(3)	0.8707(5)	0.6641(4)	0.6190(4)	3.62(10)
C(4)	0.8345(6)	0.6113(4)	0.5014(4)	3.97(11)
C(5)	0.7933(6)	0.7009(4)	0.4394(4)	3.83(11)
C(6)	0.6855(6)	0.7566(4)	0.4668(4)	3.80(11)
C(7)	0.8369(5)	0.9872(4)	0.6957(3)	2.82(8)
C(8)	0.7447(4)	0.9904(4)	0.7553(3)	2.65(8)
C(9)	0.6140(6)	0.9323(4)	0.6872(4)	3.01(9)

Table 3.2. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(10)	0.7497(5)	1.1156(4)	0.8195(4)	2.87(8)
C(11)	0.6798(5)	1.1258(4)	0.8997(3)	3.25(9)
C(12)	0.6987(7)	1.2474(4)	0.9668(5)	4.95(14)
C(13)	0.7128(5)	1.1998(4)	0.7497(4)	2.71(8)
C(14)	0.5936(5)	1.1987(4)	0.6860(4)	3.82(10)
C(15)	0.5653(5)	1.2787(5)	0.6243(5)	4.59(12)
C(16)	0.6583(5)	1.3592(4)	0.6257(4)	3.41(9)
C(17)	0.7758(5)	1.3621(4)	0.6896(4)	2.84(8)
C(18)	0.8061(5)	1.2841(4)	0.7528(4)	2.86(8)
C(19)	0.8695(4)	0.9847(3)	1.3227(3)	2.51(8)
C(20)	0.8937(5)	1.0357(4)	1.4390(4)	3.09(9)
C(21)	0.8068(5)	1.1227(4)	1.4576(4)	3.59(10)
C(22)	0.8100(6)	1.2156(4)	1.3993(4)	3.92(11)
C(23)	0.7805(6)	1.1624(4)	1.2817(4)	4.11(11)
C(24)	0.8715(5)	1.0778(4)	1.2634(4)	3.36(10)
C(25)	0.7167(5)	0.8444(4)	1.1856(4)	2.70(8)
C(26)	0.8197(5)	0.8109(4)	1.1417(4)	2.72(8)
C(27)	0.9487(5)	0.8324(4)	1.2244(4)	2.95(9)
C(28)	0.7990(5)	0.6856(4)	1.0727(3)	2.80(8)
C(29)	0.7021(5)	0.6686(3)	0.9655(3)	2.66(8)
C(30)	0.7001(5)	0.5524(4)	0.8939(4)	3.21(9)
C(31)	0.7687(5)	0.5968(4)	1.1301(4)	2.70(8)
C(32)	0.6489(5)	0.5654(4)	1.1298(4)	3.05(9)
C(33)	0.6258(5)	0.4876(4)	1.1860(4)	3.41(9)
C(34)	0.7220(5)	0.4392(4)	1.2415(4)	3.34(9)
C(35)	0.8426(5)	0.4664(4)	1.2408(4)	3.18(9)
C(36)	0.8666(5)	0.5446(4)	1.1845(4)	3.20(9)
C(37)	1.1662(5)	0.3702(4)	0.7677(4)	2.81(9)
C(38)	1.2066(5)	0.2787(4)	0.8261(4)	3.17(9)
C(39)	1.2956(5)	0.2101(4)	0.7797(4)	3.48(9)
C(40)	1.2367(5)	0.1579(4)	0.6641(4)	3.56(10)
C(41)	1.1948(5)	0.2510(4)	0.6058(4)	3.43(10)
C(42)	1.1074(5)	0.3223(4)	0.6509(4)	3.43(9)
C(43)	1.1108(5)	0.5130(4)	0.8956(4)	3.08(9)
C(44)	1.2469(5)	0.5510(4)	0.9453(4)	2.84(9)
C(45)	1.3217(4)	0.5306(4)	0.8711(3)	2.65(8)
C(46)	1.2862(5)	0.6756(4)	1.0137(3)	2.90(9)

Table 3.2. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(47)	1.2373(5)	0.7021(4)	1.1077(4)	3.04(9)
C(48)	1.3073(6)	0.8142(4)	1.1867(4)	3.60(10)
C(49)	1.2507(5)	0.7662(4)	0.9495(3)	2.81(9)
C(50)	1.3454(5)	0.8278(4)	0.9288(4)	3.19(9)
C(51)	1.3159(5)	0.9084(4)	0.8685(4)	3.68(10)
C(52)	1.1947(5)	0.9277(4)	0.8298(4)	3.45(10)
C(53)	1.1018(5)	0.8701(4)	0.8532(4)	3.47(9)
C(54)	1.1297(5)	0.7885(4)	0.9120(4)	3.35(9)
C(55)	1.3275(5)	0.5539(4)	1.4999(4)	2.99(9)
C(56)	1.3540(5)	0.6021(4)	1.6159(4)	3.44(10)
C(57)	1.2460(6)	0.6616(4)	1.6393(4)	3.84(11)
C(58)	1.2148(6)	0.7547(4)	1.5779(4)	3.85(11)
C(59)	1.1859(6)	0.7037(4)	1.4607(4)	3.55(10)
C(60)	1.2941(5)	0.6448(4)	1.4378(4)	3.16(9)
C(61)	1.1993(5)	0.3834(4)	1.3784(4)	3.09(9)
C(62)	1.2972(5)	0.3746(4)	1.3245(4)	3.05(9)
C(63)	1.4267(6)	0.4258(4)	1.3968(4)	3.20(9)
C(64)	1.3007(5)	0.2518(4)	1.2584(4)	3.36(9)
C(65)	1.1834(6)	0.2116(4)	1.1619(4)	3.96(11)
C(66)	1.1864(7)	0.0941(5)	1.0939(4)	5.33(14)
C(67)	1.3283(5)	0.1611(4)	1.3221(4)	2.95(9)
C(68)	1.2379(5)	0.1118(4)	1.3555(4)	3.68(10)
C(69)	1.2637(6)	0.0284(4)	1.4144(4)	3.91(11)
C(70)	1.3774(6)	-0.0054(5)	1.4391(5)	4.73(13)
C(71)	1.4669(7)	0.0407(6)	1.4065(9)	8.1(3)
C(72)	1.4400(6)	0.1242(5)	1.3473(7)	6.15(18)

$$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

Table 3.3. Anisotropic displacement parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.050(2)	0.0294(14)	0.0343(17)	0.0020(14)	0.0145(15)	0.0082(13)
O(2)	0.0406(19)	0.0359(16)	0.0419(18)	0.0029(15)	0.0124(15)	0.0128(14)
O(3)	0.048(2)	0.0408(18)	0.0462(20)	0.0056(17)	0.0187(17)	0.0143(15)
O(4)	0.046(2)	0.0383(17)	0.0394(19)	-0.0016(16)	0.0078(16)	0.0033(14)
O(5)	0.081(3)	0.063(2)	0.036(2)	0.022(2)	0.016(2)	0.0206(18)
O(6)	0.098(3)	0.054(2)	0.052(2)	-0.010(2)	0.030(2)	0.0223(18)
O(7)	0.0398(19)	0.0345(15)	0.0301(16)	-0.0023(14)	0.0121(14)	0.0029(13)
O(8)	0.0383(19)	0.0365(16)	0.0450(19)	0.0067(14)	0.0073(15)	0.0091(14)
O(9)	0.044(2)	0.0504(19)	0.049(2)	0.0088(18)	0.0135(17)	0.0016(16)
O(10)	0.045(2)	0.0309(15)	0.0380(18)	0.0044(14)	0.0124(15)	0.0033(13)
O(11)	0.048(2)	0.0517(19)	0.0431(19)	-0.0009(17)	0.0162(16)	0.0160(16)
O(12)	0.053(2)	0.0502(19)	0.047(2)	0.0115(18)	0.0109(18)	0.0240(17)
O(13)	0.045(2)	0.0428(17)	0.0384(18)	-0.0023(16)	0.0113(15)	0.0057(14)
O(14)	0.051(2)	0.0424(18)	0.052(2)	0.0022(17)	0.0207(18)	0.0106(15)
O(15)	0.0367(19)	0.0470(18)	0.047(2)	-0.0019(16)	0.0136(15)	0.0058(15)
O(16)	0.0416(19)	0.0344(15)	0.0324(17)	-0.0057(14)	0.0120(14)	0.0084(13)
O(17)	0.055(2)	0.055(2)	0.048(2)	0.0130(19)	0.0181(19)	0.0211(17)
O(18)	0.059(2)	0.0451(18)	0.0413(19)	0.0075(17)	0.0207(17)	0.0177(15)
O(19)	0.047(2)	0.0310(15)	0.0358(17)	-0.0042(14)	0.0128(15)	0.0089(13)
O(20)	0.043(2)	0.0349(16)	0.050(2)	0.0026(16)	0.0083(16)	0.0053(15)
O(21)	0.058(3)	0.0489(19)	0.048(2)	0.0042(18)	0.0206(18)	0.0184(16)
O(22)	0.042(2)	0.0394(16)	0.0369(18)	0.0032(16)	0.0080(15)	0.0091(14)
O(23)	0.123(4)	0.060(2)	0.052(3)	0.022(3)	-0.003(3)	0.024(2)
O(24)	0.126(4)	0.053(2)	0.045(2)	0.010(3)	0.043(3)	0.0164(18)
N(1)	0.082(4)	0.0324(20)	0.034(2)	-0.001(2)	0.021(2)	0.0083(17)
N(2)	0.043(2)	0.0326(18)	0.034(2)	0.0047(18)	0.0136(18)	0.0091(16)
N(3)	0.046(3)	0.040(2)	0.032(2)	0.0132(20)	0.0158(19)	0.0130(17)
N(4)	0.106(5)	0.044(2)	0.031(2)	0.018(3)	0.014(3)	0.0124(19)
C(1)	0.045(3)	0.037(2)	0.040(3)	-0.005(2)	0.013(2)	0.008(2)
C(2)	0.060(3)	0.030(2)	0.037(3)	0.004(2)	0.015(2)	0.0114(19)
C(3)	0.065(4)	0.034(2)	0.042(3)	0.009(2)	0.022(3)	0.010(2)
C(4)	0.076(4)	0.034(2)	0.042(3)	0.007(3)	0.022(3)	0.006(2)
C(5)	0.075(4)	0.034(2)	0.034(3)	0.002(3)	0.020(3)	0.002(2)
C(6)	0.069(4)	0.038(2)	0.036(3)	0.003(3)	0.016(3)	0.007(2)
C(7)	0.054(3)	0.0251(19)	0.031(2)	0.005(2)	0.014(2)	0.0110(18)
C(8)	0.039(3)	0.036(2)	0.026(2)	0.004(2)	0.0067(19)	0.0111(18)
C(9)	0.052(3)	0.027(2)	0.035(3)	0.004(2)	0.011(2)	0.0106(18)

Table 3.3. Anisotropic displacement parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(10)	0.045(3)	0.032(2)	0.033(2)	0.005(2)	0.010(2)	0.0139(19)
C(11)	0.066(3)	0.035(2)	0.028(2)	0.010(2)	0.017(2)	0.0164(19)
C(12)	0.114(6)	0.033(2)	0.057(3)	0.014(3)	0.049(4)	0.010(2)
C(13)	0.045(3)	0.028(2)	0.031(2)	0.007(2)	0.012(2)	0.0086(18)
C(14)	0.042(3)	0.041(3)	0.064(3)	0.004(2)	0.008(3)	0.028(2)
C(15)	0.042(3)	0.055(3)	0.076(4)	0.003(3)	0.003(3)	0.037(3)
C(16)	0.055(3)	0.037(2)	0.041(3)	0.006(2)	0.013(2)	0.019(2)
C(17)	0.047(3)	0.0275(20)	0.036(2)	0.004(2)	0.012(2)	0.0136(18)
C(18)	0.038(3)	0.029(2)	0.041(3)	0.0019(20)	0.011(2)	0.0093(19)
C(19)	0.028(2)	0.029(2)	0.038(3)	0.0025(19)	0.0063(19)	0.0101(19)
C(20)	0.047(3)	0.034(2)	0.033(2)	-0.001(2)	0.008(2)	0.0073(19)
C(21)	0.059(3)	0.040(2)	0.037(3)	0.003(2)	0.017(2)	0.006(2)
C(22)	0.063(4)	0.039(3)	0.044(3)	0.013(3)	0.014(3)	0.006(2)
C(23)	0.080(4)	0.035(2)	0.040(3)	0.011(3)	0.016(3)	0.010(2)
C(24)	0.063(4)	0.031(2)	0.034(3)	-0.000(2)	0.016(2)	0.0083(19)
C(25)	0.039(3)	0.027(2)	0.035(2)	0.0011(20)	0.009(2)	0.0093(18)
C(26)	0.040(3)	0.031(2)	0.038(2)	0.004(2)	0.018(2)	0.0101(18)
C(27)	0.044(3)	0.029(2)	0.037(3)	-0.002(2)	0.013(2)	0.0055(19)
C(28)	0.044(3)	0.030(2)	0.032(2)	0.007(2)	0.011(2)	0.0069(18)
C(29)	0.044(3)	0.0268(20)	0.033(2)	0.0011(19)	0.0125(20)	0.0111(17)
C(30)	0.060(3)	0.029(2)	0.030(2)	0.003(2)	0.012(2)	0.0075(18)
C(31)	0.041(3)	0.029(2)	0.032(2)	0.0077(20)	0.010(2)	0.0069(18)
C(32)	0.047(3)	0.035(2)	0.040(3)	0.008(2)	0.017(2)	0.0168(20)
C(33)	0.051(3)	0.040(2)	0.044(3)	0.007(2)	0.021(2)	0.014(2)
C(34)	0.057(3)	0.036(2)	0.041(3)	0.010(2)	0.022(2)	0.012(2)
C(35)	0.049(3)	0.039(2)	0.037(3)	0.014(2)	0.013(2)	0.0131(20)
C(36)	0.048(3)	0.033(2)	0.042(3)	0.005(2)	0.016(2)	0.0084(20)
C(37)	0.038(3)	0.032(2)	0.038(3)	-0.002(2)	0.017(2)	0.0046(19)
C(38)	0.058(3)	0.028(2)	0.035(2)	-0.002(2)	0.014(2)	0.0100(18)
C(39)	0.054(3)	0.032(2)	0.044(3)	0.005(2)	0.016(2)	0.0063(20)
C(40)	0.058(3)	0.041(3)	0.038(3)	0.006(2)	0.016(2)	0.010(2)
C(41)	0.053(3)	0.042(2)	0.035(2)	-0.002(2)	0.013(2)	0.010(2)
C(42)	0.052(3)	0.039(2)	0.035(3)	0.000(2)	0.009(2)	0.0041(20)
C(43)	0.051(3)	0.030(2)	0.039(3)	-0.001(2)	0.018(2)	0.0095(19)
C(44)	0.045(3)	0.034(2)	0.031(2)	0.004(2)	0.011(2)	0.0131(18)
C(45)	0.038(3)	0.033(2)	0.034(2)	0.006(2)	0.014(2)	0.0115(18)
C(46)	0.047(3)	0.034(2)	0.031(2)	0.007(2)	0.011(2)	0.0139(19)

Table 3.3. Anisotropic displacement parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(47)	0.049(3)	0.038(2)	0.033(2)	0.009(2)	0.014(2)	0.0164(19)
C(48)	0.069(4)	0.034(2)	0.038(3)	0.008(2)	0.022(3)	0.008(2)
C(49)	0.047(3)	0.031(2)	0.029(2)	0.002(2)	0.011(2)	0.0099(18)
C(50)	0.046(3)	0.035(2)	0.039(3)	0.005(2)	0.010(2)	0.0091(19)
C(51)	0.059(4)	0.034(2)	0.052(3)	-0.001(2)	0.019(3)	0.017(2)
C(52)	0.062(4)	0.035(2)	0.030(2)	0.009(2)	0.004(2)	0.0147(19)
C(53)	0.053(3)	0.036(2)	0.041(3)	0.002(2)	0.009(2)	0.015(2)
C(54)	0.044(3)	0.037(2)	0.043(3)	0.004(2)	0.004(2)	0.016(2)
C(55)	0.039(3)	0.031(2)	0.038(3)	-0.005(2)	0.008(2)	0.0069(19)
C(56)	0.059(3)	0.036(2)	0.032(3)	0.000(2)	0.011(2)	0.0071(20)
C(57)	0.074(4)	0.041(3)	0.035(3)	0.006(3)	0.023(3)	0.011(2)
C(58)	0.074(4)	0.034(2)	0.043(3)	0.009(3)	0.022(3)	0.012(2)
C(59)	0.061(4)	0.035(2)	0.042(3)	0.013(2)	0.018(3)	0.012(2)
C(60)	0.059(3)	0.030(2)	0.032(2)	0.004(2)	0.014(2)	0.0101(19)
C(61)	0.049(3)	0.028(2)	0.037(3)	0.008(2)	0.008(2)	0.0084(19)
C(62)	0.046(3)	0.041(2)	0.031(2)	0.008(2)	0.013(2)	0.0107(20)
C(63)	0.055(3)	0.036(2)	0.034(3)	0.004(2)	0.018(2)	0.011(2)
C(64)	0.058(3)	0.036(2)	0.036(3)	0.009(2)	0.014(2)	0.013(2)
C(65)	0.080(4)	0.039(2)	0.029(2)	0.010(3)	0.010(3)	0.0121(20)
C(66)	0.113(6)	0.044(3)	0.035(3)	0.011(3)	0.012(3)	0.003(2)
C(67)	0.048(3)	0.031(2)	0.035(3)	0.012(2)	0.012(2)	0.0079(19)
C(68)	0.053(3)	0.048(3)	0.045(3)	0.018(3)	0.017(3)	0.020(2)
C(69)	0.073(4)	0.037(2)	0.037(3)	0.014(3)	0.013(3)	0.013(2)
C(70)	0.057(4)	0.042(3)	0.064(4)	-0.002(3)	-0.009(3)	0.019(3)
C(71)	0.052(4)	0.074(4)	0.193(10)	0.018(4)	0.017(5)	0.082(6)
C(72)	0.051(4)	0.059(3)	0.143(7)	0.014(3)	0.034(4)	0.059(4)

The general temperature factor expression: $\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 3.5. Bond lengths (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.453(6)	O(1)	C(7)	1.349(5)
O(2)	C(7)	1.217(6)	O(3)	C(9)	1.192(8)
O(4)	C(1)	1.443(7)	O(4)	C(9)	1.350(6)
O(5)	N(1)	1.219(8)	O(6)	N(1)	1.231(8)
O(7)	C(19)	1.446(5)	O(7)	C(25)	1.357(5)
O(8)	C(25)	1.200(5)	O(9)	C(27)	1.199(7)
O(10)	C(19)	1.429(6)	O(10)	C(27)	1.354(5)
O(11)	N(2)	1.235(6)	O(12)	N(2)	1.222(5)
O(13)	C(37)	1.444(6)	O(13)	C(43)	1.363(5)
O(14)	C(43)	1.208(7)	O(15)	C(45)	1.216(6)
O(16)	C(37)	1.441(6)	O(16)	C(45)	1.353(5)
O(17)	N(3)	1.211(6)	O(18)	N(3)	1.224(6)
O(19)	C(55)	1.450(5)	O(19)	C(61)	1.340(5)
O(20)	C(61)	1.208(6)	O(21)	C(63)	1.219(8)
O(22)	C(55)	1.442(7)	O(22)	C(63)	1.346(6)
O(23)	N(4)	1.202(8)	O(24)	N(4)	1.240(9)
N(1)	C(11)	1.513(7)	N(2)	C(29)	1.515(7)
N(3)	C(47)	1.510(7)	N(4)	C(65)	1.525(8)
C(1)	C(2)	1.513(7)	C(1)	C(6)	1.513(7)
C(2)	C(3)	1.550(9)	C(3)	C(4)	1.525(7)
C(4)	C(5)	1.520(8)	C(5)	C(6)	1.527(9)
C(7)	C(8)	1.501(8)	C(8)	C(9)	1.531(6)
C(8)	C(10)	1.565(6)	C(10)	C(11)	1.522(8)
C(10)	C(13)	1.530(7)	C(11)	C(12)	1.520(6)
C(13)	C(14)	1.372(7)	C(13)	C(18)	1.406(7)
C(14)	C(15)	1.402(9)	C(15)	C(16)	1.382(8)
C(16)	C(17)	1.354(7)	C(17)	C(18)	1.399(7)
C(19)	C(20)	1.521(6)	C(19)	C(24)	1.519(7)
C(20)	C(21)	1.509(8)	C(21)	C(22)	1.509(8)
C(22)	C(23)	1.533(7)	C(23)	C(24)	1.523(8)
C(25)	C(26)	1.499(8)	C(26)	C(27)	1.531(6)
C(26)	C(28)	1.565(6)	C(28)	C(29)	1.519(6)
C(28)	C(31)	1.534(7)	C(29)	C(30)	1.524(6)
C(31)	C(32)	1.384(8)	C(31)	C(36)	1.402(7)
C(32)	C(33)	1.392(8)	C(33)	C(34)	1.369(7)
C(34)	C(35)	1.387(8)	C(35)	C(36)	1.399(8)
C(37)	C(38)	1.509(7)	C(37)	C(42)	1.512(6)

Table 3.5. Bond lengths (Å) (continued)

atom	atom	distance	atom	atom	distance
C(38)	C(39)	1.532(8)	C(39)	C(40)	1.506(7)
C(40)	C(41)	1.527(8)	C(41)	C(42)	1.526(8)
C(43)	C(44)	1.488(7)	C(44)	C(45)	1.497(8)
C(44)	C(46)	1.552(6)	C(46)	C(47)	1.530(8)
C(46)	C(49)	1.538(7)	C(47)	C(48)	1.542(6)
C(49)	C(50)	1.399(8)	C(49)	C(54)	1.378(7)
C(50)	C(51)	1.396(8)	C(51)	C(52)	1.369(8)
C(52)	C(53)	1.377(9)	C(53)	C(54)	1.390(7)
C(55)	C(56)	1.508(7)	C(55)	C(60)	1.520(7)
C(56)	C(57)	1.529(9)	C(57)	C(58)	1.535(8)
C(58)	C(59)	1.526(7)	C(59)	C(60)	1.526(9)
C(61)	C(62)	1.499(8)	C(62)	C(63)	1.514(7)
C(62)	C(64)	1.571(7)	C(64)	C(65)	1.540(7)
C(64)	C(67)	1.527(7)	C(65)	C(66)	1.528(7)
C(67)	C(68)	1.389(9)	C(67)	C(72)	1.335(9)
C(68)	C(69)	1.408(8)	C(69)	C(70)	1.339(9)
C(70)	C(71)	1.357(13)	C(71)	C(72)	1.412(13)

Table 3.6. Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	O(1)	C(7)	120.3(4)	C(1)	O(4)	C(9)	121.8(4)
C(19)	O(7)	C(25)	118.3(4)	C(19)	O(10)	C(27)	120.2(3)
C(37)	O(13)	C(43)	120.1(4)	C(37)	O(16)	C(45)	119.4(4)
C(55)	O(19)	C(61)	120.8(4)	C(55)	O(22)	C(63)	120.2(4)
O(5)	N(1)	O(6)	124.3(5)	O(5)	N(1)	C(11)	119.0(5)
O(6)	N(1)	C(11)	116.5(5)	O(11)	N(2)	O(12)	123.1(4)
O(11)	N(2)	C(29)	119.9(4)	O(12)	N(2)	C(29)	117.0(4)
O(17)	N(3)	O(18)	123.5(4)	O(17)	N(3)	C(47)	118.6(4)
O(18)	N(3)	C(47)	117.9(4)	O(23)	N(4)	O(24)	123.0(6)
O(23)	N(4)	C(65)	117.8(6)	O(24)	N(4)	C(65)	119.1(5)
O(1)	C(1)	O(4)	109.9(4)	O(1)	C(1)	C(2)	110.5(4)
O(1)	C(1)	C(6)	105.9(5)	O(4)	C(1)	C(2)	110.5(5)
O(4)	C(1)	C(6)	107.1(4)	C(2)	C(1)	C(6)	112.8(4)
C(1)	C(2)	C(3)	110.9(5)	C(2)	C(3)	C(4)	111.2(4)
C(3)	C(4)	C(5)	110.7(4)	C(4)	C(5)	C(6)	111.2(5)
C(1)	C(6)	C(5)	111.5(4)	O(1)	C(7)	O(2)	117.7(5)
O(1)	C(7)	C(8)	118.0(4)	O(2)	C(7)	C(8)	124.3(4)
C(7)	C(8)	C(9)	113.3(4)	C(7)	C(8)	C(10)	109.9(4)
C(9)	C(8)	C(10)	114.8(4)	O(3)	C(9)	O(4)	119.0(4)
O(3)	C(9)	C(8)	124.8(4)	O(4)	C(9)	C(8)	116.2(5)
C(8)	C(10)	C(11)	114.6(4)	C(8)	C(10)	C(13)	112.8(4)
C(11)	C(10)	C(13)	111.4(4)	N(1)	C(11)	C(10)	110.5(5)
N(1)	C(11)	C(12)	106.7(4)	C(10)	C(11)	C(12)	112.1(5)
C(10)	C(13)	C(14)	123.6(5)	C(10)	C(13)	C(18)	117.9(4)
C(14)	C(13)	C(18)	118.5(5)	C(13)	C(14)	C(15)	120.9(5)
C(14)	C(15)	C(16)	120.1(5)	C(15)	C(16)	C(17)	119.3(5)
C(16)	C(17)	C(18)	121.7(5)	C(13)	C(18)	C(17)	119.4(4)
O(7)	C(19)	O(10)	109.4(3)	O(7)	C(19)	C(20)	107.6(4)
O(7)	C(19)	C(24)	109.9(3)	O(10)	C(19)	C(20)	106.8(3)
O(10)	C(19)	C(24)	111.6(4)	C(20)	C(19)	C(24)	111.4(3)
C(19)	C(20)	C(21)	111.8(4)	C(20)	C(21)	C(22)	112.5(5)
C(21)	C(22)	C(23)	110.3(4)	C(22)	C(23)	C(24)	110.4(4)
C(19)	C(24)	C(23)	111.4(5)	O(7)	C(25)	O(8)	118.6(5)
O(7)	C(25)	C(26)	117.8(4)	O(8)	C(25)	C(26)	123.6(4)
C(25)	C(26)	C(27)	113.8(4)	C(25)	C(26)	C(28)	115.5(4)
C(27)	C(26)	C(28)	109.1(4)	O(9)	C(27)	O(10)	118.4(4)
O(9)	C(27)	C(26)	124.8(4)	O(10)	C(27)	C(26)	116.8(5)

Table 3.6. Bond angles (°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(26)	C(28)	C(29)	113.5(4)	C(26)	C(28)	C(31)	111.9(4)
C(29)	C(28)	C(31)	110.8(4)	N(2)	C(29)	C(28)	111.0(4)
N(2)	C(29)	C(30)	104.9(4)	C(28)	C(29)	C(30)	112.0(4)
C(28)	C(31)	C(32)	122.8(4)	C(28)	C(31)	C(36)	118.4(5)
C(32)	C(31)	C(36)	118.8(5)	C(31)	C(32)	C(33)	121.1(5)
C(32)	C(33)	C(34)	120.0(6)	C(33)	C(34)	C(35)	120.2(5)
C(34)	C(35)	C(36)	120.1(5)	C(31)	C(36)	C(35)	119.7(5)
O(13)	C(37)	O(16)	109.0(3)	O(13)	C(37)	C(38)	111.5(5)
O(13)	C(37)	C(42)	106.4(4)	O(16)	C(37)	C(38)	111.1(4)
O(16)	C(37)	C(42)	105.8(4)	C(38)	C(37)	C(42)	112.8(4)
C(37)	C(38)	C(39)	109.7(5)	C(38)	C(39)	C(40)	111.5(4)
C(39)	C(40)	C(41)	110.4(4)	C(40)	C(41)	C(42)	111.9(5)
C(37)	C(42)	C(41)	110.5(4)	O(13)	C(43)	O(14)	117.6(4)
O(13)	C(43)	C(44)	117.2(5)	O(14)	C(43)	C(44)	125.2(4)
C(43)	C(44)	C(45)	114.4(4)	C(43)	C(44)	C(46)	117.0(4)
C(45)	C(44)	C(46)	108.6(4)	O(15)	C(45)	O(16)	117.1(5)
O(15)	C(45)	C(44)	125.2(4)	O(16)	C(45)	C(44)	117.7(4)
C(44)	C(46)	C(47)	114.7(4)	C(44)	C(46)	C(49)	112.7(3)
C(47)	C(46)	C(49)	108.8(4)	N(3)	C(47)	C(46)	108.9(4)
N(3)	C(47)	C(48)	106.8(3)	C(46)	C(47)	C(48)	111.2(5)
C(46)	C(49)	C(50)	118.5(4)	C(46)	C(49)	C(54)	122.5(5)
C(50)	C(49)	C(54)	119.1(5)	C(49)	C(50)	C(51)	119.9(5)
C(50)	C(51)	C(52)	120.3(6)	C(51)	C(52)	C(53)	120.0(5)
C(52)	C(53)	C(54)	120.3(5)	C(49)	C(54)	C(53)	120.4(5)
O(19)	C(55)	O(22)	109.6(3)	O(19)	C(55)	C(56)	106.1(4)
O(19)	C(55)	C(60)	110.5(4)	O(22)	C(55)	C(56)	108.0(4)
O(22)	C(55)	C(60)	110.7(5)	C(56)	C(55)	C(60)	111.9(4)
C(55)	C(56)	C(57)	111.7(4)	C(56)	C(57)	C(58)	110.8(5)
C(57)	C(58)	C(59)	110.4(4)	C(58)	C(59)	C(60)	111.1(4)
C(55)	C(60)	C(59)	111.3(5)	O(19)	C(61)	O(20)	118.5(5)
O(19)	C(61)	C(62)	117.5(4)	O(20)	C(61)	C(62)	124.0(4)
C(61)	C(62)	C(63)	113.6(4)	C(61)	C(62)	C(64)	115.6(4)
C(63)	C(62)	C(64)	110.3(4)	O(21)	C(63)	O(22)	118.1(4)
O(21)	C(63)	C(62)	123.9(4)	O(22)	C(63)	C(62)	118.0(5)
C(62)	C(64)	C(65)	112.1(4)	C(62)	C(64)	C(67)	114.4(4)
C(65)	C(64)	C(67)	111.8(4)	N(4)	C(65)	C(64)	108.8(4)
N(4)	C(65)	C(66)	104.8(4)	C(64)	C(65)	C(66)	113.2(5)

Table 3.6. Bond angles (°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(64)	C(67)	C(68)	121.6(5)	C(64)	C(67)	C(72)	121.7(6)
C(68)	C(67)	C(72)	116.7(6)	C(67)	C(68)	C(69)	121.5(6)
C(68)	C(69)	C(70)	119.9(6)	C(69)	C(70)	C(71)	119.6(7)
C(70)	C(71)	C(72)	120.0(7)	C(67)	C(72)	C(71)	122.2(8)

Chapter 4: Catalytic Enantioselective Protonation of Nitronates Utilizing an Organocatalyst Chiral Only at Sulfur

The highly enantioselective protonation of nitronates formed upon addition of α-substituted Meldrum's acids to terminally unsubstituted nitroalkenes is described. This work represents the first enantioselective catalytic addition of any type of nucleophile to this class of nitroalkenes. Moreover, for the successful implementation of this method, a new type of N-sulfinyl urea catalyst was developed with chirality residing only at the sulfinyl group, which thereby enabled incorporation of a diverse range of achiral diamine motifs. Finally, the Meldrum's acid addition products are readily converted in high yield to pharmaceutically relevant α,γ-disubstituted γ-lactams.

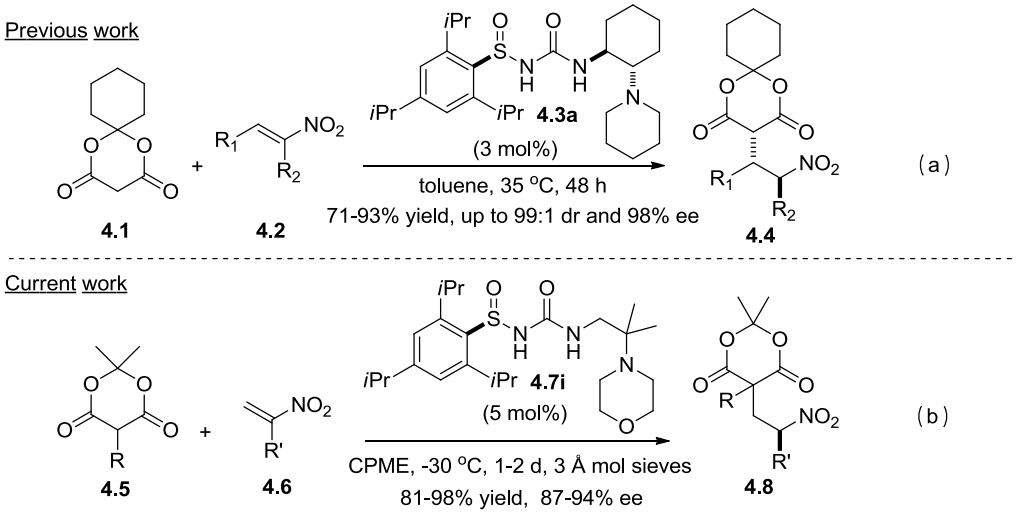
Authorship

The work on enantioselective protonation of nitronates was conducted in collaboration with Dr. Jimmie Weaver and Melissa Lee.

Introduction

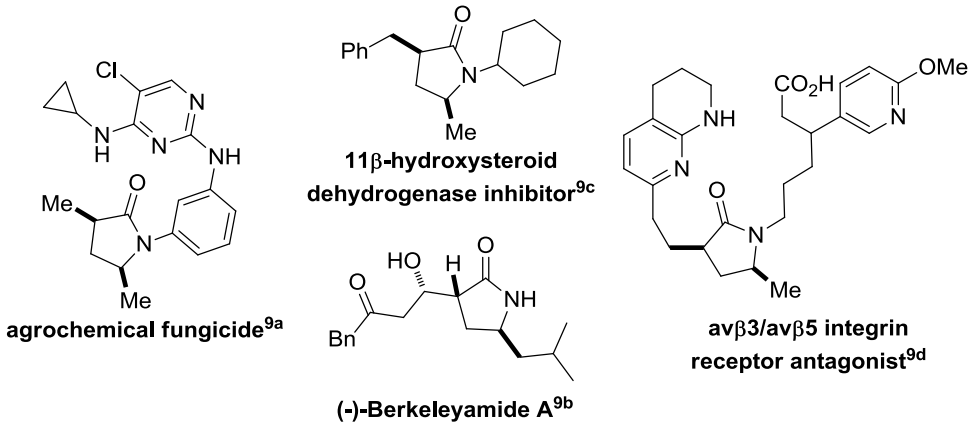
Recently, we reported the enantio- and diastereoselective addition of cyclohexyl Meldrum's acid to α,β-disubstituted nitroalkenes (Figure 4.1a).[1-3] This transformation represented the first example where high enantio- and diastereoselectivity was achieved upon addition of a carbon nucleophile to acyclic α,β-disubstituted nitroalkenes. The key advance enabling this transformation is ***kinetic*** protonation of the nitronate addition product, which is possible because Meldrum's acid (pK_a in DMSO 7-8)[4] is considerably more acidic than the product nitroalkane (pK_a in DMSO 16-17),[4] and thus, the newly formed stereocenter is preserved. We hypothesized that *N*-sulfinyl urea[5,6] catalyzed addition of Meldrum's acid derivatives to α-substituted nitroalkenes lacking β-substituents should also be followed by kinetic protonation, which had the potential to proceed by an enantioselective process. However, no examples of catalytic enantioselective addition of any type of nucleophile to terminally unsubstituted nitroalkenes using either transition metal or organic catalysts had previously been reported.[7,8]

Figure 4.1. Previous and Current Work



In this chapter, we describe the discovery and development of the first example of an enantioselective protonation of nitronates – the addition of α-substituted Meldrum's acids to terminal nitroalkenes, providing adducts **4.8** in good yields and with high enantioselectivities (Figure 4.1b). Notably, successful addition was achieved using a versatile new *N*-sulfinyl urea catalyst **4.7i** that is chiral solely at sulfur and thus allowed for straightforward exploration of a variety of achiral diamine motifs. Importantly, the Meldrum's acid addition products **4.8** are readily converted in a convenient and high yielding two-step process to α,γ-disubstituted γ-lactams, a class of the therapeutically relevant compounds (Figure 4.2).[9,10]

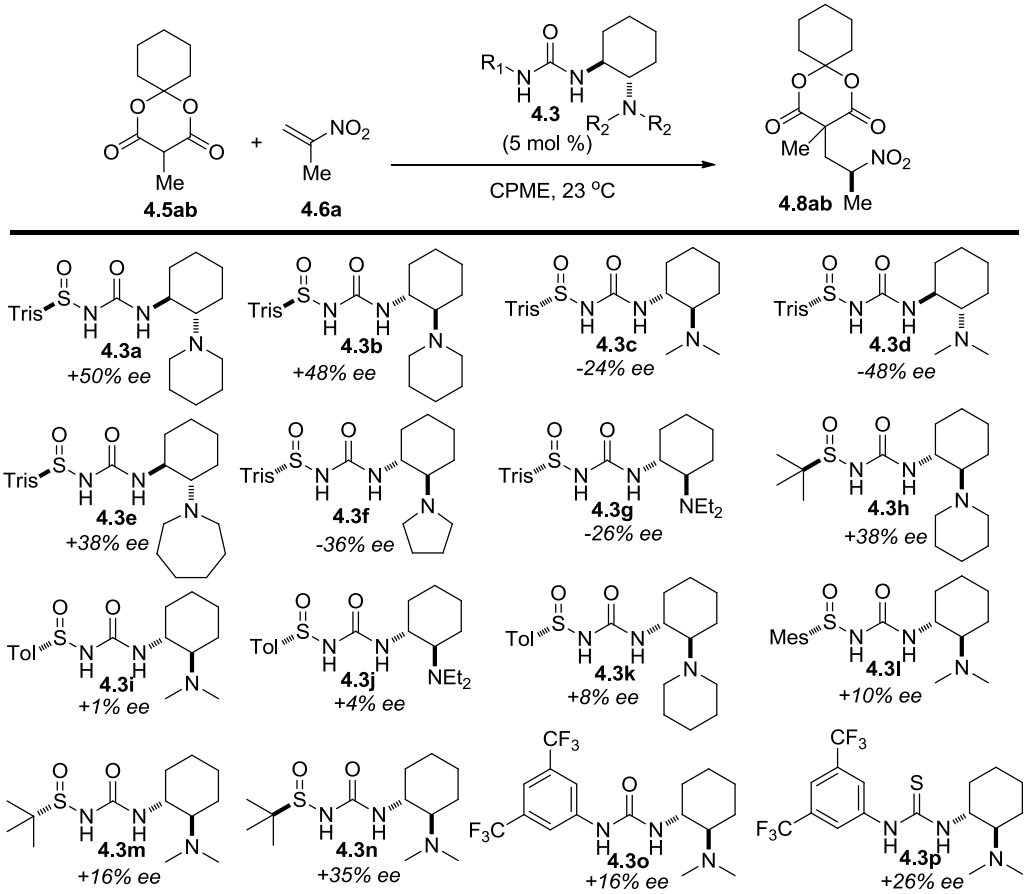
Figure 4.2. Representative Bioactive α,γ-Disubstituted γ-Lactam Derivatives



Results and Discussion

I. Reaction Development

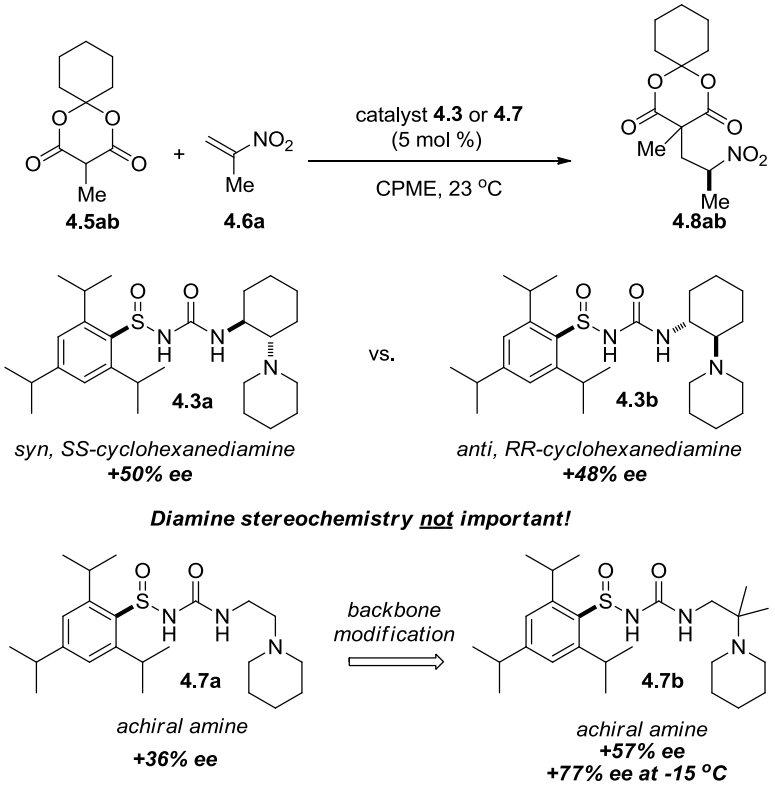
Scheme 4.1. Initial Catalyst Screen for Enantioselective Protonation Reaction



Our investigation began with the addition of α-methyl cyclohexyl Meldrum's acid **4.5ab** to 2-nitropropene (**4.6a**) using catalysts **4.3** (Scheme 4.1).[11] While *N*-sulfinyl urea catalyst **4.3a**, which had previously successfully been employed for additions to α,β-disubstituted nitroalkenes,[1] resulted in an encouraging 50% ee, a screen of various *N*-sulfinyl urea catalysts incorporating different chiral diamines did not result in improved selectivity (Scheme 4.1). It should also be noted that Takemoto's benchmark urea and thiourea catalysts **4.3o** and **4.3p** also provided low enantioselectivities.

Despite failing to uncover a more selective catalyst, this screen did prove useful because it established that catalysts **4.3a** and **4.3b**, which incorporate enantiomeric (1S, 2S) and (1R, 2R) 1,2-cyclohexanediamine components, gave similiar selectivities with the *same* sense of stereo induction (Scheme 4.2). This result suggests that for this transformation the *N*-sulfinyl group is the dominant stereocontrolling element, which contrasts with previously successful *N*-sulfinyl urea catalysts that rely upon the cooperative effect of an additional chiral controlling element along with the sulfinyl stereocenter.[6a-c] The potential ramifications of exclusive *N*-sulfinyl stereocontrol include 1) a simplified catalyst without multiple stereocenters, and 2) greater degree of structural versatility in catalyst optimization.

Scheme 4.2. Discovery of Dominant Sulfinyl Stereocontrol

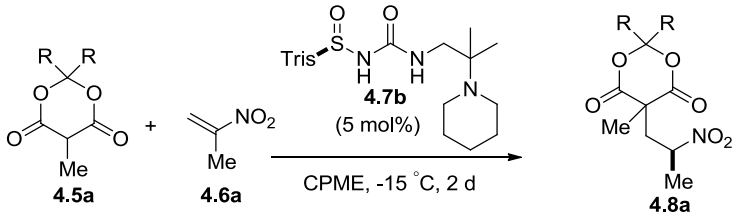


To probe whether a catalyst that possessed only a sulfur stereocenter could be used, catalyst **4.7a**, with a simplified ethylene diamine backbone, was synthesized, evaluated and provided addition product **4.8ab** with 36% ee (Scheme 4.2). The enantioselectivity was only marginally diminished thereby demonstrating that the chiral cyclohexane diamine backbone was not an essential stereodetermining element. Furthermore, placement of geminal dimethyl substitution on the ethylene diamine linker (**4.7b**) provided **4.8ab** with 57% ee indicating that this type of *N*-

sulfinyl urea catalyst could indeed be further modified to increase the selectivity. Importantly, catalyst **4.7b** displayed a significant temperature effect. Cooling the reaction solution from room temperature to -15 °C increased the enantioselectivity from 57% ee to 77% ee. The cyclohexane diamine-based catalyst **4.3a** displayed a comparatively marginal temperature effect, increasing the enantioselectivity from 50% ee at room temperature to 62% ee at -15 ^{o}C. One potential explanation for the greater temperature effect observed with catalyst **4.7b** is the increased amount of rotational freedom in **4.7b**, which upon cooling increasingly reacts through a more selective conformer. Encouraged by this result, we sought to further optimize this transformation using catalysts prepared from *achiral* diamines.

Prior to the full exploration of the diamine component of the catalyst, Meldrum's acid derivatives (**4.5a**) incorporating different acetal substituents (R) were evaluated (Table 4.1). The simplest derivative **4.5aa** (R = Me) gave the highest yield and selectivity and was employed in all subsequent studies. Meldrum's acid **4.5aa** is preferable to derivatives with other R groups due to its low cost, and because the hydrolysis of its addition products produces the volatile and easily removed acetone byproduct (vide infra).

Table 4.1. Influence of Meldrum's Acid Acetal Substituents



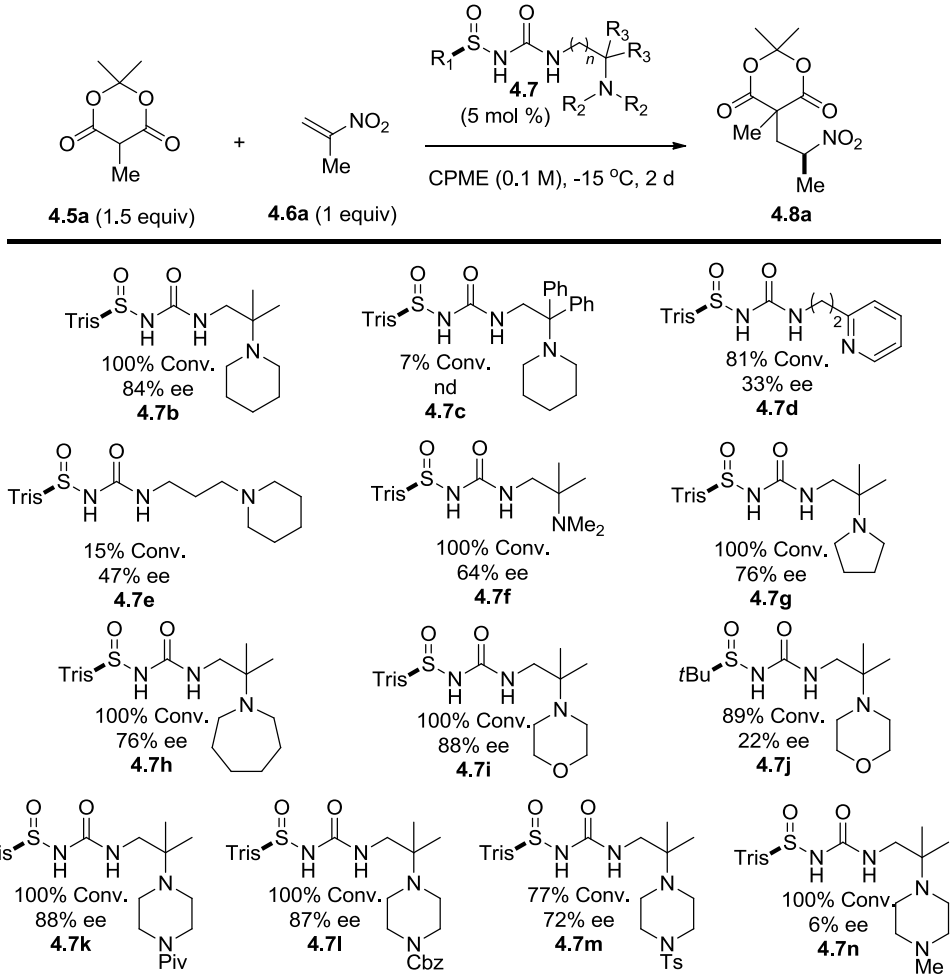
entry	product	R	conv[a] (%)	ee[b] (%)
1	**4.8aa**	Me	100	84
2	**4.8ab**	*c*-Hex	100	77
3	**4.8ac**	Et	100	52
4	**4.8ad**	*c*-Pent	89	84
5	**4.8ae**	*c*-Bu	5	82

[a]Conversion was determined by ^{1}H NMR analysis based upon the ratio of product to Meldrum's acid starting material, taking into account that excess was used (0.5 equiv remaining is equal to full conversion). [b]Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel IA column and hexanes/EtOH as eluent.

We next synthesized a range of *N*-sulfinyl urea catalysts to explore several different aspects of the achiral diamine structure, including tether length, geminal substituents, and modulation of the steric environment and basicity of the tertiary amine base (Scheme 4.3). In evaluating the different catalysts, a slight excess of Meldrum's acid (1.5 equiv) was employed to buffer the reaction solution and thereby ensure that no post reaction racemization occurred. Changing the geminal substituents from methyl to phenyl (**4.7c**) caused the reaction to become too sluggish to be considered. Interestingly, the pyridine catalyst, **4.7d**, gave relatively high conversion though with decreased selectivity, suggesting that the catalyst structure is not necessarily limited to those in which alkylamine bases are incorporated. Catalyst **4.7e**, possessing an increased tether length relative to **4.7b**, provided the product with reduced conversion but comparable selectivity, indicating that a three-carbon linker could be a viable alternative to a two-carbon linker in

subsequent studies.[12] Comparison of catalysts **4.7b**, **f**, **g**, and **h** suggests that the six-membered piperidine ring provides the optimal amine geometry. The high conversion observed with the less basic pyridinyl catalyst **4.7d** prompted us to explore less basic analogs of the optimal piperidine catalyst **4.7b**. To our delight, catalyst **4.7i**, which possessed a morpholine unit,[13] increased the enantioselectivity to 88% ee. The corresponding *tert*-butanesulfinamide-derived catalyst incorporating the morpholine base **4.7j** gave poor selectivity and further defines the importance of the trisylsulfinyl group. Piperazine derivatives **4.7k** and **4.7l**, with *N*-pivaloyl and carbobenzyloxy groups, respectively, also performed well. In contrast, piperazine catalyst **4.7m**, with an *N*-tosyl group, was much less efficient and less selective. Not surprisingly, piperazine **4.7n**, with an additional basic site, did not perform well.

Scheme 4.3. Identification of the Optimal Catalyst

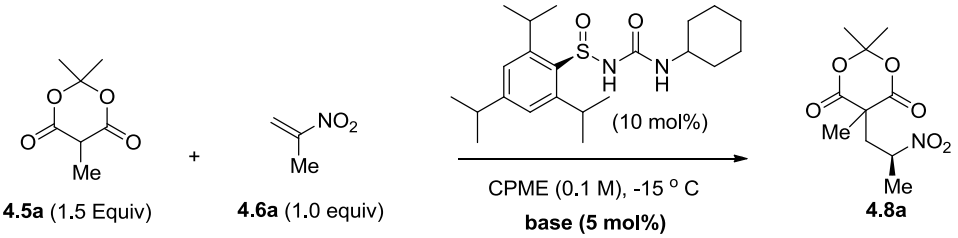


[a]Conversion was determined by ^{1}H NMR analysis based upon the ratio of product to Meldrum's acid starting material, taking into account that excess was used (0.5 equiv remaining is equal to full conversion). [b]Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel IA column and hexanes/EtOH as eluent.

Given that the *N*-sulfinyl group is the dominant stereocontrolling element, the possibility of using an exogenous base was also investigated. Using a simple cyclohexyl trisylsulfinyl urea catalyst, a number of bases were surveyed including several tertiary amines, such as *N*-methylmorpholine and pyridine as well as inorganic bases (Table 4.2). However, all exogenous

bases tested gave <10% ee, indicating that it may be essential to have the base tethered to the urea in order to properly orient the nucleophile for selective attack. Overall, our catalyst screening revealed that the tethered morpholine and *N*-pivaloyl piperazine sulfinyl ureas performed best, but morpholine catalyst **4.7i** was selected for further experiments due to its ease of preparation in a single step from commercially available components.[14]

Table 4.2. Effect of Replacing the Tethered Base with an Exogenous Base

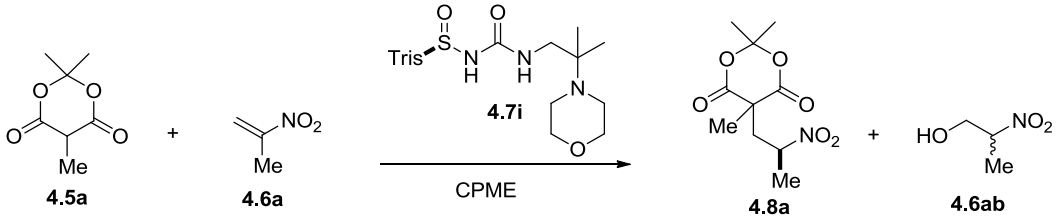


entry	base	conv[a] (%)	ee[b] (%)
1	Et_3N	94	2
2	*i*Pr_2EtN	100	6
3	*N*-methylmorpholine	44	2
4	pyridine	2	nd
5	Cs_2CO_3	100	5

[a]Conversion was determined by ^{1}H NMR analysis based upon the ratio of product to Meldrum's acid starting material, taking into account that excess was used (0.5 equiv remaining is equal to full conversion). [b]Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel IA column and hexanes/EtOH as eluent.

Using catalyst **4.7i**, the reaction conditions were further optimized for yield and enantioenrichment (Table 4.3). Lowering the reaction temperature from -15 ^{o}C to -30 ^{o}C was found to improve the enantioselectivity when solubility constraints were overcome by switching to an excess of nitroalkene (entries 1-4). Under these conditions, hydration of the nitroalkene to form racemic nitroalcohol **4.6ab** caused irreproducible results (entries 4-7), but the addition of 3 Å molecular sieves was found to prevent nitroalcohol formation and improve the reproducibility of enantioselectivity and conversion to the desired product **4.8a** (entry 8).

Table 4.3. Optimization of Enantioselective Protonation Reaction



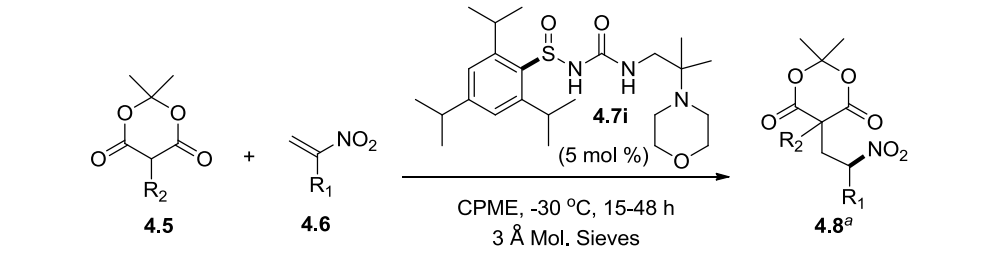
entry	temp (^{o}C)	[**4.6a**] (M)	**4.5a** (equiv)	**4.6a** (equiv)	**4.7i** (mol %)	additive	time (h)	**4.6ab** (%)	conv[a] (%)	ee[b] (%)
1	-15	0.1	1.5	1.0	5	None	48	~0	100	88
2	-30	0.1	1.5	1.0	5	None	23	5	52	84
3	-30	0.3	1.5	1.0	5	None	23	~1	67	84
4	-30	0.2	1.0	2.0	5	None	20	29	32	92
5	-30	0.2	1.0	2.0	1	None	15	11	7	67
6	-30	0.2	1.0	2.0	2.5	None	15	13	20	83
7	-30	0.2	1.0	2.0	15	None	15	20	94	87
8	-30	0.2	1.0	2.0	5	3Å MS	20	~0	94	92

[a]Conversion to **4.8a** was determined by ^{1}H NMR analysis based upon the ratio of product to Meldrum's acid starting material, taking into account that excess was used (0.5 equiv remaining at full conversion). [b]Enantiomeric excess of **4.8a** was determined by chiral HPLC analysis using a Chiralcel IA column and hexanes/EtOH as eluent.

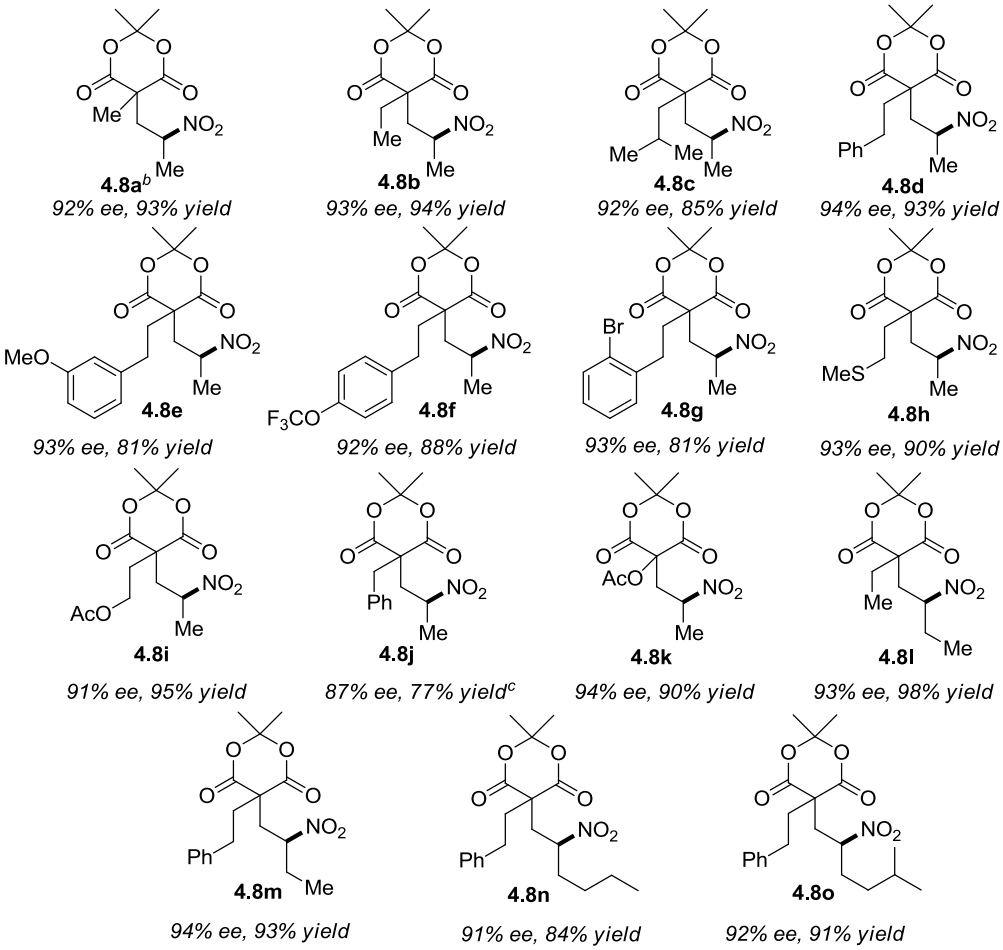
II. Synthetic Scope

With optimized conditions in hand, we explored the reaction scope (Table 4.4). A range of α-alkyl substituted Meldrum's acids served as effective coupling partners with methyl, ethyl, isobutyl and phenethyl substituents all providing the addition products in good yields and with >92% ee (adducts **4.8a-d**). Importantly, the reaction was tolerant of a number of functional groups, including aryl ethers, aryl bromides, thioethers, and esters (adducts **4.8e-i**,**k**). Given the scope of the Meldrum's acid component and the straightforward introduction of diverse alkyl substituents, this method should serve as an excellent means of incorporation of functionality into more complex molecules. While α-benzyl Meldrum's acid provided the product with somewhat lowered selectivity (83% ee) at -30 °C, by lowering the temperature to -50 °C and extending the reaction time, the selectivity was increased to 87% ee (adduct **4.8j**). The substituted Meldrum's acid derivative is not limited to compounds bearing an α-alkyl group. Despite being significantly more acidic, α-acetoxy Meldrum's acid was also an excellent substrate, providing the product **4.8k** in 90% yield and 94% ee. While 2-nitropropene proved to be an excellent substrate for the reaction, a number of other nitroalkenes performed equally well. Specifically, comparable yields and selectivities were further observed for additions to other linear (adducts **4.8l-n**) as well as branched (**4.8o**) terminal nitroalkenes.

Table 4.4. Catalytic Conjugate Addition-Enantioselective Protonation of Nitroalkenes with α-Substituted Meldrum's Acids



4.5 **4.6** **4.8**[a]



4.8a[b] *92% ee, 93% yield*

4.8b *93% ee, 94% yield*

4.8c *92% ee, 85% yield*

4.8d *94% ee, 93% yield*

4.8e *93% ee, 81% yield*

4.8f *92% ee, 88% yield*

4.8g *93% ee, 81% yield*

4.8h *93% ee, 90% yield*

4.8i *91% ee, 95% yield*

4.8j *87% ee, 77% yield*[c]

4.8k *94% ee, 90% yield*

4.8l *93% ee, 98% yield*

4.8m *94% ee, 93% yield*

4.8n *91% ee, 84% yield*

4.8o *92% ee, 91% yield*

[a]Yields are of isolated products after chromatography. Enantiomeric excess was determined using chiral HPLC analysis. [b]Absolute stereochemistry of **4.8a** was determined by X-ray analysis. Stereochemistry of **4.8b-o** is assigned by analogy to **4.8a**. [c]Yield and ee correspond to a reaction run at -50 °C for 90 h. Standard conditions provide **4.8j** in 83% ee and 87% yield.

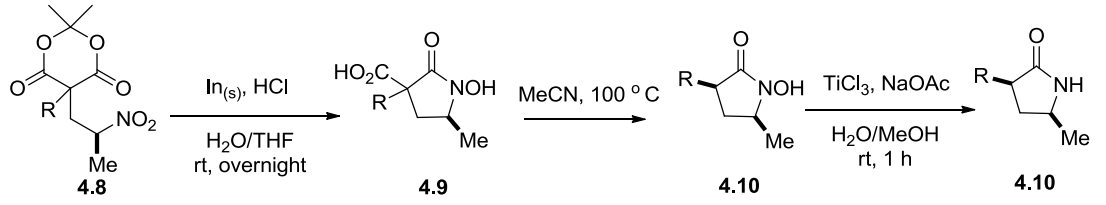
III. Application to the Synthesis of α,γ-Disubstituted γ-Lactams

We envisioned that addition products **4.8** would be versatile intermediates for the asymmetric synthesis of γ-amino acid derivatives and in particular for pharmaceutically relevant α,γ-disubstituted γ-lactams. This transformation requires reduction of the nitro group in adducts **4.8** without epimerization followed by lactamization with extrusion of acetone, and subsequently,

diastereoselective decarboxylative protonation (Scheme 4.4). However, we could not find relevant precedent for racemization-free reduction and cyclization of α-substituted nitroalkanes. Although many reducing conditions give incomplete conversion, racemization or multiple products, clean reduction to the corresponding hydroxamic acids and spontaneous cyclization was found to occur in near quantitative yield upon treatment of **4.8a** with metallic indium and HCl in H_2O/THF (Scheme 4.4).[15] The reduction occurred with complete preservation of the α-nitro stereocenter under the indium/HCl conditions. The cyclization occurred with only moderate diastereoselectivity, but because the subsequent decarboxylative protonation step presumably proceeds through an enol intermediate, the diastereoselectivity of this process is unimportant. Indium-mediated reduction and cyclization was also demonstrated to proceed in high yield and with preservation of the α-nitro stereocenter for α-phenethyl adduct **4.8d** and α-acetoxy derivative **4.8k**.

We next turned our attention to the diastereoselective decarboxylative protonation of intermediates **4.9** to generate α,γ-disubstituted γ-lactam hydroxamic acids **4.10**. Only a single literature report was available for diastereoselective decarboxylative protonation of α-substituted, α-carboxy γ-lactam derivatives, and the transformations proceeded with only modest selectivities.[16] We therefore explored thermal decarboxylation of intermediate **4.9a** using a range of aprotic solvents and reaction temperatures, and decarboxylative protonation in acetonitrile at 100 °C proceeded with 95:5 dr,[17] to provide **4.10a** as single diastereomer in 67% yield after column chromatography (Scheme 4.4). Facile conversion of hydroxamic acids **4.10** to lactams **4.11** was achieved in high yield using $TiCl_3$ as reductant. Furthermore, our optimized three-step process for nitro reduction/cyclization, decarboxylative protonation and N-O bond cleavage provided high yields and comparably high diastereoselectivities for α-phenethyl substituted adduct **4.11d**, and α-acetoxy derivative **4.11k**, showing that this route may serve as a general strategy for accessing α,γ-disubstituted γ-lactams with either α-carbon or α-heteratom substitution.

Scheme 4.4. Rapid Synthesis of α,γ-Disubstituted γ-Lactams



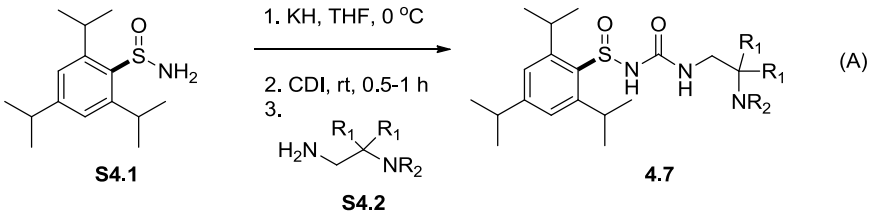
Conclusion

In summary, we have developed a catalytic enantioselective addition of α-substituted Meldrum's acids to α-substituted nitroalkenes. This reaction is the first example of nucleophilic addition to a terminally unsubstituted nitroalkene followed by enantioselective protonation and demonstrates the viability of this disconnection in asymmetric synthesis. In the development of this transformation, a new type of *N*-sulfinyl urea catalyst with chirality residing only at the sulfinyl group was also identified, thereby allowing modifications to the diamine portion of the

catalyst structure that previously were not possible. Finally, we demonstrated that the addition products can readily be converted with high diastereoselectivity to the important class of α,γ-disubstituted γ-lactams, which are present in a number of bioactive compounds and serve as convenient intermediates to substituted γ-amino acids and pyrrolidines.

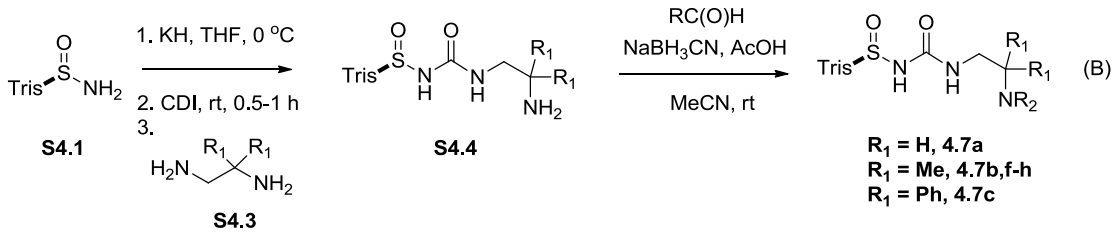
Experimental Section

I. General Experimental. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Cyclopentyl methyl ether (CPME), tetrahydrofuran (THF), diethyl ether, methylene chloride (CH_2Cl_2) and dioxane were passed though columns of activated alumina under nitrogen pressure immediately prior to use. Cyclopentyl methyl ether was additionally distilled prior to passage through alumina to remove BHT stabilizer. Dry potassium hydride was stored and weighed under inert atmosphere in the glove box. Triisopropylbenzenesulfinamide **S4.1** was prepared according to literature procedure.[18,19] Diamines **S4.2**[20] and **S4.3**[21] and were either purchased and used as received or prepared according to literature procedure. Experimental procedures and full analytical data for compounds **4.3** have been previously reported.[1,2a,6c-d] Meldrum's acid substrates were either purchased and used as received or prepared according to literature procedures.[22-25] 2-Nitropropene and 2-nitrobutene were prepared according to literature procedure.[26] The procedure for indium-mediated nitro reduction was adapted from the literature.[15] Indium powder for nitro reduction was purchased from Strem Chemicals as ~325 mesh, 99.99% and used as received. Reactions were monitored by thin layer chromatography (TLC) and visualized with ultraviolet light and potassium permanganate stain. Flash column chromatography was carried out with Merck 60 230-240 mesh silica gel. NMR spectra were obtained on a Bruker AVB-400, Bruker AVB-500 or Varian 400 spectrometer, and unless otherwise noted, ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to either the residual solvent peak (^1H, ^{13}C) or TMS (^1H) as an internal standard. Enantiomeric excess was determined using an Agilent 1100 or 1200 series HPLC equipped with a Chiralcel IA, IB, AS-H and AD-H columns and a multiwavelength detector. IR spectra were recorded on a Nicolet 6700 FTIR spectrometer equipped with an attenuated total reflectance accessory as thin films on a KBr beamsplitter, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. Specific rotations were determined using a Perkin-Elmer 341 polarimeter with a sodium lamp, and concentrations are reported in g/dL. Mass spectra (HRMS) analysis was performed by the Yale Protein Expression Database facility on a 9.4T Bruker Qe FT-ICR MS.

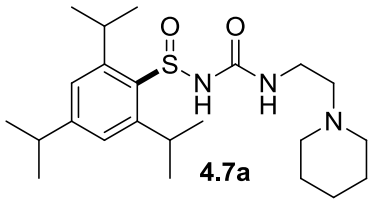


II. General Procedure for the Preparation of Sulfinyl Ureas (Procedure A). To an oven-dried round-bottomed flask equipped with a magnetic stir bar and N_2 inlet was added potassium hydride (3 equiv) and sulfinamide **S4.1** (1.0 equiv). The reaction flask was cooled in an ice-water bath, and THF (0.6 M) was added. The suspension was stirred at 0 °C until bubbling ceased. The ice-water bath was removed, and the reaction mixture was allowed to warm to

ambient temperature. 1,1'-Carbonyldiimidazole (1.0 equiv) was added to the reaction mixture, resulting in the formation of a white precipitate, and the reaction mixture was stirred for 1 h. A solution of diamine **S4.2** (1.2 equiv) in THF (1.0 M) was added, and the suspension was stirred at room temperature for 15-24 h. The reaction was quenched with a solution of acetic acid (3 equiv) in THF (1.0 M). The crude product was concentrated *in vacuo* and purified by reverse phase chromatography, performed with a Teledyne Isco automated chromatography system with a 15.5 g C18 gold column, 5-100% MeOH:H_2O (with 0.1% Et_3N) gradient over 39 column volumes, 30mL/min flow rate, with product detection at 210 and 254 nm.

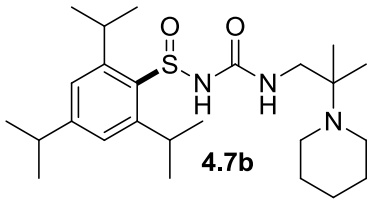


III. General Procedure for the Preparation of Sulfinyl Ureas (Procedure B). To an oven-dried round-bottomed flask equipped with a magnetic stir bar and N_2 inlet was added potassium hydride (3 equiv) and sulfinamide **S4.1** (1.0 equiv). The reaction flask was cooled in an ice-water bath, and THF (0.6 M) was added. The suspension was stirred at 0 °C until bubbling ceased. The ice-water bath was removed, and the reaction mixture was allowed to warm to ambient temperature. 1,1'-Carbonyldiimidazole (1.0 equiv) was added to the reaction mixture, resulting in the formation of a white precipitate, and the reaction mixture was stirred for 1 h. A solution of free amine diamine **S4.3** (3.0 equiv) in THF (1.0 M) was added, and the suspension was stirred at room temperature for 15-24 h. The reaction was quenched with a solution of acetic acid (3 equiv) in THF (1.0 M). The crude product was concentrated *in vacuo* and purified by reverse phase chromatography. To a solution of sulfinyl urea **S4.4** in acetonitrile (0.2 M) was added the appropriate aldehyde (5 equiv). After the reaction mixture was stirred for 15 min, $NaBH_3CN$ (2.1 equiv), and 15 min later, acetic acid (5 equiv) were added. The reaction mixture was stirred 3-12 h, and then the reaction was quenched by addition of 1 N $NaOH_{(aq)}$. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with 1 N NaOH. The crude product was concentrated *in vacuo* and purified by reverse phase chromatography. Chromatography was performed under the conditions described in Procedure II.



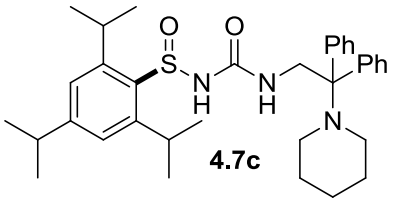
Urea 4.7a. The general procedure (B) was followed using *R*-trisyl sulfinamide (534 mg, 2.00 mmol), KH (240 mg, 6.00 mmol), CDI (324 mg, 2.00 mmol), and ethylene diamine (0.4 mL, 6 mmol) to afford **S4.4c** in 80% yield (560 mg, 1.59 mmol). Then, **S4.4c** (100 mg, 0.28 mmol) was subjected to reductive amination conditions with glutaraldehyde (84 uL, 0.42 mmol) and $NaBH_3CN$ (37 mg, 0.59 mmol) and AcOH (32 uL, 0.56 mmol) to afford **4.7a** in 20% yield (23 mg, 0.056 mmol) as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 7.13 (s, 2H), 3.82 (m, 2H),

3.28 (m, 2H), 2.85 (septet, *J* = 6.9 Hz, 1H), 2.40 (m, 6H), 1.51 (m, 4H), 1.39 (m, 2H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.93, 148.45, 136.25, 123.20, 120.83, 57.36, 54.34, 37.50, 34.35, 28.50, 25.88, 24.45, 24.26, 24.11, 23.68. HRMS (ESI) calcd for $C_{23}H_{39}O_2N_3S$ $[M+H]^+$ 422.283575; found 422.28167.



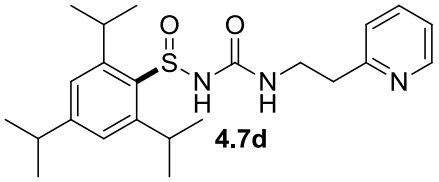
4.7b

Urea 4.7b. The general procedure (B) was followed using *R*-trisyl sulfinamide (100 mg, 0.375 mmol), KH (45 mg, 1.13 mmol), CDI (61 mg, 0.375 mmol), and 2-methylpropane-1,2-diamine (0.12 mL, 1.13 mmol) to afford **S4.4d** in 80% yield (560 mg, 1.59 mmol). Then, **S4.4d** (50 mg, 0.13 mmol) was subjected to reductive amination conditions with glutaraldehyde (28 uL, 0.14 mmol) and $NaBH_3CN$ (17 mg, 0.27 mmol) and AcOH (15 uL, 0.26 mmol) to afford **4.7b** in 38% yield (22 mg, 0.049 mmol) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (s, 2H), 6.93 (br s, 1H), 6.37 (s, 1H), 3.94 (m, 2H), 3.24 (d, *J* = 13.6 Hz, 1H), 3.19 (d, *J* = 13.6 Hz, 1H), 2.87 (septet, *J* = 6.9 Hz, 1H), 2.60 – 2.35 (m, 4H), 1.70 – 1.47 (m, 4H), 1.41 (m, 2 H), 1.32 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 7.0 Hz, 12H), 1.02 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.39, 152.80, 148.09, 136.21, 123.15, 55.63, 48.40, 46.11, 34.27, 28.51, 27.03, 24.70, 24.41, 23.98, 23.63, 21.61, 21.40. HRMS (ESI) calcd for $C_{25}H_{43}O_2N_3S$ $[M+H]^+$ 450.314875; found 450.31267

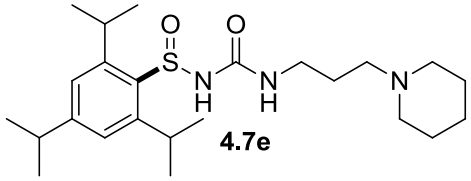


4.7c

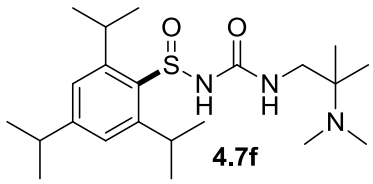
Urea 4.7c. The general procedure (B) was followed using *R*-trisyl sulfinamide (100 mg, 0.375 mmol), KH (43 mg, 1.083 mmol), CDI (58 mg, 0.36 mmol), and 1,1-diphenylethane-1,2-diamine (152 mg, 0.72 mmol) to afford **S4.4e** in 85% yield (155 mg, 0.306 mmol). Then, **S4.4e** (50 mg, 0.11 mmol) was subjected to reductive amination conditions with glutaraldehyde (24 uL, 0.12 mmol) and $NaBH_3CN$ (14 mg, 0.23 mmol) and AcOH (13 uL, 0.22 mmol) to afford **4.7c** in 19% yield (12 mg, 0.0209 mmol) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.39 – 7.22 (m, 10H), 7.20 (s, 2H), 4.16 (d, *J* = 13.5 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.86 (m, 2H), 3.04 – 2.85 (septet, *J* = 6.8 Hz, 1H), 2.30 (m, 4H), 1.74 – 1.49 (m, 4H), 1.35 (d, *J* = 6.8 Hz, 12H), 1.31-1.23 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, MeOD) δ 157.42, 154.44, 141.58, 136.33, 130.26, 128.68, 128.63, 128.19, 128.10, 124.27, 72.04, 35.75, 29.85, 27.89, 26.11, 25.30, 24.28, 24.24, 24.11. HRMS (ESI) calcd for $C_{35}H_{48}O_2N_3S$ $[M+H]^+$ 574.3467; found 574.3461.



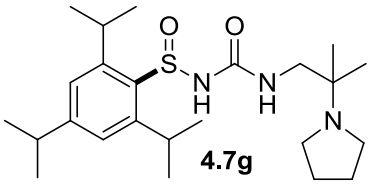
Urea 4.7d. The general procedure (A) was followed using *R*-trisyl sulfinamide (150 mg, 0.562 mmol), KH (67 mg, 1.69 mmol), CDI (91 mg, 0.562 mmol), and 2-(pyridin-2-yl)ethanamine (137 mg, 1.124 mmol) to afford **4.7d** in 91% yield (212 mg, 0.511 mmol) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.47 (s, 1 H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.27 (m, 1H), 7.22 (s, 2H), 3.89 (m, 2H), 3.69 – 3.56 (m, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.98 – 2.89 (septet, *J* = 6.9 Hz, 1H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.22 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.91, 148.79, 148.53, 136.69, 136.28, 123.60, 123.24, 123.19, 121.58, 39.57, 36.87, 34.37, 28.49, 24.53, 23.95, 23.73. HRMS (ESI) calcd for $C_{23}H_{33}O_2N_3S$ $[M+H]^+$ 416.236624; found 416.23440.



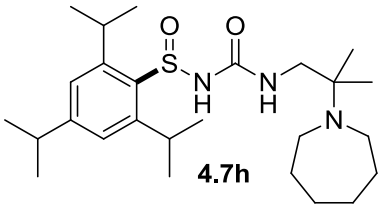
Urea 4.7e. The general procedure (A) was followed using *R*-trisyl sulfinamide (150 mg, 0.562 mmol), KH (67 mg, 1.69 mmol), CDI (91 mg, 0.562 mmol), and 3-(piperidin-1-yl)propan-1-amine (160 mg, 1.124 mmol) to afford **4.7e** in 90% yield (221 mg, 0.508 mmol) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H), 7.03 (s, 2H), 3.89 (s, 2H), 3.28 – 3.05 (m, 2H), 2.83 (septet, *J* = 6.9 Hz, 1H), 2.44 – 2.17 (m, 6H), 1.67 – 1.55 (m, 2H), 1.55 – 1.45 (m, 4H), 1.44 – 1.30 (m, 2H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.18 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.97, 152.89, 148.51, 136.63, 123.29, 58.39, 54.83, 41.02, 34.48, 28.70, 26.10, 25.32, 24.67, 24.47, 24.18, 23.86. HRMS (ESI) calcd for $C_{24}H_{42}O_2N_3S$ $[M+H]^+$ 436.29977; found 436.29783.



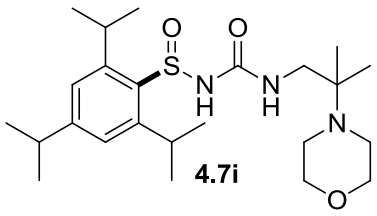
Urea 4.7f. The general procedure (B) was followed using *R*-trisyl sulfinamide (100 mg, 0.375 mmol), KH (45 mg, 1.13 mmol), CDI (61 mg, 0.375 mmol), and 2-methylpropane-1,2-diamine (0.12 mL, 1.13 mmol) to afford **S4.4d** in 80% yield (560 mg, 1.59 mmol). Then, **S4.4d** (50 mg, 0.13 mmol) was subjected to reductive amination conditions with formaldehyde (37% aq) (24 uL, 0.301 mmol) and $NaBH_3CN$ (17 mg, 0.27 mmol) and AcOH (15 uL, 0.26 mmol) to afford **4.7f** in 76% yield (41 mg, 0.100 mmol) as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 7.13 (s, 2H), 3.82 (s, 2H), 3.18 (d, *J* = 13.8 Hz, 1H), 3.14 (d, *J* = 13.8 Hz, 1H), 2.85 (septet, *J* = 6.9 Hz, 1H), 2.17 (s, 6H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.17 (dd, *J* = 6.9, 1.7 Hz, 6H), 1.14 (d, *J* = 6.7 Hz, 6H), 0.96 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.61, 152.97, 148.31, 136.37, 123.30, 55.69, 48.63, 38.17, 34.42, 28.58, 24.60, 24.09, 23.77, 20.56, 20.29. HRMS (ESI) calcd for $C_{22}H_{40}O_2N_3S$ $[M+H]^+$ 410.2841; found 410.2846.



Urea 4.7g. The general procedure (B) was followed using *R*-trisyl sulfinamide (100 mg, 0.375 mmol), KH (45 mg, 1.13 mmol), CDI (61 mg, 0.375 mmol), and 2-methylpropane-1,2-diamine (0.12 mL, 1.13 mmol) to afford **S4.4d** in 80% yield (560 mg, 1.59 mmol). Then, **S4.4d** (50 mg, 0.13 mmol) was subjected to reductive amination conditions with succinaldehyde (0.2 mL, 0.301 mmol) and $NaBH_3CN$ (17 mg, 0.27 mmol) and AcOH (15 uL, 0.26 mmol) to afford **4.7g** in 56% yield (32 mg, 0.073 mmol) as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 7.17 (s, 2H), 3.88 (m, 2H), 3.23 (d, *J* = 13.6 Hz, 1H), 3.18 (d, *J* = 13.6 Hz, 1H), 2.89 (septet, *J* = 6.9 Hz, 1H), 2.66 (m, 4H), 1.72 (m, 4H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 6H), 1.04 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.56, 152.96, 148.26, 136.42, 123.28, 54.30, 49.64, 45.27, 34.38, 28.57, 24.52, 24.05, 23.88, 23.69, 20.91, 20.83. HRMS (ESI) calcd for $C_{24}H_{41}O_2N_3S$ $[M+H]^+$ 436.299225; found 436.29730

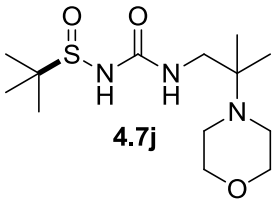


Urea 4.7h. The general procedure (B) was followed using *R*-trisyl sulfinamide (100 mg, 0.375 mmol), KH (45 mg, 1.13 mmol), CDI (61 mg, 0.375 mmol), and 2-methylpropane-1,2-diamine (0.12 mL, 1.13 mmol) to afford **S4.4d** in 80% yield (560 mg, 1.59 mmol). Then, **S4.4d** (50 mg, 0.13 mmol) was subjected to reductive amination conditions with adipaldehyde (1.5 M (aq))(0.2 mL, 0.301 mmol) and $NaBH_3CN$ (17 mg, 0.27 mmol) and AcOH (15 uL, 0.26 mmol) to afford **4.7h** in 45% yield (27 mg, 0.058 mmol) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 2H), 6.67 (s, 1H), 6.35 (s, 1H), 3.95 (m, 2H), 3.20 (m, 2H), 2.90 (septet, *J* = 6.9 Hz, 1H), 2.63 (m, 4H), 1.62 (m, 8H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.26 (d, *J* = 6.7 Hz, 6H), 1.25 (d, *J* = 6.7 Hz, 6H), 1.09 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.07, 153.09, 148.09, 136.22, 123.33, 56.56, 49.41, 47.74, 34.38, 30.31, 28.67, 26.72, 24.53, 24.02, 23.71, 22.30, 21.80. HRMS (ESI) calcd for $C_{26}H_{45}O_2N_3S$ $[M+H]^+$ 464.330525; found 464.32857.



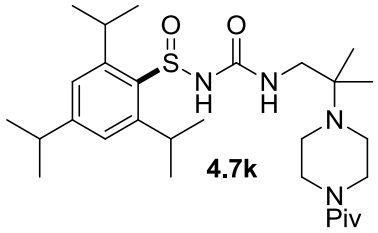
Urea 4.7i. The general procedure (A) was followed using *R*-trisyl sulfinamide (267 mg, 1.0 mmol), KH (128 mg, 3.2 mmol), CDI (162 mg, 1.0 mmol), and 2-methyl-2-morpholinopropan-1-amine (237 mg, 1.5 mmol) to afford **4.7i** in 79% yield (358 mg, 0.79 mmol) as a white solid, mp 165 ^{o}C [decomp]. The crude product was concentrated *in vacuo* and purified by reverse phase

chromatography. Reverse phase chromatography was performed with a Teledyne Isco automated chromatography system with a 50 g C18 gold column, 5-100% MeOH:H_2O (with 0.1% Et_3N) gradient, 40 mL/min flow rate, with product detection at 210 and 254 nm. IR(neat): 3335, 3223, 2962, 2870, 2813, 1693, 1645, 1597, 1549, 1385, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H), 6.76 (s, 1H), 6.20 (s, 1H), 3.94 (m, 2H), 3.71 (m, 4H), 3.21 (m, 2H), 2.89 (septet, *J* = 6.9 Hz, 1H), 2.53 (m, 4H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.25 (d, *J* = 6.6 Hz, 12H), 1.07 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.46, 153.19, 148.26, 136.01, 123.32, 67.72, 55.69, 47.73, 45.63, 34.37, 28.60, 24.52, 24.03, 23.68, 21.17, 21.03. HRMS (ESI) calcd for $C_{24}H_{41}O_3N_3S$ $[M+H]^+$ 452.294139; found 452.29187



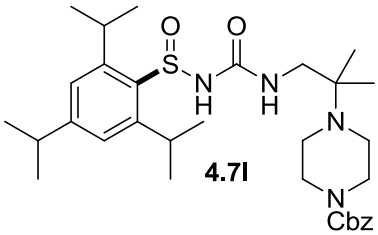
4.7j

Urea 4.7j. The general procedure (A) was followed using *R*-tertbutane sulfinamide (24 mg, 0.10 mmol), KH (12 mg, 0.39 mmol), CDI (16 mg, 0.10 mmol), and 2-methyl-2-morpholinopropan-1-amine (19 mg, 0.12 mmol) to afford **4.7j** in 49% yield (15 mg, 0.049 mmol) as a white solid. ^1H NMR (501 MHz, $CDCl_3$) δ 7.65 – 7.29 (br s, 1H), 6.36 (s, 1H), 3.74 (m, 4H), 3.17 (m, 2H), 2.55 (m, 4H), 1.29 (s, 9H), 1.03 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.86, 67.69, 56.79, 54.95, 47.60, 45.63, 22.21, 21.12, 20.85. HRMS (ESI) calcd for $C_{13}H_{28}O_3N_3S_2$ $[M+H]^+$ 306.1851; found 306.1841.



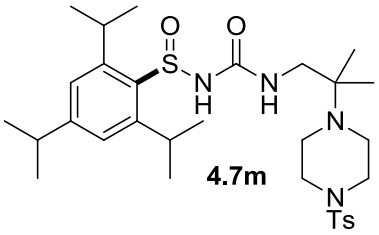
4.7k

Urea 4.7k. The general procedure (A) was followed using *R*-trisyl sulfinamide (21 mg, 0.077 mmol), KH (9.2 mg, 0.23 mmol), CDI (15 mg, 0.09 mmol), and 1-(4-(1-amino-2-methylpropan-2-yl)piperazin-1-yl)-2,2-dimethylpropan-1-one (28 mg, 0.12 mmol) to afford **4.7k** in 49% yield (20 mg, 0.037 mmol) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H), 6.82 (s, 1H), 6.20 (s, 1H), 3.93 (m, 2H), 3.64 (m, 4H), 3.25 (m, 2H), 2.89 (septet, *J* = 6.8 Hz, 1H), 2.53 (m, 4H), 1.33 (d, *J* = 6.6 Hz, 6H), 1.28 – 1.17 (m, 21H), 1.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.30, 154.66, 153.26, 148.36, 135.92, 123.27, 55.78, 47.99, 45.78, 45.45, 38.59, 34.39, 28.60, 28.37, 24.56, 24.03, 23.70, 21.43, 21.34. HRMS (ESI) calcd for $C_{29}H_{50}O_3N_4S$ $[M+H]^+$ 535.367639; found 535.36347.



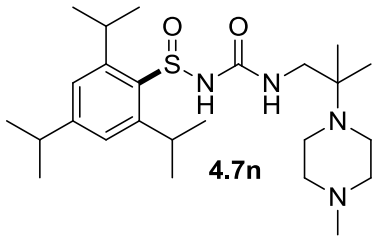
4.7l

Urea 4.7l. The general procedure (A) was followed using *R*-trisyl sulfinamide (30 mg, 0.11 mmol), KH (15 mg, 0.33 mmol), CDI (21 mg, 0.132 mmol), and benzyl 4-(1-amino-2-methylpropan-2-yl)piperazine-1-carboxylate (48 mg, 0.165 mmol) to afford **4.7l** in 45% yield (28 mg, 0.049 mmol) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 7.39 – 7.21 (m, 7H), 3.92 (m, 2H), 3.52 (m, 2H), 3.27 (d, *J* = 13.3 Hz, 1H), 3.17 (d, *J* = 13.5 Hz, 1H), 2.97 (septet, *J* = 6.7 Hz, 1H), 2.74 – 2.33 (m, 8 H), 1.40 (d, *J* = 6.7 Hz, 6H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.24 (d, *J* = 6.6 Hz, 6H), 1.06 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 154.21, 153.08, 148.11, 138.02, 136.18, 129.16, 128.46, 128.20, 127.99, 127.85, 127.04, 123.30, 63.09, 55.49, 54.11, 48.11, 44.94, 34.38, 28.60, 24.57, 24.09, 23.72, 21.57, 21.30. HRMS (ESI) calcd for $C_{32}H_{48}O_4N_4S$ $[M+H]^+$ 585.346903; found 585.34433.



4.7m

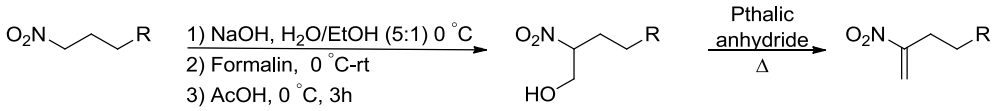
Urea 4.7m. The general procedure (A) was followed using *R*-trisyl sulfinamide (30 mg, 0.11 mmol), KH (15 mg, 0.33 mmol), CDI (21 mg, 0.132 mmol), and 2-methyl-2-(4-tosylpiperazin-1-yl)propan-1-amine (52 mg, 0.165 mmol) to afford **4.7m** in 95% yield (64 mg, 0.106 mmol) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.09 (s, 2H), 6.57 (s, 1H), 5.85 (s, 1H), 3.80 (m, 2H), 3.18 (m, 2H), 3.04 (m, 4H), 2.90 (septet, *J* = 6.9 Hz, 1H), 2.63 (m, 4H), 2.28 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 12H), 1.19 (d, *J* = 6.7 Hz, 6H), 1.05 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.33, 153.29, 148.22, 143.56, 135.87, 132.58, 129.69, 127.79, 123.29, 55.91, 47.91, 46.76, 44.62, 34.39, 28.52, 24.50, 23.92, 23.70, 21.58, 21.35, 21.32. HRMS (ESI) calcd for $C_{31}H_{48}O_4N_4S_2$ $[M+H]^+$ 605.311;, found 605.31230.



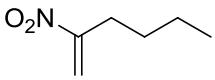
4.7n

Urea 4.7n. The general procedure (A) was followed using *R*-trisyl sulfinamide (30 mg, 0.11 mmol), KH (13 mg, 0.33 mmol), CDI (18 mg, 0.11 mmol), and 2-methyl-2-(4-methylpiperazin-1-yl)propan-1-amine (45 mg, 0.17 mmol) to afford **4.7n** in 79% yield (40 mg, 0.087 mmol) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 2H), 6.70 (s, 1H), 6.27 (s, 1H), 3.95 (m, 2H), 3.21 (m, 2H), 2.89 (septet, *J* = 6.9 Hz, 1H), 2.59 (m, 4H), 2.44 (m, 4H), 2.28 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 6H), 1.27 (s, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.27, 153.01, 148.11, 136.07, 123.22, 55.98, 55.47, 48.04, 45.88, 44.85, 34.32, 28.55, 24.51, 24.03, 23.67, 21.48, 21.20. HRMS (ESI) calcd for $C_{25}H_{45}O_2N_4S$ $[M+H]^+$ 465.32577; found 465.32363.

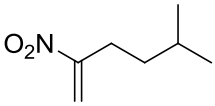
IV. General procedure for synthesis of 2-nitrohex-1-ene and 5-methyl-2-nitrohex-1-ene.



The procedure for the synthesis of 1,1-disubstituted nitroalkenes was adapted from an *Organic Syntheses* procedure by Seebach et al.[26]



2-nitrohex-1-ene: A 50-mL 3-neck flask was evacuated and refilled with N_2. Then a solution of NaOH (1.71g, 42.8 mmol) in H_2O (16.5 mL) and EtOH (3 mL) was added and cooled to 0 °C. Then nitropentane (4.77 g, 40.8 mmol) was added dropwise over 10 min. With rapid stirring the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 1 h the reaction mixture was recooled to 0 °C. Then a 37% solution of formaldehyde in H_2O (3.47 mL, 42.8 mmol) was added dropwise over 10 min. After 3 h the reaction was quenched by the dropwise addition (3 min) of AcOH (2.56 mL, 44.9 mmol) at 0 °C. The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (2 X 25 mL). The combined organic layer was washed with a brine solution (1 X 25 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The crude product was diluted with toluene and reconcentrated *in vacuo* (2 X 25 mL). Without further purification the nitro alcohol and phthalic anhydride (7.89 g, 53 mmol) were placed in 25-mL round bottom flask equipped with a magnetic stir bar. The flask was fitted with a short path distillation apparatus (with a chilled water condenser) and a receiving flask immersed in an ice bath. The system was placed under vacuum (300 torr) then the flask containing the biphasic mixture was stirred and heated to 150 °C. Gradually the vacuum was increased to 110 torr. Then the reaction mixture was heated to 180 °C. The product co-distills with water and a small amount of phthalic anhydride (100 °C at 95 torr). Once the distillation of the product ceased (~15 min), *the system was cooled and backfilled with N_2* (this is important in avoiding dangerous fume-offs (see ref. 27). Then the product was separated from the H_2Odried with a minimal amount of $MgSO_4$ and filtered. The dried nitroalkene was redistilled using a shortpath distillation apparatus with 5 cm Vigoureux column into a flask immersed in an ice bath. Redistillation of the nitroalkene (50-35 torr – not heated above 100 °C) afforded 2-nitrohexene (caution! potent lachrymator) as a yellow oil (2.43 g, 18.8 mmol) in a 46% yield over two steps from nitropentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 5.53 (s, 1H), 2.59 (t, J = 7.6 Hz, 2H), 1.54-1.48 (m, 2H), 1.45-1.38 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.59, 116.97, 30.03, 29.42, 22.24, 13.90.

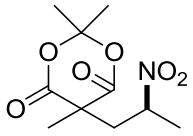


2-nitro-5-methylhexene: As described in the representative procedure above, 4-methyl-nitropentane (1.3 g, 10 mmol) was subject to hydroxymethylenation reaction conditions to afford the corresponding nitro alcohol, which is then subjected to the elimination conditions (phthalic anhydride, 1.92 g, 13 mmol). Redistillation of the product (69 °C/30 torr) afforded pure 5-methyl-2-nitrohex-1-ene (0.37 g, 26% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 5.53 (s, 1H), 2.60 (t, J = 8.8 Hz, 2H), 1.69-1.57 (m, 1H), 1.45-1.39 (m, 2H), 0.94 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.68, 116.64, 36.14, 28.09, 27.62, 22.29.

V. General Procedure for the Addition of Substituted Meldrum's Acid to Nitroalkenes (Procedure C). To a 4 mL scintillation vial were added a stir bar, Meldrum's acid (1.0 equiv), catalyst (0.05 equiv), and 3 Å molecular sieves (250 mg/mmol). The vial was capped with an open top screw cap (Fisher catalog # 03-378-315) with a pierceable PTFE/silicone rubber septum (Fisher catalog # 03-340-10G) and flushed with N_2. Under positive, but static, N_2 pressure, the vial was placed in a pre-chilled cryo-cool bath (-30 °C) and after equilibration (~ 5 min) a precooled solution of nitroalkene (3 equiv) in CPME (0.3 M) was injected, all at once. The heterogeneous mixture was stirred for 15-48 h. After 12 h the reaction progress was monitored by ^{1}H NMR by removing ~10 μL of the reaction mixture, via syringe, and quickly quenching the reaction with a 1% of TFA in CPME solution (~50 μL). Upon reaction completion, the reaction was quenched at -30 °C via the addition of 1% of TFA in CPME solution equal to the reaction volume. The crude reaction mixture was concentrated *in vacuo* and isolated via a Biotage automated chromatography system set at a monitor wavelength of 210 nm to afford the analytically pure adducts.

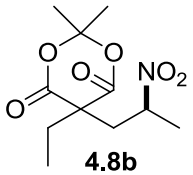
VI. General Procedure for Authentic Racemates Meldrum's Acid Adducts (Procedure D). To a 4 mL scintillation vial were added Meldrum's acid (0.1 mmol) and 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (Schreiner's catalyst) (0.05 mmol). Then a solution of nitroalkene (0.5 mL, 0.6 M) in DCM was added, followed by 20 μL of Et_3N. After 12 h at rt, the adduct was isolated via chromatography.

VII. General Procedure for Authentic Racemates Meldrum's Acid Adducts (Procedure E). 3-5 mg of *isolated* enantioenriched adduct was dissolved in ~250 uL of DCM. ~1 uL of Et_3N was added. The epimerization reaction was stirred for 12 h at 23 °C before confirming complete epimerization via chiral HPLC. For nitropropene-derived products, Procedure E more cleanly provided authentic racemates than Procedure D. However, for all other nitroalkenes, Procedure D was used.



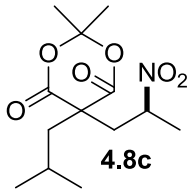
4.8a

4.8a: (S)-2,2,5-trimethyl-5-(2-nitropropyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-methyl Meldrum's acid (47 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8a** in 93% yield (68 mg, 0.28 mmol) as a white solid, mp 97-99 °C. **4.8a** was isolated by column chromatography using 94:6 hexanes:ethyl acetate (1 col. vol.), then gradient 94:6- 50:50 hexanes:ethyl acetate (over 10 col. vol.), then hold at 50:50 hexanes:ethyl acetate (over 2 col. vol.): 92% ee (Chiracel IA, 90:10 hexanes:EtOH, 1 mL/min, 210 nm, t_r (minor) = 15.7 min, t_r (major) = 17.9 min) For 99% ee $[\alpha]_D^{20}$ = 64.7 (c 0.3, $CHCl_3$): IR (neat): 2998, 2945, 1773, 1735, 1552 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 – 4.62 (m, 1H), 2.87 (dd, *J* = 14.9, 10.2 Hz, 1H), 2.27 (dd, *J* = 14.9, 3.5 Hz, 1H), 1.85 (s, 3H), 1.79 (s, 3H), 1.67 (s, 3H), 1.54 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.51, 167.52, 106.36, 78.82, 46.65, 41.90, 29.31, 28.78, 26.46, 19.40. HRMS-ESI (m/z): $[M+Na]^+$ = calcd for $C_{10}H_{15}NO_6Na$, 268.07916; found, 268.07890.



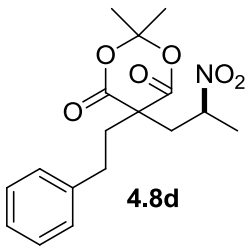
4.8b

4.8b: (*S*)-5-ethyl-2,2-dimethyl-5-(2-nitropropyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-ethyl Meldrum's acid[23] (52 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8b** in 94% yield (72 mg, 0.28 mmol) as a white solid, mp 51-52 °C. **4.8b** was isolated by column chromatography using 94:6 hexanes:ethyl acetate (1 col. vol.), then gradient 94:6-50:50 hexanes:ethyl acetate (over 10 col. vol.), then hold at 50:50 hexanes:ethyl acetate (over 2 col. vol.): 93% ee (Chiralcel ADH , 80:20 hexanes:EtOH, 1 mL/min, 210 nm, t_r (minor) = 8.4 min, t_r (major) = 7.2 min) $[\alpha]_D^{20}$ = 57.9 (c 1.3, $CHCl_3$): IR (neat): 2983, 2945, 1771, 1735, 1553 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 – 4.69 (m, 1H), 2.86 (dd, *J* = 15.2, 10.0 Hz, 1H), 2.22 (dd, *J* = 15.2, 2.9 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.84 (s, 3H), 1.77 (s, 3H), 1.56 (d, *J* = 6.7 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.72, 167.05, 106.46, 78.83, 52.03, 39.57, 33.90, 29.52, 29.12, 20.28, 9.31. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{17}NO_6$ Na, 282.09481; found, 282.09427.



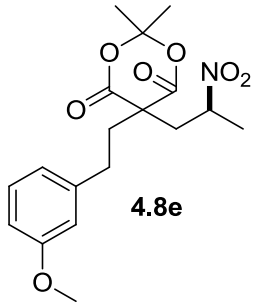
4.8c

4.8c: (S)-5-isobutyl-2,2-dimethyl-5-(2-nitropropyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-isobutyl Meldrum's acid[22] (60 mg, 0.30 mmol), nitropropene (78 mg, 0.90 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8c** in 85% yield (73 mg, 0.25 mmol) as a white solid, mp 95-99 °C. **4.8c** was isolated by column chromatography using 96:4 hexanes(1% AcOH):ethyl acetate(1% AcOH) (1 col. vol.), then gradient 96:4-72:38 hexanes (1% AcOH):ethyl acetate (1% AcOH) (over 10 col. vol.), then hold at 72:38 hexanes (1% AcOH):ethyl acetate (1% AcOH) (over 2 col. vol.): 92% ee (Chiralcel ASH, 85:15 hexanes:EtOH, 1 mL/min, 210 nm, t_r (minor) = 10.1 min, t_r (major) = 11.1 min) $[\alpha]_D^{20}$ = 22.0 (c 0.8, $CHCl_3$): IR (neat): 2965, 2876, 1765, 1725, 1551 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.92 – 4.77 (m, 1H), 2.92 (dd, *J* = 15.4, 9.8 Hz, 1H), 2.20 (dd, *J* = 15.4, 1.4 Hz, 1H), 1.98 (dd, *J* = 13.6, 5.9 Hz, 1H), 1.90 (dd, *J* = 13.7, 6.3 Hz, 1H), 1.86 (s, 3H), 1.79 (s, 3H), 1.77 – 1.68 (m, 1H), 1.58 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.68, 167.64, 78.49, 50.30, 48.58, 40.85, 29.64, 28.85, 25.04, 23.60, 23.43, 20.87. HRMS-ESI (m/z): $[M+Na]^+$ = calcd for $C_{13}H_{21}NO_6Na$, 310.12611; found, 310.1254.



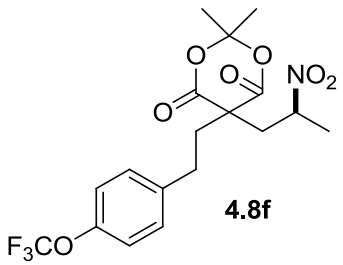
4.8d

4.8d: (S)-2,2-dimethyl-5-(2-nitropropyl)-5-phenethyl-1,3-dioxane-4,6-dione: The general procedure (C) was followed using α-phenethyl Meldrum's acid[24] (74 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8d** in 93% yield (93 mg, 0.28 mmol) as a white solid, mp 96-97 °C. **4.8d** was isolated by column chromatography using 97:3 hexanes:ethyl acetate (1 col. vol.), then gradient 97:3-50:50 hexanes:ethyl acetate (over 10 col. vol.) then hold at 50:50 hexanes:ethyl acetate (over 2 col. vol.): 94% ee (Chiralcel ASH , 80:20 hexanes:IPA, 1 mL/min, 254 nm, t_r (minor) = 10.5 min, t_r (major) = 12.2 min) $[\alpha]_D^{20}$ = 32.5 (c 0.4, $CHCl_3$): IR (neat): 3028, 3002, 2943, 1772, 1736, 1553 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 7.15 – 7.11 (m, 2H), 4.86 – 4.77 (m, 1H), 2.96 (dd, *J* = 15.3, 9.9 Hz, 1H), 2.62 (d, *J* = 8.1 Hz, 1H), 2.60 (d, *J* = 8.1 Hz, 1H), 2.35 – 2.18 (m, 3H), 1.88 (s, 3H), 1.80 (s, 3H), 1.58 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.62, 167.16, 139.12, 128.75, 128.31, 126.74, 106.64, 78.65, 51.45, 42.03, 40.04, 31.14, 29.50, 29.21, 20.58. HRMS-ESI (m/z): $[M+Na]^+$ = calcd for $C_{17}H_{21}NO_6Na$, 358.12611; found, 358.12563.



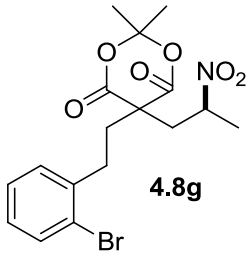
4.8e

4.8e: (S)-5-(3-methoxyphenethyl)-2,2-dimethyl-5-(2-nitropropyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using α-(3-methoxyphenethyl) Meldrum's acid[24] (83 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8e** in 81% yield (72 mg, 0.24 mmol) as a clear colorless oil. **4.8e** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.) then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.) then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 93% ee (Chiralcel ASH, 80:20 hexanes:IPA, 1 mL/min, 210 nm, t_r (minor) = 13.5 min, t_r (major) = 15.9 min) $[\alpha]_D^{20}$ = 30.6 (c 1.0, $CHCl_3$): IR (neat): 3000, 2943, 2837, 1772, 1737, 1586, 1554 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.74 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 6.65 – 6.25 (app t, 1H), 4.88 – 4.68 (m, 1H), 3.76 (s, 3H), 2.94 (dd, *J* = 15.3, 9.9 Hz, 1H), 2.57 (d, *J* = 8.9 Hz, 1H), 2.55 (d, *J* = 8.5 Hz, 1H), 2.33 – 2.14 (m, 3H), 1.86 (s, 3H), 1.78 (s, 3H), 1.56 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.59, 167.13, 159.83. 140.66, 129.75, 120.58, 113.99, 112.10, 106.65, 78.61, 55.20, 51.37, 41.91, 39.97, 31.15, 29.49, 29.18, 20.56. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{23}NO_7Na$, 388.136674; found, 388.13547.



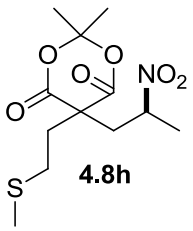
4.8f

4.8f: (S)-2,2-dimethyl-5-(2-nitropropyl)-5-(4-(trifluoromethoxy)phenethyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-(4-(trifluoromethoxy)phenethyl) Meldrum's acid[24] (100 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8f** in 88% yield (110 mg, 0.26 mmol) as a clear colorless oil. **4.8f** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.) then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.) then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 92% ee (Chiralcel ASH, 80:20 hexanes:IPA, 1 mL/min, 210 nm, t_r (minor) = 9.1 min, t_r (major) = 12.5 min) $[\alpha]_D^{20}$ = 29.1 (c 0.9, $CHCl_3$): IR (neat): 3002, 2944, 1773, 1737, 1551 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.11 (m, 4H), 4.91 – 4.74 (m, 1H), 2.97 (dd, *J* = 15.4, 9.9 Hz, 1H), 2.62 (d, *J* = 7.9 Hz, 1H), 2.60 (d, *J* = 7.9 Hz, 1H), 2.36 – 2.14 (m, 3H), 1.89 (s, 3H), 1.80 (s, 3H), 1.58 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.69, 167.33, 148.14, 138.09, 129.85, 121.44, 120.59 (q, *J* = 256.8 Hz), 106.84, 78.77, 51.51, 41.71, 40.21, 30.60, 29.55, 29.32, 20.80. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{20}F_3NO_7Na$, 442.108408; found, 442.10720.



4.8g

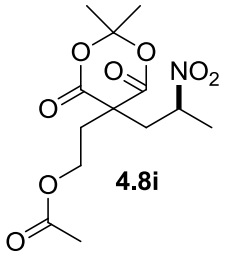
4.8g: (S)-5-(2-bromophenethyl)-2,2-dimethyl-5-(2-nitropropyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-(2-bromophenethyl) Meldrum's acid[24] (98 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8g** in 81% yield (101 mg, 0.24 mmol) as a colorless oil. **4.8g** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.), then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 93% ee (Chiralcel ASH, 80:20 hexanes:IPA, 1 mL/min, 210 nm, t_r (minor) = 12.4 min, t_r (major) = 20.6 min) $[\alpha]_D^{20}$ = 13.9 (c 1.6, $CHCl_3$): IR (neat): 2999, 2941, 1772, 1736, 1553 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.87 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.80 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.73 (td, *J* = 7.7, 1.7 Hz, 1H), 4.49 – 4.39 (m, 1H), 2.61 (dd, *J* = 15.2, 10.0 Hz, 1H), 2.44 – 2.36 (m, 2H), 1.98 (dd, *J* = 15.2, 3.0 Hz, 1H), 1.91 – 1.80 (m, 2H), 1.52 (s, 3H), 1.47 (s, 3H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.31, 166.60, 138.45, 133.09, 130.37, 128.60, 127.91, 124.11, 106.75, 78.69, 51.17, 39.86, 39.53, 31.54, 29.50, 29.21, 20.16. HRMS-ESI (m/z): $[M+Na]^+$ = calcd for $C_{17}H_{20}BrNO_6Na$, 438.034802; found, 438.03253.



4.8h

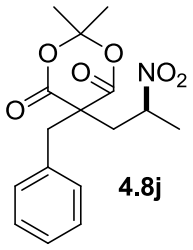
4.8h: (S)-2,2-dimethyl-5-(2-(methylthio)ethyl)-5-(2-nitropropyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using 2,2-dimethyl-5-(2-(methylthio)ethyl)-1,3-

dioxane-4,6-dione[24] (65 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8h** in 90% yield (82 mg, 0.27 mmol) as a white solid, mp 84-85.5 °C. **4.8h** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.), then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 93% ee (Chiralcel ASH, 80:20 hexanes:IPA , 1 mL/min, 230 nm, t_r (minor) = 14.7 min, t_r (major) = 18.7 min) $[\alpha]_D^{20}$ = 21.1 (c 1.1, $CHCl_3$): IR (neat): 2999, 2943, 2920, 1769, 1733, 1553 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.84 – 4.75 (m, 1H), 2.92 (dd, *J* = 15.3, 9.8 Hz, 1H), 2.46 (t, *J* = 8.0 Hz, 2H), 2.34 – 2.19 (m, 3H), 2.06 (s, 3H), 1.85 (s, 3H), 1.79 (s, 3H), 1.58 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.09, 166.74, 106.79, 78.50, 50.80, 40.16, 38.57, 29.38, 29.13, 28.81, 20.61, 15.38. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{19}NO_6SNa$, 328.082529; found, 328.08223.



4.8i

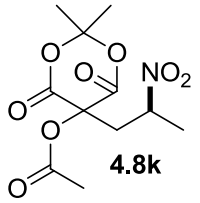
4.8i: (S)-2-(2,2-dimethyl-5-(2-nitropropyl)-4,6-dioxo-1,3-dioxan-5-yl)ethyl acetate: The general procedure (C) was followed using *α*-(2-ethyl acetate) Meldrum's acid[24] (35 mg, 0.15 mmol), nitropropene (39 mg, 0.45 mmol), and catalyst **4.7i** (3.4 mg, 0.0075 mmol) to afford **4.8i** in 95% yield (45 mg, 0.14 mmol) as a white solid, mp 76-82 °C. **4.8i** was isolated by column chromatography using 92:8 hexanes:ethyl acetate (1 col. vol.), then gradient 92:8-45:55 hexanes:ethyl acetate (over 11 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 91% ee (Chiralcel ASH, 80:20 hexanes:IPA, 1 mL/min, 210 nm, t_r (minor) = 18.8 min, t_r (major) = 20.6 min) $[\alpha]_D^{20}$ = 18.3 (c 0.7, $CHCl_3$): IR (neat): 3000, 2946, 1771, 1735, 1554 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 – 4.69 (m, 1H), 4.26 – 4.03 (m, 2H), 2.95 (dd, *J* = 15.4, 9.6 Hz, 1H), 2.46 – 2.28 (m, 2H), 2.22 (dd, *J* = 15.4, 2.5 Hz, 1H), 2.01 (s, 3H), 1.86 (s, 3H), 1.80 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.09, 167.11, 166.98, 106.76, 78.44, 59.43, 48.97, 41.09, 37.49, 29.34, 28.90, 20.97, 20.52. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{19}NO_8Na$, 340.100288; found, 340.09917.



4.8j

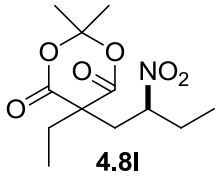
4.8j: (S)-5-benzyl-2,2-dimethyl-5-(2-nitropropyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-benzyl Meldrum's acid[23] (70 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (3.4 mg, 0.015 mmol) to afford **4.8j** in 86% yield (82 mg, 0.26 mmol) as a white solid, mp 104-105.5 °C. **4.8j** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.), then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 83% ee (87% ee at -50 °C) (Chiralcel ADH, 80:20 hexanes:EtOH, 1 mL/min, 254 nm, t_r (minor) = 8.4 min, t_r

(major) = 7.3 min) $[\alpha]_D^{20}$ = 41.1 (c 0.9, $CHCl_3$): IR (neat): 3033, 3000, 2943, 1770, 1735, 1554 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 3H), 7.21 – 7.11 (m, 2H), 4.78 – 4.58 (m, 1H), (d, *J* = 12.8 Hz, 1H), 3.26 (d, *J* = 12.8 Hz, 1H), 3.03 (dd, *J* = 15.1, 9.6 Hz, 1H), 2.39 (dd, *J* = 15.1, 3.0 Hz, 1H), 1.66 (s, 3H), 1.59 (d, *J* = 6.7 Hz, 3H), 0.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.66, 166.73, 133.68, 130.46, 129.05, 128.37, 107.05, 79.41, 54.39, 45.92, 42.60, 29.06, 28.48, 20.55. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{19}NO_6Na$, 344.110459; found, 344.10927.



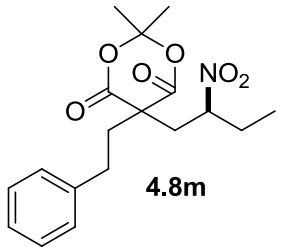
4.8k

4.8k: (S)-2,2-dimethyl-5-(2-nitropropyl)-4,6-dioxo-1,3-dioxan-5-yl acetate: The general procedure (C) was followed using *α*-acetoxy Meldrum's acid[25] (61 mg, 0.30 mmol), nitropropene (52 mg, 0.60 mmol), and catalyst **4.7i** (3.4 mg, 0.015 mmol) to afford **4.8k** in 90% yield (78 mg, 0.27 mmol) as a white solid, mp 94.5-97 °C. **4.8k**, was isolated by column chromatography using 92:8 hexanes:ethyl acetate (1 col. vol.), then gradient 92:8-45:55 hexanes:ethyl acetate (over 11 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 94% ee (Chiralcel ASH , 80:20 hexanes:IPA, 1 mL/min, 230 nm, t_r (minor) = 14.0 min, t_r (major) = 15.5 min) $[\alpha]_D^{20}$ = 1.7 (c 0.6, $CHCl_3$): IR (neat): 3002, 2946, 1789, 1753, 1559 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 – 4.89 (m, 1H), 3.10 (dd, *J* = 15.8, 8.3 Hz, 1H), 2.30 (dd, *J* = 15.8, 2.6 Hz, 1H), 2.16 (s, 3H), 1.87 (s, 3H), 1.86 (s, 3H), 1.64 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.68, 163.58, 162.81, 108.45, 77.21, 72.83, 38.96, 28.59, 28.39, 21.47, 19.62. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{15}NO_8Na$, 312.068988; found, 312.06850.



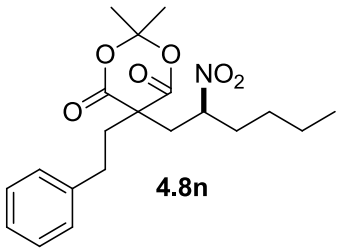
4.8l

4.8l: (S)-5-ethyl-2,2-dimethyl-5-(2-nitrobutyl)-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-ethyl Meldrum's acid[23] (52 mg, 0.30 mmol), nitrobutene (91 mg, 0.90 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8l** in 98% yield (80 mg, 0.29 mmol) as a clear colorless oil. **4.8l** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.), then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 92% ee (Chiralcel IB , 85:15 hexanes:EtOH, 1 mL/min, 250 nm, t_r (minor) = 5.8 min, t_r (major) = 6.0 min) $[\alpha]_D^{20}$ = 26.6 (c 0.7, $CHCl_3$): IR (neat): 2978, 2944, 2884, 1773, 1738, 1554 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 – 4.45 (m, 1H), 2.84 (dd, *J* = 15.3, 10.0 Hz, 1H), 2.22 (dd, *J* = 15.3, 2.1 Hz, 1H), 2.10 – 1.92 (m, 3H), 1.81 (s, 3H), 1.80 – 1.76 (m, 1H), 1.74 (s, 3H), 1.01 – 0.86 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.09, 167.43, 106.54, 85.60, 52.49, 38.42, 33.95, 29.73, 29.25, 28.31, 10.08, 9.57. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{19}NO_6Na$, 296.11046; found,296.10980.



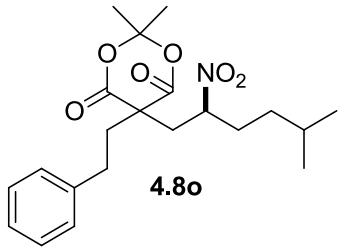
4.8m

4.8m: (S)-2,2-dimethyl-5-(2-nitrobutyl)-5-phenethyl-1,3-dioxane-4,6-dione: The general procedure (C) was followed using α-phenethyl Meldrum's acid[24] (74 mg, 0.30 mmol), nitrobutene (91 mg, 0.90 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8m** in 93% yield (97 mg, 0.28 mmol) as a white solid, mp 75-76.5 °C. **4.8m** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.), then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 92% ee (Chiralcel IB , 85:15 hexanes:EtOH, 1 mL/min, 250 nm, t_r (minor) = 5.8 min, t_r (major) = 6.0 min) $[\alpha]_D^{20}$ = 23.6 (c 1.0, $CHCl_3$): IR (neat): 3028, 2975, 2941, 1773, 1738, 1554 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.0 Hz, 2H), 4.68 – 4.51 (m, 1H), 2.93 (dd, *J* = 15.4, 10.0 Hz, 1H), 2.58 (d, *J* = 8.4 Hz, 1H), 2.56 (d, *J* = 8.9 Hz, 1H), 2.35 – 2.13 (m, 3H), 2.06 – 1.91 (m, 1H), 1.86 (s, 3H), 1.83 – 1.78 (m, 1H), 1.77 (s, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). .^{13}C NMR (126 MHz, $CDCl_3$) δ 167.76, 167.33, 139.09, 128.69, 128.30, 126.68, 106.54, 85.04, 51.60, 41.90, 38.61, 31.22, 29.51, 29.16, 28.33, 9.89. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{23}NNaO_6$, 372.3681; found, 372.1415.



4.8n

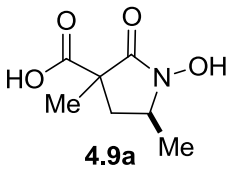
4.8n: (S)-2,2-dimethyl-5-(2-nitrohexyl)-5-phenethyl-1,3-dioxane-4,6-dione: The general procedure (C) was followed using α-phenethyl Meldrum's acid[24] (74 mg, 0.30 mmol), 2-nitrohexene (116 mg, 0.90 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8n** in 84% yield (95 mg, 0.25 mmol) as a colorless oil. **4.8n** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.), then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 91% ee (Chiralcel IA , 90:10 hexanes:EtOH, 1 mL/min, 210 nm, t_r (minor) = 7.3 min, t_r (major) = 8.7 min) $[\alpha]_D^{20}$ = 7.9 (c 1.5, $CHCl_3$): IR (neat): 2959, 2873, 1774, 1734, 1554, 1455, 1394, 1364, 1307, 1270, 1205, 1074, 972 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.22-7.17 (m, 1H), 7.14-7.09 (m, 2H), 4.70-4.62 (m, 1H), 2.94 (dd, *J* = 15.4, 10.0 Hz, 1H), 2.59 (t, *J* = 8.7 Hz, 2H), 2.33 – 2.18 (m, 3H), 2.00-1.95 (m, 1H), 1.87 (s, 3H), 1.79 (s, 3H), 1.78 – 1.66 (m, 1H), 1.40 – 1.20 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.81, 167.34, 139.16, 128.75, 128.36, 126.74, 106.59, 83.89, 51.70, 41.94, 38.95, 34.70, 31.26, 29.54, 29.22, 27.50, 22.01, 13.68. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{27}NO_6$, 400.17306; found, 400.17307.



4.8o

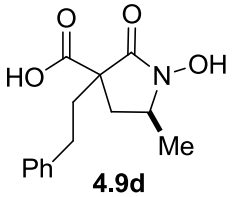
4.8o: (S)-2,2-dimethyl-5-(2-nitro-5-methylhexyl)-5-phenethyl-1,3-dioxane-4,6-dione: The general procedure (C) was followed using *α*-phenethyl Meldrum's acid[24] (74 mg, 0.30 mmol), 2-nitro-5-methylhexene (129 mg, 0.90 mmol), and catalyst **4.7i** (6.8 mg, 0.015 mmol) to afford **4.8o** in 91% yield (107 mg, 0.27 mmol) as a colorless oil. **4.8o** was isolated by column chromatography using 95:5 hexanes:ethyl acetate (1 col. vol.), then gradient 95:5-60:40 hexanes:ethyl acetate (over 12 col. vol.), then hold at 0:100 hexanes:ethyl acetate (over 2 col. vol.): 92% ee (Chiralcel IA , 90:10 hexanes:EtOH, 1 mL/min, 210 nm, t_r (minor) = 6.5 min, t_r (major) = 7.7 min) $[\alpha]_D^{20}$ = 4.3 (c 1.3, $CHCl_3$): IR (neat): 2957, 2871, 1774, 1739, 1555, 1455, 1394, 1364, 1270, 1206, 1074, 974 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.22-7.18 (m, 1H), 7.13-7.09 (m, 2H), 4.74 – 4.52 (m, 1H), 2.95 (dd, *J* = 15.4, 10.0 Hz, 1H), 2.59 (t, *J* = 8.7 Hz, 2H), 2.33 – 2.17 (m, 3H), 2.04 – 1.92 (m, 1H), 1.87 (s, 3H), 1.79 (s, 3H), 1.74-1.68 (m, 1H), 1.60 – 1.48 (septet, *J* = 6.8 Hz, 1H), 1.22 – 1.13 (m, 2H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.82, 167.35, 139.15, 128.75, 128.36, 126.74, 106.61, 84.14, 51.69, 41.73, 38.94, 34.25, 32.98, 31.26, 29.54, 29.22, 27.61, 22.32, 22.18. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{29}NO_6$, 414.18871; found, 414.18807.

VIII. General Procedure for Indium-mediated Reduction and Cyclization of Meldrum's Acid Adducts. The procedure for reduction and lactamization was adapted from a procedure for nitro reduction by Singh et al.[15] To a scintillation vial containing a stir bar and Meldrum's acid adduct **7** (1.0 equiv) was added THF (1.0 M) and 2 N HCl (6.0 equiv). Metallic indium (4.0 equiv) was then added all at once and the reaction mixture was stirred vigorously. The reaction mixture was initially a suspension of gray indium powder and white solid starting material but over time transformed into a clear solution containing a single metallic chunk. The reaction progress was monitored by LCMS, and upon completion the liquid layer was removed and the THF was evaporated *in vacuo*. The resulting aqueous crude product was loaded directly on a reverse phase samplet and purified with reverse phase chromatography (5-100% methanol in TFA-buffered water). The purification was conducted on a Teledyne ISCO automated chromatography system and the product elution was visualized at 210 nm. The fractions containing product were combined and the solvent was evaporated *in vacuo* in a 40-50 °C water bath, then dried under vacuum overnight to afford the carboxy lactam as a mixture of diastereomers. This procedure was found to give similarly high yields over two orders of magnitude in scale.



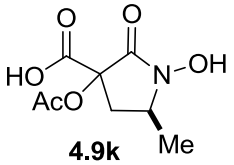
4.9a

4.9a: (S)-1-hydroxy-5-methyl-3-carboxy-3-methyl-pyrrolidinone: The general procedure was followed using adduct **7a** recrystallized from CPME/hexanes (0.50 g, 2.0 mmol, 99% ee), THF (2.0 mL), aqueous 2 N HCl (6.0 mL) and metallic indium (0.94 g). Lactam **4.9a** (0.32 g, 90% yield) was isolated as a white solid 78:22 mixture of diastereomers after reverse phase chromatography: 99% ee (Chiracel ADH, 90:10 hexanes (1% TFA):EtOH, 1 mL/min, 230 nm, major diastereomer [t_r (minor) = 8.9 min, t_r (major) = 8.0 min)], minor diastereomer [(t_r (minor) = 11.0 min, t_r (major) = 11.2 min]). ^{1}H NMR (400 MHz, MeOD) [major diastereomer] δ 4.03 – 3.87 (m, 1H), 2.66 (dd, *J* = 13.1, 6.9 Hz, 1H), 1.55 (dd, *J* = 13.1, 8.2 Hz, 1H), 1.40 (s, 3H), 1.34 (d, *J* = 6.1 Hz, 3H) [minor diastereomer] δ 3.81 (m, 1H), 2.18 (m, 2H), 1.40 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) [major diastereomer] δ 175.25, 171.41, 55.08, 50.10, 39.32, 21.48, 19.55 [minor diastereomer] δ 175.61, 171.41, 54.46, 49.68, 38.07, 20.45, 19.23. LRMS-ESI (m/z): $[M+H]^+$ calcd for $C_7H_{11}NO_4$, 174.08; found, 174.08.



4.9d

4.9d: (5S)-1-hydroxy-5-methyl-2-oxo-3-phenethylpyrrolidine-3-carboxylic acid: The general procedure was followed using adduct **4.8d** recrystallized from CPME/hexanes (70 mg, 0.20 mmol, 97% ee), THF (0.40 mL), aqueous 3 N HCl (0.40 mL) and metallic indium (92 mg). Lactam **4.9d** (52 mg, 99% yield), an oil, was isolated as a 79:21 mixture of diastereomers: ^{1}H NMR (400 MHz, CD_3CN) [major diastereomer] δ 8.95 (s, 1H), 7.36 – 7.28 (m, 2H), 7.28 – 7.18 (m, 3H), 3.99 – 3.90 (m, 1H), 2.76 – 2.64 (m, 2H), 2.51 (td, *J* = 12.8, 4.4 Hz, 1H), 2.23 – 2.12 (m, 1H), 2.03 – 1.95 (m, 1H), 1.71 (dd, *J* = 13.3, 8.2 Hz, 1H), 1.35 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, CD_3CN) [major diastereomer] δ 173.09, 169.43, 142.66, 129.50, 129.37, 127.04, 54.42, 53.67, 37.09, 35.18, 31.33, 19.50. LRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{17}NO_4$, 264.12; found, 264.12.

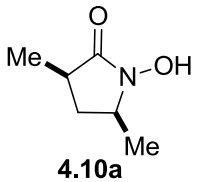


4.9k

4.9k: (5S)-1-hydroxy-3-acetoxy-5-methyl-pyrrolidinone-3-carboxylic acid: The general procedure was followed using adduct **7k** (0.80 g, 2.77 mmol, 94% ee), THF (2.77 mL), aqueous 2 N HCl (5.54 mL) and metallic indium (1.27 g). Lactam **10k** (0.51 g, 85% yield) was isolated as a a white solid77:23 mixture of diastereomers: 94% ee (Chiracel ADH, 90:10 hexanes (1% TFA):EtOH, 1 mL/min, 230 nm, major diastereomer [t_r (minor) = 8.9 min, t_r (major) = 8.0 min)], minor diastereomer [(t_r (minor) = 11.0 min, t_r (major) = 11.2 min]). ^{1}H NMR (400 MHz, MeOD) [major diastereomer] δ 4.03 – 3.85 (m, 1H), 3.25 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.15 (s, 3H), 1.86 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.37 (d, *J* = 6.0 Hz, 3H) [minor diastereromer] δ 4.03 – 3.85 (m, 1H), 2.69 – 2.52 (m, 2H), 2.14 (s, 3H), 1.41 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, CD_3CN) [major diastereomer] δ 169.27, 167.24, 161.45, 79.31, 52.60, 36.59, 19.70, 17.93 [minor

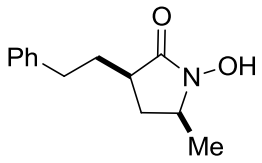
diastereomer] δ 169.36, 167.53, 160.18, 78.90, 40.23, 34.70, 19.67, 17.53. LRMS-ESI (m/z): $[M+H]^+$ calcd for $C_8H_{11}NO_6$, 218.07; found, 218.07.

IX. General Procedure for Diastereoselective Decarboxylative Protonation of Carboxy Lactam Hydroxamic Acids. To a scintillation vial fitted with an open top screw cap (Fisher catalog # 03-378-315) with a piercable PTFE/silicone rubber septum (Fisher catalog # 03-340-10G) or a J. Young tube was added carboxy lactam (**4.9**). The vial or tube was flushed with N_2, dry acetonitrile was added (0.1-0.2 M), and the reaction mixture was heated in the sealed vial or tube in a 100 °C oil bath for the specified amount of time. Upon cooling the solvent was evaporated *in vacuo*, and the crude product was purified with silica gel chromatography. Under these conditions, the decarboxylative protonation occurred with a diastereoselectivity of ~20:1.



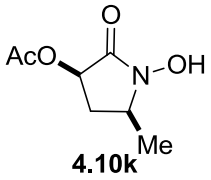
4.10a

4.10a: (3S,5R)-1-hydroxy-3,5-dimethylpyrrolidinone: The general procedure was followed using lactam **4.9a** (64 mg, 0.37 mmol) in acetonitrile (2.0 mL). The reaction was monitored by TLC and run for 3 d, then purified by silica gel chromatography using 95:5:0.5 DCM:MeOH:NH_4OH as eluent. 32 mg (67% yield) of white solid lactam **4.10a** [27] was isolated as a single diastereomer after chromatography. $[\alpha]_D^{20}$ = -12.3 (c 0.6, $CHCl_3$): IR (neat): 3133, 2972, 2933, 2875, 1687, 1508, 1457, 1380, 1271 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 3.69 (m, 1H), 2.47 – 2.26 (m, 2H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.13 (m, 1H), 1.13 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.01, 54.12, 33.98, 33.89, 19.59, 17.03. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_6H_{11}NO_2$, 152.06820; found, 152.06800.



4.10d

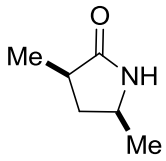
4.10d: (3R,5S)-1-hydroxy-5-methyl-3-phenethylpyrrolidin-2-one: The general procedure was followed using lactam **4.9d** (40 mg, 0.15 mmol) in acetonitrile (1.0 mL). The reaction was monitored by ^1H NMR and determined to reach completion after 32 h, then purified on a Biotage automated chromatgraphy system using a 10 g SNAP column and eluting with a gradient of 1-10% MeOH in DCM. 26 mg (78% yield) of an oil was isolated as a 95:5 diastereomeric mixture after chromatography: 97% ee (Chiracel ADH, 90:10 hexanes:*i*PrOH, 1 mL/min, 210 nm, t_r (major) = 11.0 min, t_r (minor) = 12.9 min). IR (neat): 3026, 2862, 1680, 1496, 1453, 1379, 1358, 1274, 1053, 1028, 909, 728, 699 cm^{-1}. ^1H NMR (501 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.30 – 7.25 (m, 2H), 7.22 – 7.14 (m, 3H), 3.79 – 3.68 (m, 1H), 2.73 – 2.65 (m, 1H), 2.65 – 2.58 (m, 1H), 2.46 – 2.33 (m, 2H), 2.21 – 2.11 (m, 1H), 1.67 – 1.57 (m, 1H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.28 – 1.19 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.60, 141.38, 128.60, 128.55, 126.21, 54.27, 38.43, 33.55, 32.95, 31.91, 19.78. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{13}H_{17}NO_2$, 220.13321; found, 220.13310.



4.10k

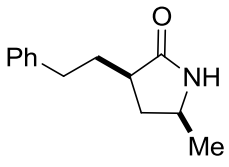
4.10k: (3S,5R)-1-hydroxy-5-methyl-3-acetoxypyrrolidinone: The general procedure was followed using lactam **4.9k** (23 mg, 0.11 mmol) in acetonitrile (1.0 mL). The reaction was monitored by ^{1}H NMR and determined to reach completion after 15 h, then purified on a biotage automated chromatgraphy system using a 10 g SNAP column and eluting with a gradient of 2-20% MeOH in DCM. 15 mg (82% yield) of a white solid was isolated as a 94:6 diastereomeric mixture after chromatography. IR (neat): 3125, 2850, 1746, 1704, 1507, 1449, 1374, 1276, 1231, 1122, 1088, 1055, 1027, 947, 779, 691, 665 cm^{-1}. ^{1}H NMR (501 MHz, $CDCl_3$) δ 5.33 (apparent t, *J* = 8.1 Hz, 1H), 3.87 – 3.70 (m, 1H), 2.87 – 2.70 (m, 1H), 2.14 (s, 3H), 1.60 – 1.53 (m, 1H), 1.40 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.99, 165.31, 68.35, 52.88, 32.95, 20.79, 19.23. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_7H_{11}NO_4$, 174.07608; found, 174.07600.

X. General Procedure for Titanium(III)-Mediated N-O Bond Reduction of Lactam Hydroxamic Acids. To a scintillation vial fitted with a rubber septum and N_2 inlet was added lactam hydroxamic acid (**4.10**). The vial was flushed with N_2 and dry methanol was added (0.2 M). NaOAc (12 equiv) was then weighed and quickly added, followed by DI water (0.2 M) and the reaction mixture was cooled in an ice-water bath. After ~5 min a 20% solution of $TiCl_3$ in aqueous 2% HCl was added dropwise (2.2 equiv). The cooling bath was removed and the reaction mixture was stirred at room temperature and monitored by TLC and LCMS until completion (< 1 h). The reaction mixture was then diluted with water, extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated to give pure lactams **4.11**.



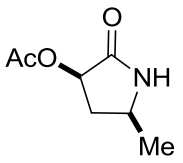
4.11a

4.11a: (3S,5R)-3,5-dimethylpyrrolidinone: The general procedure was followed using lactam **4.10a** (35 mg, 0.27 mmol), $TiCl_3$ (0.46 mL, 0.60 mmol), and NaOAc (0.27 g, 3.3 mmol) in 1:1 methanol/water (2.7 mL) to afford lactam **4.11a** (27 mg, 90% yield) as an amorphous solid. $[\alpha]_D^{20}$ = +20.1 (c 2.1, $CHCl_3$): IR (neat): 2977, 2963, 2869, 1703, 1452, 1426, 1378, 1254 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (br s, 1H), 3.64-3.62 (m, 1H), 2.46-2.40 (m, 2H), 1.25-1.21 (m, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.63, 48.10, 38.84, 37.30, 22.08, 15.95. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_6H_{11}NO$, 136.07383; found, 136.07320.



4.11d

4.11d: (3R,5S)-5-methyl-3-phenethylpyrrolidin-2-one: The general procedure was followed using lactam **4.10d** (40 mg, 0.18 mmol), $TiCl_3$ (0.31 mL, 0.40 mmol), and NaOAc (0.18 g, 2.2 mmol) in 1:1 methanol/water (1.8 mL) to afford lactam **4.11d** (34 mg, 92% yield) as an amorphous solid: IR (neat): 2965, 2925, 2861, 1686, 1496, 1453, 1379, 1253 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.22-7.19 (m, 2H), 7.17-7.12 (m, 3H), 6.64 (br s, 1H), 3.66-3.53 (m, 1H), 2.69-2.65 (m, 1H), 2.64-2.57 (m, 1H), 2.40-2.31 (m, 2H), 2.24-2.17 (m, 1H), 1.62-1.54 (m, 1H), 1.25-1.20 (m, 1H), 1.18 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.83, 141.53, 128.48, 128.38, 125.94, 48.28, 41.84, 36.78, 33.50, 32.79, 22.19. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{13}H_{17}NO$, 204.13829; found, 204.13800.



4.11k

4.11k: (3S,5R)-5-methyl-3-acetoxypyrrolidinone: The general procedure was followed using lactam **4.10k** (40 mg, 0.23 mmol), $TiCl_3$ (0.39 mL, 0.51 mmol), and NaOAc (0.23 g, 2.8 mmol) in 1:1 methanol/water (2.3 mL) to afford lactam **4.11k** (34 mg, 94% yield) as a colorless oil: IR (neat): 2972, 1701, 1431, 1372, 1229 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (br s, 1H), 5.26 (dd, J = 9.3, 8.3 Hz, 1H), 3.65 (m, 1H), 2.71 (m, 1H), 2.09 (s, 3H), 1.53 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.32, 170.28, 71.18, 46.55, 36.67, 22.03, 20.82. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_7H_{11}NO_3$, 180.06311; found, 180.06300.

References

(1) Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121.

(2) For enantioselective catalytic additions of Meldrum's acid to β-substituted nitroalkenes proceeding with modest selectivities, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Bassas, O.; Huuskenon, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340. (c) Kleczkowska, E.; Sas, W. *Polish J. Chem.* **2007**, *81*, 1457.

(3) For leading references on the organocatalytic addition of the related malonates to β-substituted and cyclic α,β-disubstituted nitroalkenes, see: (a) Ref. 2a. (b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (c) Li, H.; Wang, L. T.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (d) Xu, F.; Corley, E.; Zacuto, M.; Conlon, D. A.; Pipik, B.; Humphrey, G.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2010**, *75*, 1343. (e) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (f) Zhang, L.; Lee, M-M.; Lee, S-M.; Lee, J.; Cheng, M.; Jeong, B-S.; Park, H-G.; Jew, S-S. *Adv. Synth. Catal.* **2009**, *351*, 3063. (g) Chen, W-Y.; Li, P.; Xie, J-W.; Li, X-S. *Catal. Commun.* **2011**, *12*, 502.

(4) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(5) For reviews of H-bonding catalysis, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (e) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516-532. (f) Terada, M. *Synthesis*

2010, *12*, 1929. (g) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem. Eur. J.* **2010**, *16*, 9350.

(6) For examples of organocatalysts containing sulfinamide, see: (a) Ref. 1. (b) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (c) Kimmel, K. L.: Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754. (d) Kimmel, K. L.; Robak, M. T.; Thomas, S.; Lee, M.; Ellman, J. A. *Tetrahedron* **2012**, *68*, 2704. (e) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Tetrahedron* **2011**, *67*, 4412. (f) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N.; *Science* **2010**, *327*, 986. (g) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913.

(7) For an example of a chiral auxiliary approach to asymmetric [4+2] cycloaddition involving a terminally unsubstituted nitroalkene see: (a) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.*, **1997**, *62*, 6746. For an example of nucleophilic addition to a terminally unsubstituted nitroalkene to form a cyclic product with diastereoselective protonation via thermodynamic control, see entry 13 (Table 2) in: (b) Wang, Y.; Zhu, S.; Ma, D. *Org. Lett.* **2011**, *13*, 1602.

(8) For a review on enantioselective protonation, see: (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nature Chem.* **2009**, *1*, 359. For select examples of enantioselective protonation not involving nitroalkenes, see: (b) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (c) Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131. (d) Sadow, A. D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* **2004**, *126*, 14704.

(9) (a) Gruel, J. N.; Gaertzen, O.; Helmke, H.; Hilebrand, S.; Ilg, K.; Mattes, A.; Wasnaire, P.; Nising, C. F.; Wachendorff-Neumann, U.; Voerste, A.; Dahmen, P.; Meisssner, R.; Braun, C. A.; Kaussmann, M.; Hadano, H. Preparation of Analinopyrimidines as Agrochemical Fungicides. Patent WO 2010025831 (A1). (b) Stierle, A. A.; Stierle, D. B.; Patachini, B. *J. Nat. Prod.* **2008**, *71*, 856. (c) Aicher, T. D.; Chicarelli, M. J.; Hinklin, R. J.; Tian, H.; Wallace, O. B.; Chen, Z.; Marby, T. E.; McCowan, J. R.; Snyder, N. J.; Winneroski, L. L.; Leonard, L.; Allen, J. G. Preparation of Cycloalkyl Lactam Derivatives, Particularly N-Substituted Pyrrolidines-2-ones, as Inhibitors of 11beta-Hydroxysteroid Dehydrogenase 1. Patent WO 200649952 A1. (d) Askew, B. C.; Smith, G. R. Synthesis and Use of Substituted Pyrrolidin-1-yl-Hexanoic Acid Derivatives as avβ3 and avβ5 Integrin Receptors. Patent WO2001024797 A1.

(10) For catalytic enantioselective methods that provide access to the 4-substituted pyrrolidinones see: (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. For a general method to access 4,5-disubstituted pyrrolidinones, see: (b) Ref. 1. To access to 3,4,5-trisubstituted pyrrolidinones see: (c) Duschmalé, J.; Wennemers, H. *Chem. Eur. J.* **2012**, *18*, 1111. For a nice review on diastereoselective methods, see: (d) Ordóñez, M.; Cativiela, C.; *Tetrahedron Asymmetry* **2007**, *18*, 3.

(11) Use of unsubstituted Meldrum's acid led to overalkylation.

(12) For a nice example of the design of an innovative four-carbon chiral diamine linker, see: Palacio, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849.

(13) Morpholine is known to be ~2 pka units less basic than piperidine. See: Ref. 4.

(14) Catalyst **3k** has been made via a CDI coupling of commercially available trisyl sulfinamide and 2-methyl-2-morpholinopropan-1-amine in approximately 80% yield on a 1 mmol scale. Access to piperazine diamines (catalysts **3m-p**) requires a 7-step synthesis: see Ref. 22.

(15) For indium-mediated nitro reduction, see: Singh, V.; Kanojiya, S.; Batra, S. *Tetrahedron* **2006**, *62*, 10100.
(16) (a) Diastereoselective decarboxylative protonation of 3-substituted pyrrolidinones has only been reported with ~3:1 dr for an N-H pyrrolidinone and with 55:45 dr for an *N*-pivaloyl pyrrolidinone. See: Hook, D.; Thomas, R.; Bernhard, R.; Wietfeld, B.; Sedelmeier, G.; Napp, M.; Baenziger, M.; Hawker, S.; Ciszewski, L.; Waykole, L. M. New Process. WO2008083967 (A2). (b) In analogy with Meyers' alkylations of simple *N*-methyl-5-methyl pyrrolidinone enolates, it was expected that the decarboxylative protonation should also take place from the face opposite the 5-substituent, and that the magnitude of diastereoselectivity would be greater for N-H than *N*-carbamoyl pyrrolidinones. For an excellent explanation of this phenomenon see: Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565.
(17) The relative configuration of decarboxylated lactam **9a** was determined to be *cis* by correlation with literature ^{1}H NMR data. See: Crich, D.; Ranganathan, K. *J. Am. Chem. Soc.* **2005**, *127*, 9924.
(18) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880.
(19) Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894.
(20) (a) Chen, C.; Tran, J. A.; Trucci, F. C.; Chen, W-C. C.; Jiang, W.; Marinkovic, D.; Arellano, M.; White, N. Preparation of Piperazinyl Carboxamide and Related Cyclic Homologs as Ligands of Melanocortin Receptors and Compositions and Methods Related Thereto. PCT Int. WO 2005040109(A1), May 6, 2005. (b) Lim, M. J.; Murray, C. A.; Tronic, T. A.; deKrafft, K. E.; Ley, A. N.; deButts, J. C.; Pike, R. D.; Lu, H.; Patterson, H. H. *Inorg. Chem.* **2008**, *47*, 6931.
(21) (a) Sato, N.; Jitsuoka, M.; Ishikawa, S.; Nagai, K.; Tsuge, H.; Ando, M.; Okamato, O.; Iwaasa, H.; Gomori, A.; Ishihara, A. *Bioorg. Med. Chem.* **2009**, *19*, 1670. (b) Ojima, I.; Inaba, S.; Nakatsugawa, K.; Nagai, Y. *Chem. Lett.* **1975**, 331. (c) O'Neill, B. T. Preparation of Acyclic Ethylene Diamine Derivatives as Substance P Receptor Antagonists. PCT Int. WO 9310073(A1), May 27, 1993.
(22) Frost, C. G.; Penrose, S. D.; Gleave, R. *Synthesis* **2009**, 627.
(23) Abramovitch, R. A. *Can. J. Chem.* **1959**, *37*, 361.
(24) Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, *67*, 7365.
(25) Nutaitis, C. F.; Schultz, R. A.; Obaza, J.; Smith, F. X. *J. Org. Chem.* **1980**, *45*, 4606.
(26) Masaaki, M.; Tetsuji, Y.; Akira, Y.; Seebach, D.; Siegel, H.; Wilka, E. *Org. Synth.* **1981**, *60*, 101.
(27) NMR spectra match previously characterized compound. See: Crich, D.; Ranganthan, K. *J. Am. Chem. Soc.*, **2005**, *127*, 9924.

Appendix: Chapter 4. X-ray Crystal Data

Structure Determined by Dr. Arnold Rheingold

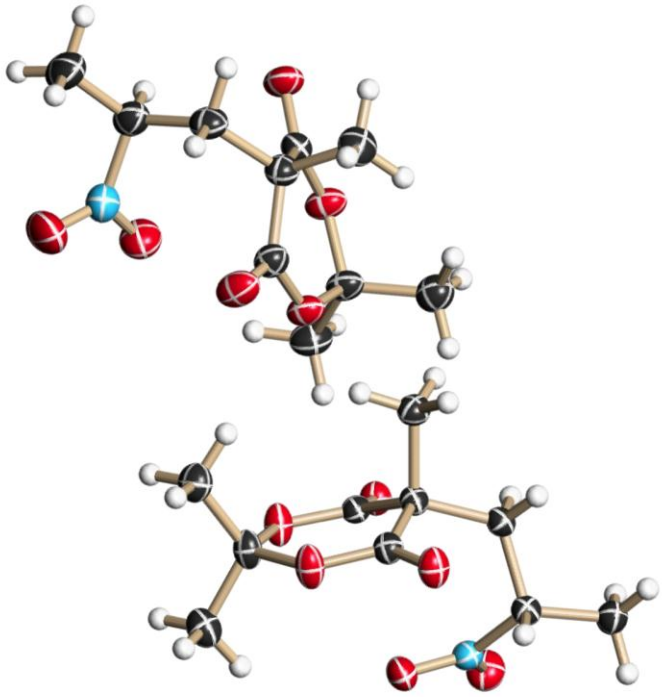


Table 4.1. Crystal data and structure refinement for ellm07.

Empirical formula	C10 H15 N O6	
Formula weight	245.23	
Temperature	273(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.8901(7) Å	α= 90°
	b = 11.4722(11) Å	β= 91.536(3)°
	c = 12.9352(12) Å	γ = 90°
Volume	1170.43(19) $Å^3$	
Z	4	
Density (calculated)	1.392 g/cm^3	
Absorption coefficient	0.993 mm^{-1}	
F(000)	520	
Crystal size	0.29 x 0.13 x 0.08 mm^3	
Crystal color, habit	Colorless blade	
Theta range for data collection	3.42 to 68.15°	
Index ranges	-9<=h<=9, -11<=k<=13, -15<=l<=14	
Reflections collected	9004	
Independent reflections	3480 [R(int) = 0.0154]	
Completeness to theta = 66.00°	97.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9248 and 0.7616	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3480 / 1 / 315	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2sigma(I)]	R1 = 0.0250, wR2 = 0.0682	
R indices (all data)	R1 = 0.0250, wR2 = 0.0682	
Absolute structure parameter	-0.01(11)	
Largest diff. peak and hole	0.228 and -0.139 e $Å^{-3}$	

Table 4.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)for ellm07. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-2209(1)	4457(1)	6985(1)	33(1)
O(1')	4663(2)	5564(2)	355(1)	54(1)
O(2)	530(1)	4528(1)	7026(1)	28(1)
O(2')	1956(2)	5375(1)	501(1)	39(1)
O(3)	3111(1)	2070(1)	6599(1)	27(1)
O(3')	-338(1)	3126(1)	-793(1)	33(1)
O(4)	3974(1)	3689(1)	5900(1)	29(1)
O(4')	-1261(1)	3658(1)	706(1)	29(1)
O(5)	2128(1)	4837(1)	4794(1)	26(1)
O(5')	613(1)	3760(1)	2200(1)	27(1)
O(6)	-548(1)	4366(1)	4595(1)	22(1)
O(6')	3323(1)	3419(1)	2065(1)	36(1)
N(1)	-826(2)	3988(1)	6986(1)	22(1)
N(1')	3307(2)	5111(1)	117(1)	34(1)
C(1)	-2316(2)	2089(2)	7248(1)	25(1)
C(1')	4784(2)	4164(2)	-1337(1)	43(1)
C(2)	-697(2)	2672(1)	6915(1)	20(1)
C(2')	3237(2)	4135(2)	-662(1)	32(1)
C(3)	-279(2)	2321(1)	5809(1)	19(1)
C(3')	3074(2)	2967(2)	-103(1)	29(1)
C(4)	1259(2)	2870(1)	5287(1)	18(1)
C(4')	1578(2)	2787(2)	632(1)	25(1)
C(5)	2823(2)	2838(1)	5991(1)	20(1)
C(5')	-63(2)	3202(2)	118(1)	24(1)
C(6)	3822(2)	4678(1)	5229(1)	23(1)
C(6')	-1127(2)	3798(2)	1811(1)	26(1)
C(7)	852(2)	4080(1)	4888(1)	18(1)
C(7')	1932(2)	3365(2)	1673(1)	26(1)
C(8)	1641(2)	2106(1)	4329(1)	24(1)
C(8')	1429(2)	1465(2)	857(1)	35(1)
C(9)	5027(2)	4533(2)	4356(1)	30(1)
C(9')	-2124(2)	2849(2)	2317(1)	33(1)
C(10')	-1757(2)	5004(2)	2043(1)	34(1)
C(10)	4165(2)	5735(2)	5894(1)	31(1)

Table 4.3. Bond lengths [Å] and angles [°] for ellm07.

O(1)-N(1)	1.2164(17)	N(1')-C(2')	1.506(2)
O(1')-N(1')	1.2219(19)	C(1)-C(2)	1.514(2)
O(2)-N(1)	1.2366(16)	C(1')-C(2')	1.520(2)
O(2')-N(1')	1.2263(19)	C(2)-C(3)	1.5303(18)
O(3)-C(5)	1.1988(19)	C(2')-C(3')	1.530(2)
O(3')-C(5')	1.1958(18)	C(3)-C(4)	1.5393(18)
O(4)-C(5)	1.3411(18)	C(3')-C(4')	1.548(2)
O(4)-C(6)	1.4316(18)	C(4)-C(7)	1.512(2)
O(4')-C(5')	1.3353(19)	C(4)-C(5)	1.5151(18)
O(4')-C(6')	1.4399(16)	C(4)-C(8)	1.5531(19)
O(5)-C(7)	1.3370(18)	C(4')-C(5')	1.517(2)
O(5)-C(6)	1.4474(16)	C(4')-C(7')	1.519(2)
O(5')-C(7')	1.3385(18)	C(4')-C(8')	1.550(2)
O(5')-C(6')	1.4498(17)	C(6)-C(9)	1.505(2)
O(6)-C(7)	1.2041(17)	C(6)-C(10)	1.507(2)
O(6')-C(7')	1.1984(19)	C(6')-C(10')	1.503(3)
N(1)-C(2)	1.516(2)	C(6')-C(9')	1.504(3)

C(5)-O(4)-C(6)	125.78(10)	C(7')-C(4')-C(3')	111.14(12)
C(5')-O(4')-C(6')	125.11(12)	C(5')-C(4')-C(8')	108.77(13)
C(7)-O(5)-C(6)	124.95(11)	C(7')-C(4')-C(8')	105.87(13)
C(7')-O(5')-C(6')	125.14(11)	C(3')-C(4')-C(8')	107.97(13)
O(1)-N(1)-O(2)	123.59(14)	O(3)-C(5)-O(4)	118.45(12)
O(1)-N(1)-C(2)	120.14(13)	O(3)-C(5)-C(4)	123.35(14)
O(2)-N(1)-C(2)	116.26(12)	O(4)-C(5)-C(4)	118.15(12)
O(1')-N(1')-O(2')	123.90(15)	O(3')-C(5')-O(4')	118.50(14)
O(1')-N(1')-C(2')	120.05(14)	O(3')-C(5')-C(4')	122.68(13)
O(2')-N(1')-C(2')	116.00(14)	O(4')-C(5')-C(4')	118.82(12)
C(1)-C(2)-N(1)	111.35(12)	O(4)-C(6)-O(5)	113.37(11)
C(1)-C(2)-C(3)	110.77(12)	O(4)-C(6)-C(9)	108.82(13)
N(1)-C(2)-C(3)	109.58(11)	O(5)-C(6)-C(9)	108.52(11)
N(1')-C(2')-C(1')	110.65(14)	O(4)-C(6)-C(10)	106.31(12)
N(1')-C(2')-C(3')	109.69(12)	O(5)-C(6)-C(10)	105.71(12)
C(1')-C(2')-C(3')	111.69(15)	C(9)-C(6)-C(10)	114.21(13)
C(2)-C(3)-C(4)	119.67(12)	O(4')-C(6')-O(5')	112.60(11)
C(2')-C(3')-C(4')	118.81(14)	O(4')-C(6')-C(10')	106.58(13)
C(7)-C(4)-C(5)	112.93(12)	O(5')-C(6')-C(10')	105.90(13)
C(7)-C(4)-C(3)	111.28(11)	O(4')-C(6')-C(9')	109.01(13)
C(5)-C(4)-C(3)	111.39(11)	O(5')-C(6')-C(9')	109.20(13)
C(7)-C(4)-C(8)	106.87(11)	C(10')-C(6')-C(9')	113.58(13)
C(5)-C(4)-C(8)	107.07(11)	O(6)-C(7)-O(5)	118.81(13)
C(3)-C(4)-C(8)	106.93(12)	O(6)-C(7)-C(4)	122.78(13)
C(5')-C(4')-C(7')	112.71(12)	O(5)-C(7)-C(4)	118.26(11)
C(5')-C(4')-C(3')	110.17(12)	O(6')-C(7')-O(5')	118.88(13)

O(6')-C(7')-C(4')	122.81(14)
O(5')-C(7')-C(4')	118.16(12)

Table 4.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for ellm07. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(1)	31(1)	41(1)	0(1)	6(1)	8(1)
O(1')	46(1)	60(1)	57(1)	-16(1)	5(1)	-23(1)
O(2)	28(1)	26(1)	31(1)	-4(1)	2(1)	-8(1)
O(2')	36(1)	39(1)	43(1)	-5(1)	9(1)	5(1)
O(3)	23(1)	24(1)	34(1)	10(1)	-4(1)	-1(1)
O(3')	31(1)	49(1)	20(1)	-6(1)	-1(1)	-5(1)
O(4)	19(1)	27(1)	40(1)	13(1)	-7(1)	-5(1)
O(4')	24(1)	43(1)	20(1)	-3(1)	-2(1)	6(1)
O(5)	17(1)	22(1)	38(1)	11(1)	-4(1)	-1(1)
O(5')	23(1)	38(1)	19(1)	-3(1)	0(1)	1(1)
O(6)	18(1)	23(1)	25(1)	2(1)	-2(1)	2(1)
O(6')	24(1)	58(1)	26(1)	-2(1)	-4(1)	2(1)
N(1)	22(1)	24(1)	19(1)	-1(1)	3(1)	-1(1)
N(1')	34(1)	33(1)	34(1)	2(1)	4(1)	-6(1)
C(1)	24(1)	28(1)	24(1)	1(1)	2(1)	-4(1)
C(1')	35(1)	59(1)	34(1)	-4(1)	9(1)	-8(1)
C(2)	20(1)	20(1)	20(1)	-1(1)	0(1)	-1(1)
C(2')	28(1)	41(1)	26(1)	-2(1)	0(1)	-5(1)
C(3)	18(1)	19(1)	20(1)	-1(1)	-1(1)	-1(1)
C(3')	27(1)	34(1)	27(1)	-7(1)	3(1)	3(1)
C(4)	17(1)	17(1)	21(1)	-1(1)	1(1)	0(1)
C(4')	25(1)	25(1)	24(1)	-3(1)	1(1)	2(1)
C(5)	17(1)	21(1)	23(1)	0(1)	2(1)	2(1)
C(5')	24(1)	25(1)	23(1)	-3(1)	1(1)	-5(1)
C(6)	15(1)	22(1)	32(1)	7(1)	-3(1)	-1(1)
C(6')	22(1)	37(1)	19(1)	-3(1)	-2(1)	2(1)
C(7)	18(1)	19(1)	17(1)	-1(1)	2(1)	1(1)
C(7')	24(1)	31(1)	23(1)	1(1)	0(1)	1(1)
C(8)	26(1)	21(1)	24(1)	-1(1)	3(1)	3(1)
C(8')	39(1)	27(1)	40(1)	-1(1)	4(1)	3(1)
C(9)	22(1)	33(1)	34(1)	2(1)	2(1)	-1(1)
C(9')	28(1)	39(1)	32(1)	0(1)	2(1)	1(1)
C(10')	38(1)	36(1)	28(1)	-3(1)	2(1)	9(1)
C(10)	26(1)	27(1)	40(1)	-2(1)	-1(1)	-1(1)

Table 4.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ellm07.

	x	y	z	U(eq)
H(1A)	-2535	2298	7950	38
H(1B)	-2195	1258	7198	38
H(1C)	-3243	2340	6807	38
H(1'A)	4875	4918	-1651	64
H(1'B)	4671	3580	-1866	64
H(1'C)	5784	4011	-919	64
H(2A)	232	2413	7377	24
H(2'A)	2226	4245	-1108	38
H(3A)	-1271	2487	5374	23
H(3B)	-121	1483	5803	23
H(3'A)	4116	2839	296	35
H(3'B)	3005	2361	-625	35
H(8A)	2541	2455	3951	35
H(8B)	642	2051	3892	35
H(8C)	1976	1341	4554	35
H(8'A)	552	1336	1345	53
H(8'B)	2489	1181	1140	53
H(8'C)	1155	1057	227	53
H(9A)	4680	3879	3938	44
H(9B)	6151	4401	4634	44
H(9C)	5017	5226	3940	44
H(9'A)	-1662	2104	2137	49
H(9'B)	-3287	2890	2082	49
H(9'C)	-2059	2946	3054	49
H(10A)	-1068	5567	1702	51
H(10B)	-1694	5135	2776	51
H(10C)	-2912	5078	1800	51
H(10D)	3313	5795	6408	47
H(10E)	4141	6422	5470	47
H(10F)	5261	5663	6229	47