Enantioselective Organocatalytic Friedel-Crafts Alkylations of Heterocycles and Electron-Rich Benzenes

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Abstract

The development of the first organocatalytic asymmetric Friedel-Crafts alkylation is described in the context of conjugate additions of pyrroles to α,β-unsaturated aldehydes. Catalytic amounts of chiral imidazolidinone salts are used to activate the electrophile component *via* reversible formation of iminium ions. Ensuing conjugate additions of pyrroles afford aldehyde products in good yield and high enantiopurity using a range of alkyl–, aryl–, and heteroatom-substituted enals and nucleophiles. This reaction demonstrates the feasibility of using iminium catalysis to promote reactions of electron-deficient olefins beyond simple cycloaddition reactions. Observations were also made regarding the role of Brønsted acid cocatalysts in these organocatalytic reactions. The synthetic utility of asymmetric conjugate additions of pyrroles was demonstrated in a concise, enantioselective synthesis of the analgesic Ketorolac.

An enantioselective organocatalytic conjugate addition of electron-rich benzenes to α,β-unsaturated aldehydes has been developed. A new chiral secondary amine promotes exclusive *para*-alkylation of dialkylamino-substituted benzenes in good yield and with a high degree of stereocontrol. The process tolerates a range of substitutents on the electrophile component as well as a high degree of flexibility in the *ortho*- and *meta*-positions on the benzene ring. Particularly, the unique ability of this methodology to efficiently generate bisbenzyllic stereocenters by addition of electron-rich benzenes to cinnamaldehyde derivatives is demonstrated.

A general procedure for the cleavage of dialkylamino substituents from aromatic rings has also been developed. To accomplish this cleavage, a dialkylaniline is first converted to the corresponding quaternary ammonium salt with methyl iodide or methyl trifluromethanesulfonate. In a second step, dissolving metal reduction of the salt liberates the deaminated arene in high yields for the overall process. A range of alkyl, aryl, and heteroatom substitutions at the *ortho*, *meta*, and *para* positions were tolerated without significant decrease in reaction efficiency or yield. Deamination of aniline substrates bearing stereogenic centers *para* to the dialkylamino functionality proceeded with complete retention of enantiopurity. The combined utility of the asymmetric aniline alkylation and the new deamination methodology was demonstrated in the first enantioselective synthesis of the anticholinergic drug (*R*)-Tolterodine.

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Chapter 1

Recent Developments in Asymmetric Organocatalysis

Introduction

The design of new methods for the selective construction of carbon stereocenters is a fundamental pursuit of synthetic organic chemistry. This pursuit continues to grow in importance in parallel to the demand for single-enantiomer building blocks in pharmaceutical and agrochemical industries as well as the increasing complexity of natural product targets for total synthesis.[1] Chiral auxiliaries and stoichiometric chiral reagents have long been used to control selectivity in the generation of new stereocenters, but asymmetric catalytic methods for accomplishing this same goal are becoming increasingly attractive. In principle, catalytic methods should be a more economical means to effect a desired stereochemical outcome: large amounts of enantioenriched compounds can be generated free of auxiliary contaminants using prochiral starting materials and a small amount of an optically pure catalyst. In practice, however, some

[1] a) Collins, A. N.; Sheldrake, G. N.; Crosby, J. *Chirality in Industry II*, Wiley: New York, 1997; b) *Process Chemistry in the Pharmaceutical Industry* (Ed.: K. G. Gadamasetti), Marcel Dekker: New York, 1999; c) Stinson, S. C. *Chem. Eng. News* **1998**, *76*, 83-104; d) Stinson, S. C. *Chem. Eng. News* **1999**, *77*, 101-120; e) Stinson, S. C. *Chem. Eng. News* **2000**, *78*, 59-70; f) Stinson, S. C. *Chem. Eng. News* **2000**, *78*, 63-78; g) Stinson, S. C. *Chem. Eng. News* **2000**, *78*, 55-78; h) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; J. Wiley & Sons: New York, 1993; i) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: UK, 2000; j) Ager, D. A.; East, M. B. *Asymmetric Synthesis Methodology*; CRC Press: New York, 1995

features of contemporary asymmetric catalysis impose limitations on its applicability as a solution for industrial and academic problems.[2]

In its present form, the field of asymmetric catalysis has become nearly synonymous with asymmetric organometallic catalysis. The discipline was essentially founded on early successes in metal-catalyzed redox chemistry that shaped the exploration of enantioselective, catalytic reactions for decades to come. The basis for these seminal studies was that an organized, three-dimensional environment leading to stereochemical control in the transition state could be achieved through the use of chiral ligand architectures around a reactive metal center. Following such examples, countless asymmetric catalysts have been added to the organic chemist's toolbox through replacement of achiral ancillary ligands of known metal catalysts with optically pure alternatives. The resulting systems have been used to realize a number of invaluable synthetic transformations all of which, however, are subject to the sensitivity and hazards of organometallics. With regard to the former, oxygen and water can be highly deleterious to organometallic asymmetric catalysts, requiring added time and expense to ensure vigorous exclusion of these ubiquitous contaminants. The hazards arise from the exceptional toxicity that even low concentrations of metals can exhibit, both in isolated products for human consumption and in waste streams that eventually bleed into the biosphere. Despite these potential drawbacks, the unique activity and efficiency of many organometallic catalysts guarantee their continued exploitation for decades to come; however, in the development of new asymmetric catalytic reactions it would seem desirable to pare down the technical and environmental problems associated with the use

[2] Most asymmetric, catalytic systems are not yet economically sound because of various factors as described below. For a treatise on the characteristics of an economical asymmetric catalyst, see: Noyori, R.; *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 883.

of transition metals while preserving the core utility of asymmetric catalytic reactions. One very fundamental way in which this might be accomplished would be to eliminate the metal entirely, using organic molecules not only as bias-enforcing ligands, but as catalysts themselves.

Organic molecules have been used to catalyze organic transformations since the early days of synthetic chemistry. That asymmetric catalysis research would ignore this avenue for many years would seem unfortunate, especially in light of an intriguing example of an enantioselective metal-free reaction that was contemporary to the asymmetric reductions which defined the field. In the early 70s, Hajos[3] and Wiechert[4] independently described the use of unmodified amino acids in enantioselective intramolecular aldol reactions (Equation 1). Interest in these reports paled in comparison to that which was directed toward the organometallic redox chemistry of Kagan,[5] Knowles,[6] Noyori[7] and Sharpless.[8] Consequently, the 30 years to follow witnessed only scattered examples of metal-free asymmetric, catalytic reactions that went largely unnoticed until the late 90s when several mechanistically diverse transformations were reported in a short period of time (Scheme 1).[9] These reactions were highly selective

---

[3] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

[4] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *83*, 492-493.

[5] Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429-6433.

[6] Knowles, W. S., Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc. Chem. Commun.* **1972**, 10-11.

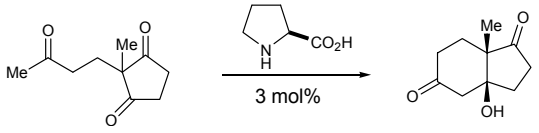
[7] Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934

[8] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *112*, 5974-5975.

[9] Some notable developments from this period: epoxidation of trans, trisubstituted olefins: a) using **1**: Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807; b) using **2**: Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491-492; c) using **3**: Denmark, S. E.; Wu, Z. C. *Synlett*, **1999**, 847-859; phase transfer reactions: d) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415; aldol: e) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem.*

(routinely >90% ee), they were tolerant of a wide range of substrates, and they involved non-trivial bond formation. In short, they were on par with the reaction efficiency of conventional organometallic catalysts. Spurred by these key developments, the hodgepodge of otherwise unrelated, enantioselective transformations catalyzed by organic molecules was collected into a cohesive discipline of intense interest under the neologistic mantle of "organocatalysis."[10]

Hajos-Parrish-Eder-Sauer-Wiechert Reaction



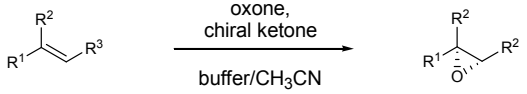
up to 95% ee (1)

Soc. **2000**, *122*, 2395-2396; Diels-Alder cycloaddition: f) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

[10] The first appearance of the term "organocatalysis" in print occurred in reference 9f.

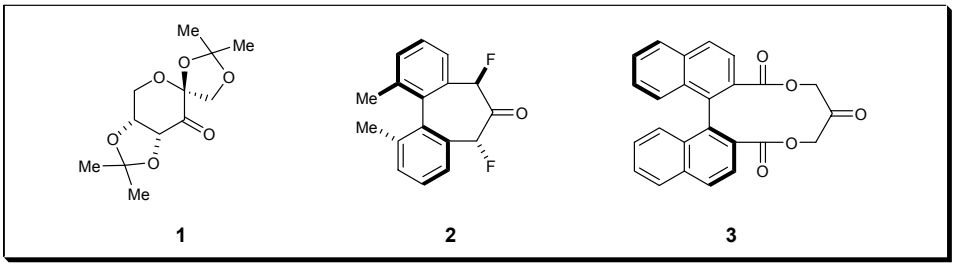
Scheme 1

Epoxidation



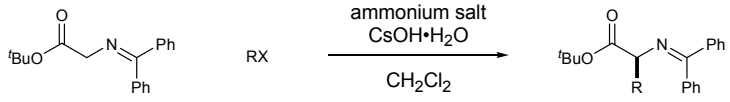
(2)

up to 95% ee



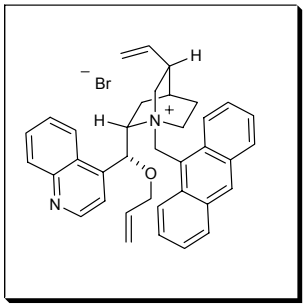
1 **2** **3**

Phase Transfer Catalysis

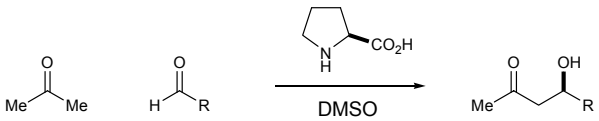


(3)

92-99% ee

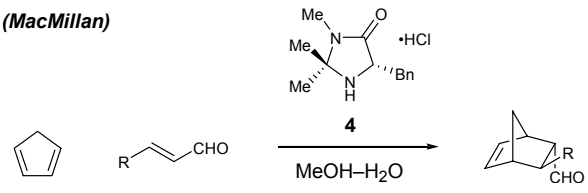


Aldol Condensation



65-96% ee (4)

Diels-Alder (MacMillan)



80-95% ee
1-20:1 dr (5)

The most notable of these catalytic systems were significant not only because they tolerated a range of *substrates* in a particular reaction, but also because their mechanisms of action lent themselves to a range of *transformations*. One of these landmark strategies of the last decade was developed in the context of the first highly enantioselective organocatalytic Diels-Alder reaction, reported by Ahrendt, Borths, and MacMillan[9f] (Scheme 1, equation 5). This study not only demonstrated a new metal-free protocol for conducting a venerable reaction, but also highlighted a novel, general mechanism for the activation of electron-deficient olefins: iminium catalysis.

Design of a New Mechanism for Organocatalysis

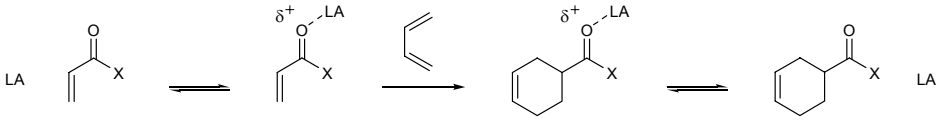
In order to achieve a broadly applicable platform for asymmetric organocatalysis, MacMillan and co-workers took inspiration from one of the most general types of conventional organometallic catalysts: chiral Lewis acids. These species have been used to activate a variety of both isolated and conjugated π-electrophiles toward nucleophilic attack and cycloaddition reactions.[11] The mechanism of Lewis acid catalysis consists of three discrete and essential steps, illustrated below in the context of a Diels-Alder reaction (Scheme 2).[12] In the first step, a Lewis acid binds reversibly to the substrate via one or more dative single bonds. The π-electron density of the substrate in the resulting adduct is polarized toward the electropositive metal center, thereby lowering the

[11] For an overview of Lewis acid catalysis, see: Yammamoto, H. *Lewis Acids in Organic Synthesis, Vol. 1 and 2*, Wiley-VCH: Weinheim, 2000.

[12] For a detailed FMO theory treatment of Lewis acid activation of acrolein in the Diels-Alder reaction, see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley: New York, 1978, pp.161-165.

energetic potential of the lowest unoccupied molecular orbital (LUMO) and rendering it more susceptible toward combination with the highest occupied molecular orbital (HOMO) of another species. The accelerated covalent bond-forming reaction ensues, affording a Lewis acid-bound product which is subsequently disrupted by other potential ligands, releasing the catalyst to engage in further iterations of the catalytic cycle.

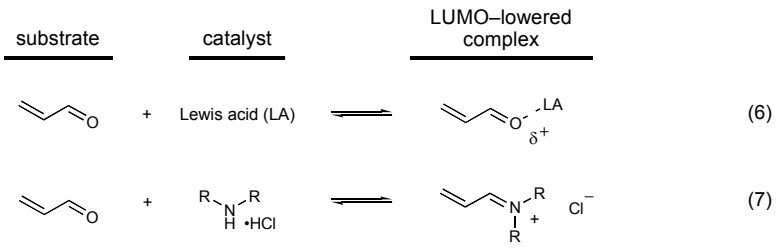
Scheme 2



Close inspection of this mechanism reveals two features that are critical to the function of Lewis acids in LUMO-lowering catalysis. Lewis acids can form kinetically labile associations to potential electrophiles and these associations serve to decrease the electron density in a ligated substrate. The observation at the crux of MacMillan's organocatalysis strategy is that simple organic molecules can also form reversible associations with substrates to access to transient quantities of relatively electron-poor intermediates. Specifically, a clear analogy was drawn between the condensation of α,β-unsaturated aldehydes with secondary amine salts and the ligation of those same aldehydes to Lewis acids (Scheme 3). In the case of the latter, equilibrium quantities of an oxonium ion are generated, thereby integrating a partial positive charge into the metal-bound substrate (equation 6). In the organocatalytic paradigm, dehydrative condensation of amine salts and aldehydes to form iminium ions also incorporates a formal positive charge, resulting in a π-system that is known to exhibit superior electrophilicity as

compared to the parent carbonyl compounds (equation 7).[13] In light of these parallel features, the investigators expected that secondary amine salts could function as LUMO-lowering catalysts. Furthermore, optically active secondary amine salts might also be used to influence the stereochemical outcome of these reactions, providing an invaluable complement to their chiral organometallic counterparts.

Scheme 3



As indicated above, initial studies demonstrated the feasibility of iminium catalysis in the context of the Diels-Alder cycloaddition. A preliminary experiment revealed a dramatic acceleration of the reaction of cyclopentadiene with cinnamaldehyde in the presence of substoichiometric amounts of (*S*)-proline methyl ester hydrochloride (equation 8). The reaction proceeded efficiently in 27 hours at ambient temperature as compared to negligible conversion in a control reaction lacking catalyst, but more significantly, the major product was isolated in 48% ee. This latter observation provided evidence that the amine was involved in the rate acceleration and that its association to the substrate in the transition state was close enough to effect a communication of stereochemistry.

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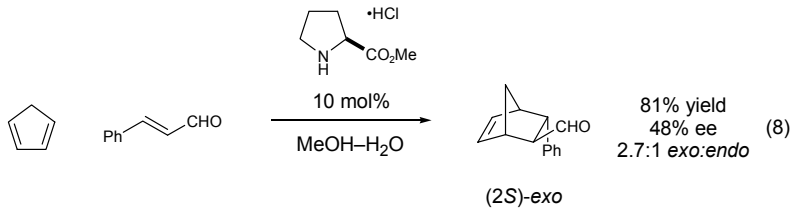
[13] Baum, J. S.; Viehe, H. G. *J. Org. Chem.* **1976**, *41*, 183.



Development of a Highly Selective Secondary Amine Catalyst

This example represented an important first step, but the level of optical purity resulting from this amine-catalyzed process was not comparable to those achieved with chiral Lewis acids, so a survey of chiral secondary amines was undertaken to identify a more selective system.[14] On analysis of the results of this survey, three empirical trends emerged to begin painting a picture of the ideal catalyst. First of all, α-amino esters were found to be eminently superior with respect to rate acceleration as compared to secondary amines lacking a proximal electron-withdrawing substituent.[15] Secondly, among acyclic α-amino esters those catalysts bearing arylmethylene substituents, as found in phenylalanine and tryptophan side chains, exhibited the highest levels of enantioselectivity as well as increased reactivity.[16] And finally, cyclic amines proved to be some of the most active and selective catalysts. In total, the amine survey was highly informative, however, the best new catalyst candidates had not substantially

[14] Some of the ensuing data are taken from reference 9f, the remainder are unpublished results of Kateri Ahrendt and Christopher Borths in these laboratories.

[15] Hydrochloride salts of a variety of commercially available chiral pyrrolidines, benzylamines, other aliphatic amines were tested in the reaction of cp with cinnamladehyde and none afforded higher than 27% conversion in 24 hours.

[16] Enantiomeric excesses of products from reactions catalyzed by hydrochloride salts *N,O*-dimethyl amino acid derivatives: valine, 9%; phenylglycine, 20%; phenylalanine, 35%, tryptophan, 59%.

outperformed proline which constituted the initial effort. Further analysis using computational models suggested an additional control element that might be required for high levels of selectivity.

In order to achieve high levels of selectivity an asymmetric catalyst should impart a well-defined, rigid chiral environment to the transition state of a given reaction. In this context iminium catalysis has an intrinsic advantage because the catalyst architecture is linked to the substrate by a carbon-nitrogen double bond in the reactive complex. This association is both intimate and rotationally restricted to either of two coplanar orientations.[17] Close inspection of iminium intermediate **5** expected in the proline-catalyzed Diels-Alder reaction reveals that only two possible geometrical isomers may still be one isomer too many for effective control. The problem lies in that these two geometries would be expected to give rise to stereodivergent transition states (Figure 1). In *trans*-**5**, the *re*-face of the pendant alkene is partially shielded by the ester functionality of the catalyst, which should lead to a preference for formation of the (2*R*) isomer of the cycloadduct. Conversely, in *cis*-**5**, approach of the *si*-face of the dienophile is hindered by the catalyst architecture resulting in a bias for the transition state that would lead to the product with a (2*S*) configuration. Molecular mechanics calculations suggested that this latter geometry is slightly favored, consistent with the observed sense of enantioinduction, but the energetic difference between intermediates is so small that both

[17] For examples of secondary control elements that restrict rotational freedom in transition states of asymmetric Lewis acid-catalyzed processes see: a) bidentate chelation: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325; b) formyl hydrogen bonding: Corey, E.J.; Barnes-Seeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron Lett.* **1997**, *38*, 6513-6516.

are accessed in significant amounts.[18] In light of these observations, an element to control iminium ion geometry was deemed a requirement of an effective catalyst.

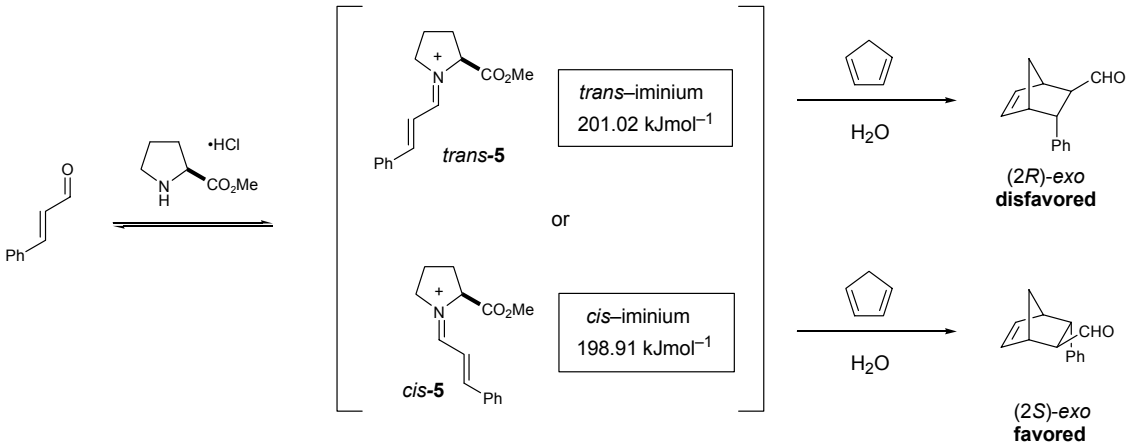


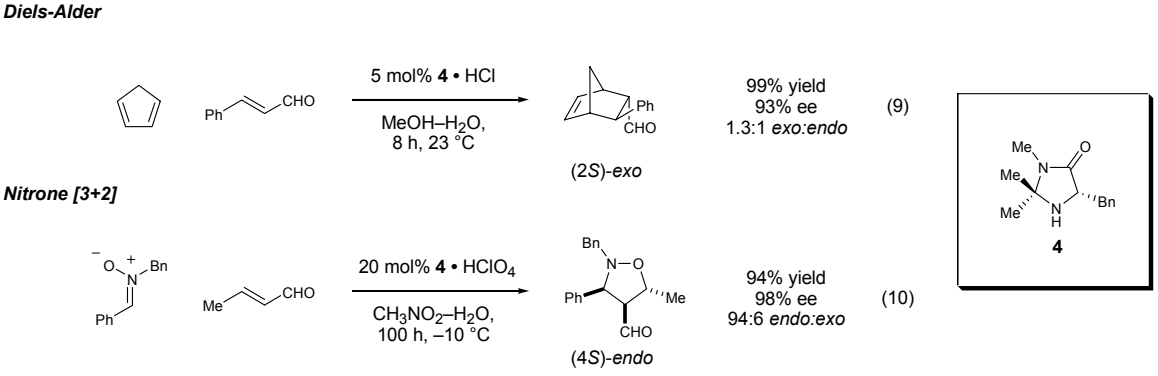
Figure 1

Two strategies were implemented in an attempt to address the issue of iminium ion geometry control. First, C_2-symmetric analogs of promising secondary amines were synthesized with the goal of imposing degeneracy on the two possible isomers of the iminium ion. Indeed, higher levels of selectivity were observed using these structures (57–74% ee). These catalysts, chosen with an eye toward geometry control, could not accommodate all of the productive features as established by the earlier survey. An alternative approach using steric constraints to control iminium ion orientation generated a catalyst scaffold with the functional flexibility to accommodate these empirically derived characteristics as well. As a result, MacMillan and co-workers arrived at

[18] These values were obtained as a result of a Monte Carlo simulation using the MM3 force-field; Macromodel V6.5. NMR analysis of a mixture of cinnamaldehyde and *O*-methyl proline hydrochloride confirmed population of both geometrical states. unpublished results, Ahrendt, K. & Borths, C. in these laboratories.

imidazolidinone salt **4** which provided the highest levels of selectivity in the reaction of cinnamaldehyde with cyclopentadiene while maintaining reaction efficiency (Scheme 4, equation 1). The reaction proved to be general for a range of dienes and α,β-unsaturated aldehydes, furnishing cycloadducts in good yields (75-99%) and optical purities (83-96% ee).[9f] Jen and Wiener in the same research group later went on to further demonstrate the applicability of **4** to a different class of cycloaddition, developing an asymmetric organocatalytic [3 + 2] dipolar condensation of nitrones with α,β-unsaturated aldehydes.[19] Following these successful applications of iminium catalysis to asymmetric cycloadditions, we turned our attention to another classic reaction of α,β-unsaturated aldehydes: conjugate addition.

Scheme 4

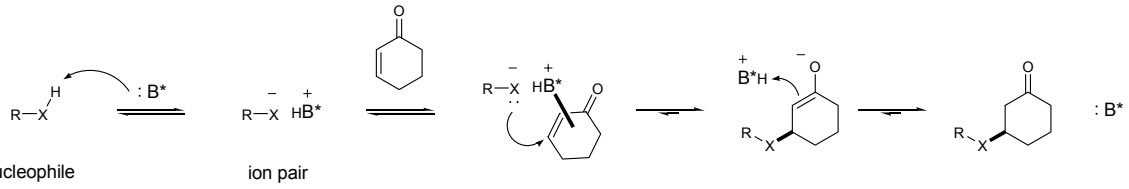


[19] Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122,* 9874-9875.

Organocatalytic Asymmetric Conjugate Addition Reactions[20]

The prospect of using a chiral base to induce chirality in the 1,4-addition of reactive methylenes and heteroatoms to Michael acceptors was introduced as early as 1973 and nearly every organocatalytic, enantioselective conjugate addition reported since has relied on a similar approach.[21,22] The first mechanistic step in such a reaction consists of deprotonation of a nucleophile by the base to generate a chiral salt (Scheme 5). This ion pair then forms a ternary complex to include the electrophile which binds to the chiral base *via* a secondary unrelated interaction. Organization within the ternary complex dictates facial selectivity in what is essentially an intramolecular delivery of the deprotonated nucleophile to the electron-deficient π-bond. Transfer of a proton from the chiral base to the resulting enolate liberates the neutral product and regenerates the catalyst for further activity.

Scheme 5



[20] For recent reviews on asymmetric, catalytic conjugate additions in general, see: a) Kanai, M.; Shibasaki, M. in *Catalytic Asymmetric Synthesis* (Ed: I. Ojima), 2nd ed., VCH: UK, 2000, pp. 569-592;b) Jacobsen, E. N.; Pfaltz, A.; Yammamoto, H. *Comprehensive Asymmetric Catalysis*, Springer:Heidelberg, 1999, pp. 1105-1139.

[21] For additions to conjugated π-electrophiles promoted by chiral bases: Langstrom, E.; Bergson, G.; *Acta Chem. Scand.* **1973**, *27*, 3118. Enantioselective additions to isolated π-bonds catalyzed by chiral bases described much earlier: Prelog, V.; Wilhelm, M. *Helv. Chim. Acta* **1954**, *37*, 1634-1661.

[22] Proline has been used to catalyze a moderately enantioselective conjugate additions of aldehydes into nitrostyrene acceptors through a fundamentally different mechanism, see: a) Enders, D.; Seki, A.; *Synlett* **2002**, 26-28; b) List, B.; Pojarliev, P.; Martin, H. J.; *Org. Lett.* **2001**, *3*, 2423-2425.

The body of existing enantioiselective, organocatalytic conjugate additions can be classified into either of two groups according to the nature of the secondary organizational interaction by which the catalyst interacts with the electrophile: hydrogen bonding or iminium ion formation. Wynberg and co-workers reported the first example of a moderately enantioselective Michael addition using a mode of catalysis that purportedly belongs in the first category.[23] The authors were able to obtain Michael adducts in up to 76% optical purity and near quantitative yield when they treated solutions of α-ketoesters with methyl vinyl ketone and cinchona alkaloid-derived catalysts (Scheme 6, equation 11). They argued that a hydrogen bond between the free hydroxyl of quinine **6** and the enone in the transition state was critical based on observations that *O*-acyl catalysts were markedly less active and use of polar solvents resulted in decreased optical yield. Wynberg would also apply this catalytic system to the conjugate addition of heteroatoms, achieving moderate selectivity in the addition of thiophenols to cyclohexenones (Scheme 6, equation 12).[24] Along the same lines, Mukaiyama achieved a selective addition reaction using proline derivative **7** (Scheme 6, equation 13).[25] He suggested a similar hydrogen-bonding arrangement between the free hydroxyl of the catalyst and the acceptor in the transition state based on similar

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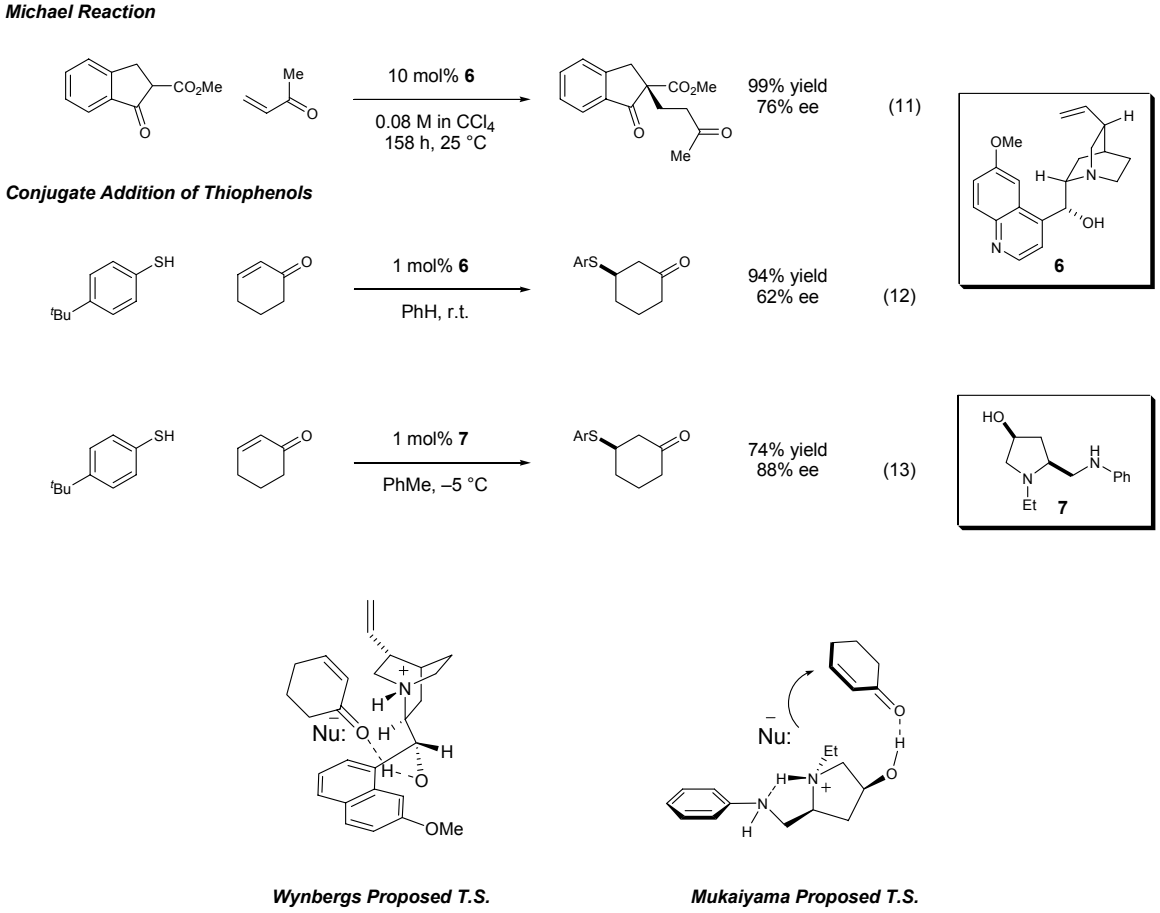
[23] a) Wynberg, H.; Helder, R.; *Tetrahedron Lett.* **1975**, *46,* 4057-4060; b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238-2244.

[24] a) Helder, R.; Arends, W.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *25*, 2181-2182; b) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417-430; c) Colonna, S.; Re, R.; Wynberg, H. *J. Chem. Soc. Perkin Trans. 1* **1981**, 547-552.

[25] Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277-3282.

observations of the effects of solvent polarity and reaction concentration.[26]

Scheme 6



The condensation of a secondary amine and a Michael acceptor to form am iminium ion bears fundamental similarities to the formation of a hydrogen-bond complex: the entropy of the two participants relative to each other is greatly diminished while the electrophile is concomitantly activated toward addition. Taguchi exploited this

[26] In a more contemporary example, Miller, et. al. described a moderately selective conjugate addition of azides to unsaturated imides using a short peptide catalyst. While not directly discussed, hydrogen bonding most likely plays a role as an organizational element in this base-promoted conjugate addition: Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem. Int. Edit.* **2000**, *39*, 3635-3638.

analogy, incorporating iminium formation as an organizational and activating element in a Michael addition of malonates to unsaturated ketones using charge-bearing chiral pyrrolidine **8** (Scheme 7, equation 14).[27] Selectivity in this transformation was modest, reaching a maximum 71% ee in the reaction of dibenzyl malonate with cyclohexenone. An iminium ion intermediate has also been implicated in the conjugate addition of nitroalkanes catalyzed by a mixture of (*S*)-proline and various bases, however, confusing non-linear effects suggest a multi-component catalyst system that is not well understood.[28] Mechanistic ambiguity does not diminish the value of the latter transformations which can furnish nitro-Michael adducts in good yields and optical purities which broach the realm of synthetic utility: generally 60-80% ee with three examples at 93% (Scheme 7, equation 15).

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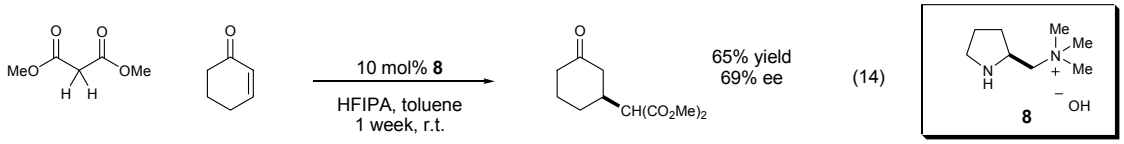
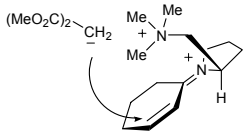
[27] Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805-8808.

[28] For various inorganic bases, see: a) Yamaguchi, M.; Shiraishi, T.; Hirama, M.; *Angew. Chem. Int. Edit.* **1993**, *32*, 1176-1179; b) Yamaguchi, M.; Shiraishi, T.; Hirama, M.; *J. Org. Chem.* **1996**, *61*, 3520-3530; For optimized results using *trans*-2,5-dimethylpiperazine, see: c) Hanessian, S.; Pham, V. Org. Lett. 2000, 2, 2975-2978.

Scheme 7

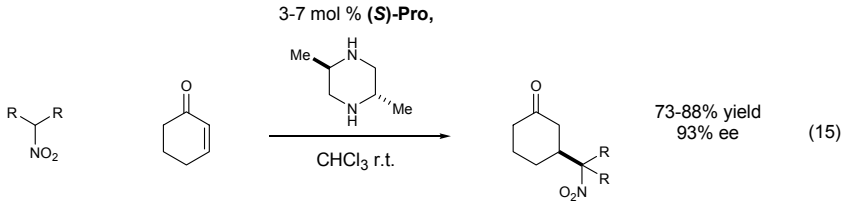
Iminium-based Michael Reaction





Proposed Transition State

Iminium-based Nitro-Michael Reaction



To date, highly selective asymmetric, catalytic conjugate additions are truly a rare breed.[20] Synthetically useful asymmetric, *organocatalytic* conjugate additions are even more elusive: in 30 years, a total of three products have been accessed in higher than 90% optical purity. Our approach is to apply iminium catalysis to this challenging reaction, employing chiral imidazolidinone salts which had already demonstrated success in promoting asymmetric cycloaddition reactions of α,β-unsaturated aldehydes. In the process, we also hoped to probe the scope and limitations of our catalysts and iminium activation in general.

Chapter 2

Development of a Highly Selective, Asymmetric Organocatalytic Conjugate Addition[1]

Reaction Design

Our approach toward the development of an asymmetric organocatalytic conjugate addition was based on iminium catalysis. Previous work in our laboratories had demonstrated that salts of chiral imidazolidinone **1** efficiently promoted asymmetric cycloadditions of α,β–unsaturated aldehydes *via* iminium ion intermediate **2** (Scheme 1).[2] In these transformations, π–facial selectivity and increased reaction rate result strictly from association of the catalyst to the electrophilic component of the reaction. We believed that such a platform should be amenable to a range of reactions of α,β–unsaturated carbonyl compounds, regardless of the nature of the HOMO-donor component, making it an excellent candidate for application to asymmetric conjugate addition reactions. Furthermore, we anticipated that the intimate association of the steric bulk of the catalyst to the carbonyl-carbon of the electrophile should favor a 1,4-addition

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[1] Parts of this work have been published previously: Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371.

[2] For Diels-Alder, see: a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244; for nitrones cycloaddition, see: b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122,* 9874-9875.

pathway over 1,2-addition (Figure 1). We began our studies by designing additions to α,β–unsaturated aldehydes in the presence of secondary amine catalyst **1**.

Scheme 1

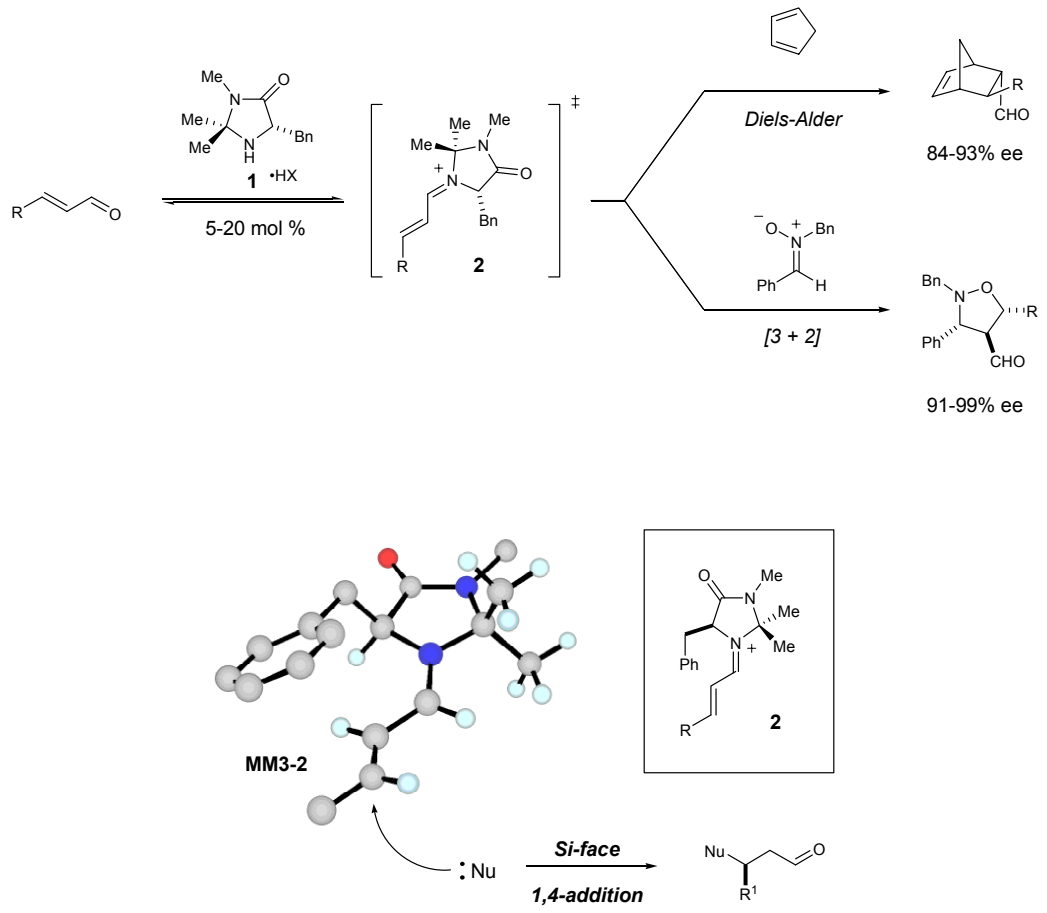


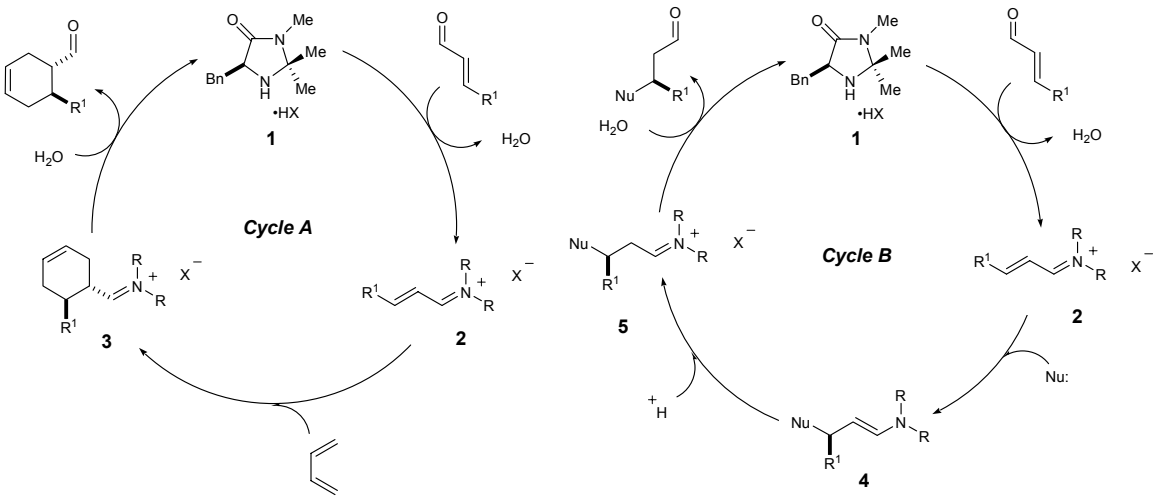
Figure 1

Based on the proposed mechanism of secondary amine-catalyzed cycloadditions (Scheme 2, cycle A), we devised a hypothetical catalytic cycle for an organocatalytic conjugate addition reaction (Scheme 2, cycle B). Both cycles commence with acid-promoted dehydrative condensation of catalyst **1** with an α,β–unsaturated aldehyde to

form α,β -unsaturated iminium ion **2**. In the cycloaddition process, this charged intermediate reacts with a diene to form iminium complex **3**, in which the catalyst is still bound to the product by a carbon-nitrogen double bond. This association can be cleaved by water directly to liberate the aldehyde cycloadduct and regenerate **1**. In contrast, attack on reactive iminium **2** by a conjugate nucleophile would quench the positive charge on the catalyst nitrogen and result in neutral enamine **4** (Scheme 2, cycle B). A hydrogen ion source would then be required to protonate enamine **4** and regenerate the carbon-nitrogen double bond in iminium intermediate **5**. Only after this arrangement has been restored can hydrolysis proceed and the catalytic cycle be completed. The practical implication of this mechanistic hypothesis is that a full equivalent of a proton source would be required for catalyst turnover. From our cycloaddition studies, we also concluded that this proton source would need to be at least as acidic as the catalyst salt or the acid co-catalyst would be consumed and iminium ion formation become impractically slow.[3]

[3] The pK_A of **1** hydrochloride was measured at 4.5 in aqueous solution. Slow or negligible iminium ion formation and Diels-Alder reactions had been observed when acid co-catalysts of $pK_A > 4$ were employed.

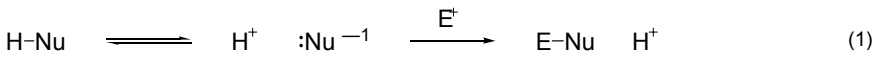
Scheme 2



Operating under this mechanistic hypothesis, we considered several strategies for the inclusion of a proton source in the reaction mixture. Particularly, we focused on methods for generating an equivalent of an effective Brønsted acid ($pK_A<5$) during the course of the addition rather than face further complications regarding protic acid-catalyzed reactions (Scheme 3). The first such method would rely on the intrinsic acidity of the nucleophile itself: ionization of a weakly bound proton under reaction conditions would reveal both an anionic nucleophile as well as an available proton (Scheme 3, equation 1). A second possible method for the generation acid *in situ* involves the use of organometallic or organosilicon nucleophiles (Scheme 3, equation 2). The electropositive metal center that is generated as a biproduct of electrophilic alkylation of these species can react with aqueous solvent to generate the requisite equivalent of acid. And finally, we also considered neutral nucleophiles that can function as latent acids after being activated by alkylation (Scheme 3, equation 3). This final class includes substrates such as stabilized enols (e.g. malonates), electron rich alkenes and aromatic compounds.

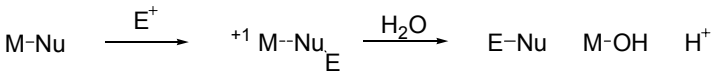
Scheme 3

Acidic Nucleophiles



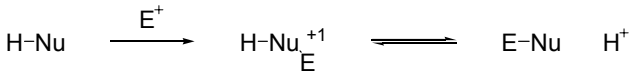
(1)

Metallo-Nucleophiles



(2)

Latently Acidic Nucleophiles



(3)

The goal of this project was to determine if chiral secondary amines could function as catalysts for enantioselective conjugate addition reactions. In the interest of time we did not focus on optimization of any one specific transformation at the outset, but instead first sought to identify a nucleophile substrate that fit our criteria: 1) relative stability in mildly acidic aqueous media and 2) ability to generate an equivalent of acid for completion of the catalytic cycle. After identifying a suitable nucleophile, we then would manipulate the imidazolidinone architecture to probe the steric and electronic requirements of an effective catalyst and identify optimal reaction conditions.

Results and Discussion

Identification of a suitable nucleophile

We began with a survey of potential nucleophiles in a reaction with crotonaldehyde in the presence of **1**· HCl in wet organic solvents (10% H_2O v/v with solvent). In a representative example from the first class of nucleophile described above (Scheme 3, equation 1), hydrazoic acid[4] reacted with crotonaldehyde to afford *β*-azido-butanal in modest yield as ascertained by GC analysis. The product mixtures analyzed from aliquots of this reaction displayed low enantiomeric excesses that steadily approached zero as the reaction progressed. Given the configurational stability of the catalyst, we attributed the degradation of selectivity to reversibility of the addition, which should lead to the thermodynamically favored racemic product. This observation revealed to us an inherent flaw of this first class of substrate: any nucleophile which can exist as an anion under our moderately acidic aqueous conditions is likely to be an excellent leaving group in a *β*-elimination reaction. Such a mechanism provides an accessible kinetic pathway toward a thermodynamic, or racemic, product mixture, making these substrates undesirable for the further development of our new catalysis platform.

[4] HN_3 generated *in situ* from sodium azide and acetic acid.

Organosilicon and organometallic reagents were also rapidly eliminated as potential nucleophiles for initial identification of a functional catalytic system.[5] These substrates were incompatible with the reaction conditions as previously established for iminium catalysis in the cycloaddition studies. For example, α-trimethylsilyloxy-styrene underwent rapid protodesilylation in the presence of imidazolidinone hydrochloride salts and aqueous solvent. In these reactions acetophenone was formed as the exclusive product and no addition to the conjugate acceptor was observed. After several more attempts to identify a reasonable test substrate, electron-rich heteroaromatic compounds finally emerged as a solution.

Aromatic heterocycles embody all three of the key properties we desired in a nucleophile. First of all, heteroaromatics can be exceptionally reactive substrates for electrophilic alkylation reactions.[6] Kinetic studies by Mayr have established that 2-methyl furan is on par with highly reactive π-nucleophiles, such as allylsilane and allylstannane reagents, in additions to photochemically generated cations.[6a] Secondly, the cationic intermediates formed on initial alkylation of these neutral compounds are highly acidic[7] and readily release a proton to restore aromaticity. Such latent acidity satisfies our requirement for an equivalent of a proton source to be generated *in situ* in accordance with the proposed catalytic cycle described above. And finally, heterocycles

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[5] After extensive optimization, silyl enol ethers have since been successfully employed as nucleophiles in asymmetric conjugate additions catalyzed by (*S,S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidinone, Borths, C. J., MacMillan, D. W. C., *manuscript in preparation*.

[6] For quantitative determination of nucleophilicity of π-electrophiles, see: a) Mayr, H. et. Al.; *J. Am. Chem. Soc.* **1998**, *120*, 3629. For examples of racemic conjugate additions of 2-methylfuran using Brønsted acid catalysts, see: b) Alder; Schmidt *Chem. Ber.* **1943**, *183*, 202. As above with Lewis acid catalyst, see: c) Simon, J.; Srinivasan, V.; L'Abbe, M. R.; Seguin, R. *Heterocycles* **1981**, 1079-1081. As above, thermal, see: d) Jenner, G.; Rimmelin, J.; Antoni, F.; Libs, S.; Schleiffer, E. *Bull. Soc. Chim. Fr.* **1981**, 65-70. For thermally promoted conjugate additions of 1-methylpyrrole, see: e) Diels; Alder; *Justus Liebigs Ann. Chem.* **1929**, 103.

[7] pK_A of furyllium cation approximately –2.5, see reference 8.

are generally insensitive to mild acidic conditions. Unlike the silyl compounds described above which are readily consumed by irreversible hydrolysis in the presence of even mild acids, heterocycles can engage in an innocuous equilibrium with their protonated form without hydrolytic decomposition.[8] Taken in combination, these attributes would appear well-suited to a substrate for our proposed transformation.

Indeed, the electron-rich heterocycle 2-methylfuran did react with crotonaldehyde in the presence of 0.20 equivalents of **1**·HCl to afford optically active 3-(5-methyl-2-furyl)-butanal, with reasonable reaction efficiency and selectivity (Table 1, entry 1; 79% yield, 59% ee). *N*-Methylpyrrole and *N*-methylindole were also examined in the same context and found to be effective nucleophiles in amine-catalyzed additions to crotonaldehyde (Table 1, entries 2-3).[9] To our knowledge, these three reactions constituted the first examples of catalytic, asymmetric conjugate additions of heterocycles to unsaturated aldehydes.[10] Of the three substrates, we elected to pursue optimization of our catalytic system in the context of pyrrole additions because the substantially faster rate they exhibited made them more conducive to rapid evaluation of reaction variables.

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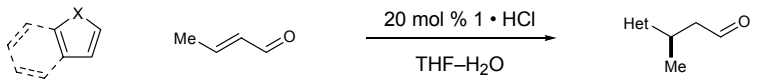
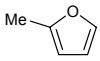
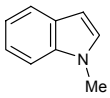
[8] Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*; Springer-Verlag: Heidelberg, Germany 1999, Vol. 3.

[9] In alkylations of 2,5-unsubstituted pyrroles and furans, a 3-5 fold excess of the nucleophile was used to suppress bis-alkylation.

[10] During the course of these studies a report of asymmetric Lewis acid-catalyzed conjugate additions of indoles and furans to β,γ-unsaturated-α-oxo-esters was published: Jensen, K. M.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 160.

Table 1



entry	heterocycle	temp (°C)	time (h)	% yield[a]	% ee[b]
1		20	8	83	59
2		20	1.5	81	66
3		–20	48	N.D.	50

[a]Yield determined by GLC analysis of an aliquot with an internal standard. [b]Product ratios determined by GLC using Bodman G-TA column or by HPLC analysis of corresponding alcohol using Chiralpak AD columns (25 + 5 cm).

Optimization of pyrrole additions

We identified five primary variables which we believed would have the greatest impact on reaction efficiency and selectivity: 1) solvent, 2) the substituent on the chiral carbon of the imidazolidinone catalyst, 3) temperature, 4) concentration, and 5) nature of the Brønsted acid co-catalyst. To probe the influence of the first variable, an extensive solvent study was performed in the context of the addition of 1-methyl pyrrole to crotonaldehyde in the presence of **1**·HCl and water (10% v/v with solvent). Cyclic ethereal solvents were found to be optimal for enantioselectivity in this transformation (THF 66% ee, 1,4-dioxane 62% ee). More polar solvents such as MeOH, DMF, DMSO, nitromethane, and acetonitrile tended to give higher reaction rates, but were uniformly

less favorable with regard to reaction selectivity (all examples less than 35% ee).[11] We suspected that a proton-catalyzed racemic pathway might be more competitive with the iminium mechanism in these media and could account for the observed erosion of selectivity. We also considered that greater solvation of a positively charged iminium ion intermediate by these polar solvents might be disruptive to conformational organization imposed by internal stabilization of charge by elements of the catalyst architecture. In the other extreme, nonpolar solvents such as toluene, CH_2Cl_2, and Et_2O failed to give appreciable conversion even at extended reaction times. These latter reactions were, in fact, biphasic and we reasoned that segregation of the hydrophilic catalyst salt from the substrates might be responsible for the depressed reaction rates.

With THF selected as a suitable solvent, we next set out to explore the effect of catalyst architecture on reaction rates and reactivity. As discussed in Chapter 1, the substitution pattern at positions 2-5 about the imidazolidinone structure had previously been established as important with regard to rapid formation of a reactive and geometrically well-defined iminium ion. We, therefore, focused our attention on variation of the substituent at the chiral C(5)-position. The syntheses of a range of homochiral 5-substituted imidazolidinones were accomplished by the dehydrative cyclization of the appropriate optically pure aminoamides with acetone in acidic MeOH.[2a] The crystalline hydrochloride salts of these amines were then tested in the reaction of *N*-methylpyrrole with crotonaldehyde (Table 2).

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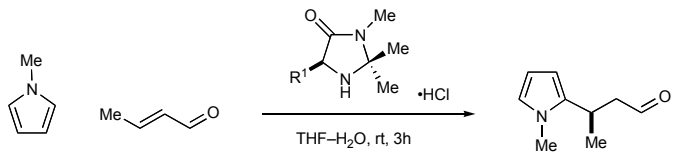
[11] Interestingly, acetone which has the potential to condense with amines was found to be an effective solvent in this study, affording rapid conversion and up to 58% ee.

Table 2



6

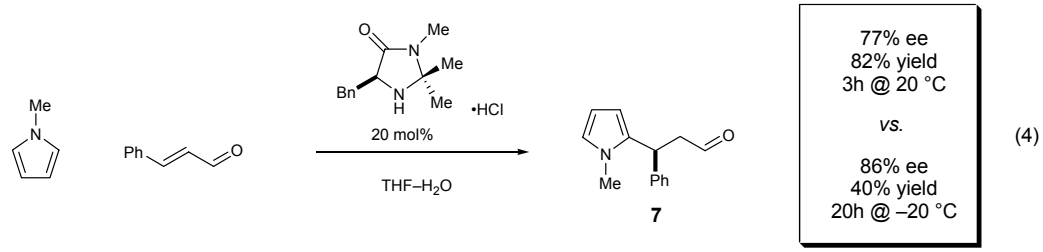
entry	R^1	% conversion[a]	%ee[b]
1	^{i}Bu	trace	33
2	^{i}Pr	26	26
3	^{t}Bu	6	68
4	Ph	86	2
5	Bn	81	66
6	PMB	83	56
7	CH_2(1-Me-3-indolyl)	81	66

[a]Conversion determined by GLC analysis of an aliquot with an internal standard.
[b]Product ratios determined by GLC using Bodman Γ-TA column.

Catalysts bearing branched alkyl chains proved to be the least effective in mediating the conversion of crotonaldehyde to *β*-(2-pyrrolyl)-aldehyde **6** (Table 2, entries 1-3). Of the three such catalysts tested, 5-*tert*-butyl imidazolidinone was the only one to furnish the conjugate adduct in reasonable enantiomeric excess, but none of these examples provided a competitive reaction rate. The phenylglycine-derived catalyst was responsible for the greatest rate acceleration in the reaction, but did so at the cost of all selectivity (Table 2, entry 4). Catalysts bearing an arene tethered to the C(5)-position by a methylene linker proved to be the most successful in mediating rapid and selective reactions. Imidazolidinones derived from phenylalanine, *O*-methyl-tyrosine, and *N′*-methyl-tryptophan catalyzed near complete conversion of crotonaldehyde to the conjugate adduct while maintaining moderate levels of enantioselectivity (Table 2, entries 5-7). Neither variation of the substituents at N(3) or C(5), nor examination of non-imidazolidinone cyclic secondary amines led to any improvement over the

effectiveness of **1**·HCl.[12] In total, these results are consistent with those observed in the previous optimization of our organocatalytic cycloaddition reactions and lend further support to our proposed structure for an iminium ion intermediate (*vide supra*).

Attempts to achieve higher levels of enantioinduction for conjugate additions of pyrroles to various enals by manipulation of reaction temperature and concentration met with mixed results. Not unexpectedly, decreased temperatures led to modest increases in selectivity at the cost of reaction rate. For example, the reaction of 1-methylpyrrole with cinnamaldehyde at ambient temperature furnishes 3,3-diarylaldehyde **7** in 77% ee and 82% yield after three hours (equation 4). The same reaction conducted at –20 ºC achieves a slightly higher level of selectivity, but proceeds sluggishly (equation 4; 86% ee, 40% conversion in 20h).



(4)

On the other hand, these alkylations appeared to be relatively insensitive to changes in concentration of the reagents. A range of solvent volumes were used to

[12] The (*5S*)-3,5-dibenzyl-2,2-dimethyl-imidazolidinone hydrochloride catalyst furnished 71% ee and 82% conversion in the addition of 1-methylpyrrole to crotonaldehyde. The (*5S*)-5-benzyl-3-methyl-2,2-spirocyclohexyl-imidazolidinone salt gave no addition of 1-methylpyrrole to cinnamaldehyde and the spirocyclopentyl structure gave 69% ee and 16% conversion as compared to 77% ee and 67% conversion in this addition under identical reaction conditions. The reaction of crotonaldehyde and 1-methylpyrrole mediated by (*S,S*)-pyrrolidine-2,5-bismethoxycabonyl • HCl gave 37% ee as compared to 66% with **1** • HCl; the reaction of cinnamaldehyde with 1-methylpyrrole went in 22% ee in the presence of (*S*)-abrine-methyl ester • HCl, and 56% ee in the presence of (S,S)-*N,N*-dibenzylamine-1,1'-bismethoxycabonyl • HCl, compared to 78% with **1** • HCl.

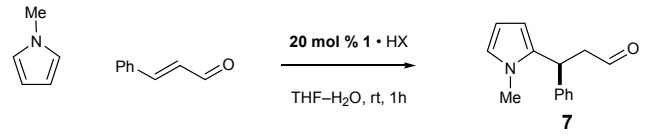
achieve reaction concentrations between 0.075 and 2.0 M, and all afforded products in the range of 76-80% ee at ambient temperature. While the lowest concentrations resulted in reactions with depressed rates, no significant acceleration was achieved at concentrations above initial 0.33 M conditions. Treatment of water as either a stoichiometric reagent or as a co-solvent (10% v/v with THF, regardless of substrate concentration) did not affect selectivity. Notably, reactions conducted in the absence of any exogenous water resulted in a high occurrence of side products, especially those resulting from 1,2-addition of pyrrole to saturated aldehyde **7**.

Having achieved limited success in optimization of basic reaction variables, we turned our investigations back to the catalyst itself. Specifically, the influence of the Brønsted acid co-catalyst was examined systematically using various pre-formed crystalline salts of imidazolidinone **1** in the reaction of 1-methylpyrrole with cinnamaldehyde (Table 3).[13] Salts of exceptionally acidic co-catalysts (i.e., the sulfonic acids) promoted substantially slower reactions which proceeded with lower enantioselectivities and a higher occurrence of side-products (Table 3, entries 1-2). *ortho*-Nitrobenzoic acid and acetic acid itself were completely ineffective as co-catalysts, furnishing no detectable amount of the desired product (Table 3, entries 8-9). Substituted acetate salts proved to be the most effective in promoting the addition with good levels of enantioselectivity, providing adduct **7** in 80-81% ee (Table 3, entries 4-7). TFA provided the greatest reaction rate among all co-catalysts screened in this reaction, achieving complete conversion in less than 3 hours. Significantly, this high reactivity could be translated to lower temperatures with gratifying results: using 20 mol% of **1**·TFA in this

[13] Imidazolidinone **1** did not form crystalline salts with *o*-nitro-benzoic acid or acetic acid (Table 3, entries 8-9). These catalysts were generated *in situ* from 0.22 mol% neutral amine **1** and 0.20 mol% acid.

same reaction conducted at –30 ºC, complete conversion was observed after 42 hours and aldehyde **7** was isolated in 87% yield and 93% ee.

Table 3



7

entry	HX	% conversion[a]	%ee[b]
1	TfOH	44	42
2	*p*-TSA	41	55
3	HCl	63	77
4	**TFA**	**76**	**81**
5	TCA	ND[c]	81
6	DCA	<5%	80
7	NCAcOH	trace	80
8	*o*-NO_2-$C_6H_4CO_2H$	NR[d]	—
9	AcOH	NR[d]	—

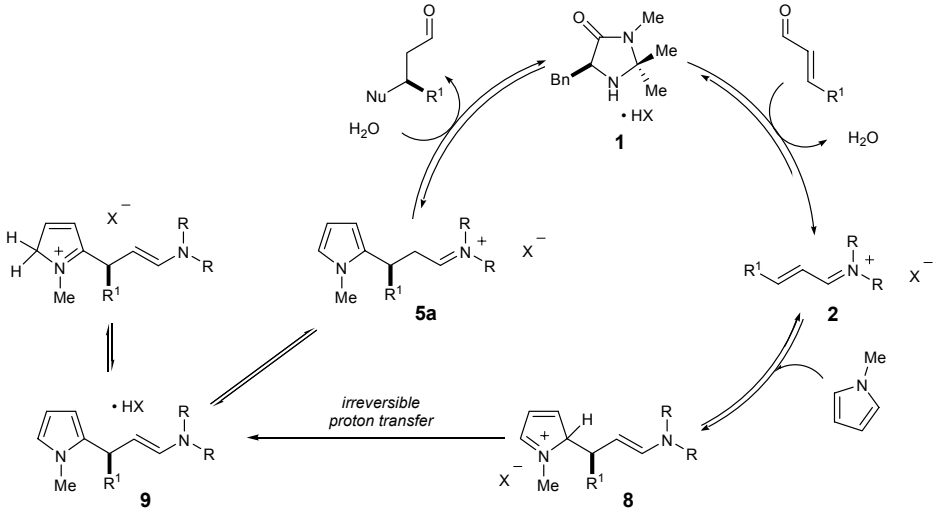
[a]Conversion determined by GLC analysis of an aliquot with an internal standard. [b]Product ratios determined by GLC using Bodman Γ-TA column. [c]Not Determined (Note: TCA after 3h gave 64% isolated yield as compared to 78% from TFA reaction.) [d]No product observed even after 6 hours.

In addition to furnishing the first synthetically useful levels of selectivity in this reaction, the data obtained from our counterion study illustrate two trends which may provide some insight into the mechanism of the transformation. The more obvious of the two is that enantioselectivity positively correlates to the pK_A of the co-catalyst, until a plateau is reached at approximately 80% ee. A slightly more complicated bimodal correlation is observed with respect to conversion. Again, a positive relationship is observed as the pK_A of the co-catalyst increases from –14 to –0.25[14], but then reaction rate begins to erode as the pK_A increases beyond that point. We propose that these trends arise because the co-catalyst serves two important functions in determining the rate and

[14] All pK_A values acid co-catalysts referenced in aqueous solution. see: Albert, A.; Serjeant, E.P. *The Determination of Ionization Constants 3 Ed*; Chapman and Hall: New York 1984.

selectivity of organocatalytic conjugate additions. Our rationale is illustrated in the following revised catalytic cycle for organocatalytic conjugate additions of latently acidic nucleophiles (Scheme 4).

Scheme 4



The initial addition of a pyrrole to an α,β-unsaturated iminium ion should result in pyrrolium-enamine intermediate **8**. Under the reaction conditions, β-elimination of the positively charged leaving group to regenerate the unsaturated iminium ion and an aromatic ring is entirely plausible. Such a possibility would mean that the product-determining step is reversible and subject to thermodynamic control, thereby undermining asymmetric bias imparted by the catalyst in a kinetic addition event. However, if proton abstraction from the C(2) position of the pyrrolium species is irreversible and fast relative to β-elimination, selectivity in the initial addition should be reflected in the final product. This hypothesis suggests two limiting cases: 1) rapid proton abstraction from the incipient pyrrolium ion would lead to rate and selectivity that

directly reflect those in the addition event, and 2) slow proton abstraction would lead to a thermodynamic equilibration of intermediate **8**, a racemic product, and a slower overall reaction.

A number of species are available in solution to effect this crucial deprotonation event, but in light of the above data we suspect that the negatively charged conjugate base of the acid co-catalyst is the most likely culprit. Specifically, we argue that triflate, tosylate, and chloride anions are poor bases for the removal of a proton from pyrrolium species **8**. This inadequacy in these cases is responsible for slower reaction rates and allows the reversibility of the conjugate addition step to erode enantioselectivity. We propose that the more basic acetate counterions effectively minimize β-elimination of intermediate **8** by rapidly abstracting a proton from the tetrahedral carbon of the pyrrolium cation. As a result, the ~80% ee observed in the products of reactions catalyzed by these substituted acetate salts reflects the intrinsic enantioselectivity of the initial conjugate addition of 1-methylpyrrole to the unsaturated iminium ion at room temperature.

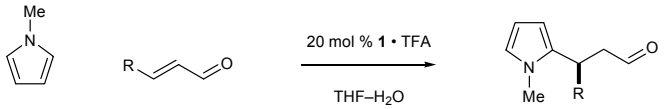
The above mechanistic hypothesis provides an explanation of the counterion effect on enantioselectivity and conversion with co-catalysts at least as acidic as TFA. Reversal of the trend in catalyst activity with respect to co-catalyst acidity for counterions that are more basic than TFA falls out neatly from our previous studies regarding the generation and reactivity of iminium ions. As observed during the development of our amine-catalyzed cycloadditions, higher concentrations of an apparently more reactive iminium ion are observed when the co-catalyst is a stronger acid.[15] Hence, as co-catalyst

[15] Unpublished results of Kateri Ahrendt and Catharine Larsen.

acidity decreases from TFA to AcOH, concentration and reactivity of **2** both decrease, so initial addition of pyrrole to the iminium ion is retarded. In the cycloaddition reactions, this trend generally holds across the entire range of co-catalysts from triflic to acetic acid. In conjugate additions of latent acids, such as pyrroles, the overall observed reaction rate is a product of the rate in the addition and proton transfer steps. The ideal co-catalyst should therefore be slightly less acidic than the expected pyrrolium intermediate in order to maximize overall performance in both steps.

Having identified **1**·TFA as an effective catalyst for the enantioselective conjugate addition of *N*-methylpyrrole to cinnamaldehyde, we next explored the scope of this new transformation. A range of α,β-unsaturated aldehydes were reacted with *N*-methylpyrrole in the presence of 0.20 equivalents of **1**·TFA in wet THF (Table 4). The reaction proceeded in good yield and selectivity for a variety of enals bearing simple and branched aliphatic substituents at the β-position (R = Me, ^{n}Pr, ^{i}Pr, entries 1-3; 80-83% yield, 90-91% ee). Electrophiles bearing aromatic functionality at the β-position also underwent selective conjugate addition under these conditions (R = Ph, PMP, 2-furyl, entries 4-6; 84-93% ee) as did electron-poor substrates which should not readily participate in iminium ion formation (R = CH_2OBn, CO_2Me, entries 7-8; 72-80% yield, 87-90% ee). To demonstrate the preparative utility of these alkylations on larger scale, alkylation of 1-methylpyrrole with cinnamaldehyde was performed on a 25 mmol scale with catalyst **1**·TFA, to afford (*S*)-**7** in 87% yield and 93% ee.

Table 4



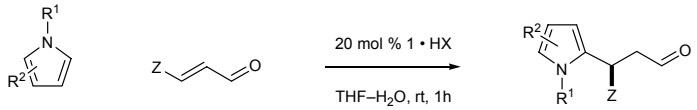
entry	R	temperature (°C)	time (h)	% yield[a]	% ee[b]
1	Me	–60	72	83	91[c]
2	CH_2OBn	–60	60	80	87[c]
3	^{n}Pr	–50	72	81	90
4	^{i}Pr	–50	72	80	91
5	Ph	–30	42	87	93
6	*p*-MeO-Ph	–30	105	79	91
7	2-furyl	–30	42	49	84
8	CO_2Me	–60	104	72	90

[a]Yield of corresponding alcohol after *in situ* reduction. [b]Product ratios determined by GLC using Bodman Γ-TA column. [c]Using 10 mol% of **1** • TFA. [d]Using 1 • CNAcOH as catalyst.

The scope of pyrrole nucleophiles tolerated in this reaction also appeared to be fairly broad (Table 5). Extension of an unbranched alkyl chain from the nitrogen position gave approximately equivalent results to those of *N*-methylpyrrole ($R^1 = {}^{n}Hex$, entry 2; 78% yield, 89% ee in addition to crotonaldehyde). Pyrroles bearing unsaturated protective groups at the N(1) position were also adequate substrates (R^1 = allyl, Bn, entries 3-4; 80-83% yield, 89-91% ee). Increasing the steric bulk at nitrogen had a negative impact on selectivity ($R^1 = {}^{i}Pr$ and ${}^{t}Bu$, entries 5 & 6; 75 and 27% ee, respectively) while pyrrole itself, without any substituents at the heteroatom, was a competent nucleophile (R^1 = H, entry 7; 74% yield, 90% ee). Interestingly, co-catalysts that are less acidic than TFA were required to achieve optimal selectivities and reaction rates in the cases of relatively electron-rich dialkyl and trialkylpyrroles. The dichloroacetic acid salt of imidazolidinone **1** was the most effective catalyst in the additions of 1,2- and 1,3-dialkylpyrroles (R^1 = Me, R^2 = 2-^{n}butyl, 3-^{n}propyl, entries 8-9; 68-87% yield, 90-97% ee). The highest selectivity achieved in the addition of *N*-methyl-

4,5,6,7-tetrahydroindole to cinnamaldehyde required the cyanoacetate counterion (entry 10; 83% ee).

Table 5



entry	R^1	R^2	Z	temp (°C)	HX	% yield[a]	% ee[b]
1	Me	H	Ph	–30	TFA	87	93
2	Hex	H	Me	–50	TFA	64[c]	89
3	Allyl	H	Ph	–30	TCA	83	91
4	Bn	H	Ph	–30	TCA	80	89
5	^{i}Pr	H	Ph	–10	TFA	ND[d]	75
6	^{t}Bu	H	Me	+20	TFA	ND[e]	27
7	H	H	CO_2Me	–60	CNAcOH	74	90
8	Me	2-butyl	Ph	–60	DCA	87	90
9	Me	3-propyl	Ph	–60	DCA	68	97
10	Me	2,3-$(-CH_2-)_4$	Ph	–60	CNAcOH	ND[g]	83

[a]Yield of corresponding alcohol after *in situ* reduction. [b]Product ratios determined by GLC using Bodman Γ-TA column or HPLC using Chiralpak AD columns (25 + 5 cm). [c]Aldehyde isolated directly, without reduction. [d]Not determined,30% consumption of aldehyde after 20h by GLC analysis. [e]Not determined, complete consumption of aldehyde after36h by GLC analysis. [f]98:2 selectivity for alkylation at 2-position vs. 5-position. [g]Not determined, complete conversion of aldehyde after 120h.

These observations are consistent with our proposed dual role of the Brønsted acid co-catalyst in this reaction. Substitution at the C(2) and C(3)-positions on the nucleophile serves to stabilize incipient pyrrolium cations (**8**) formed as intermediates in these alkylation reactions. Such stabilization has two mechanistic consequences in the context of our methodology: 1) initial conjugate addition should be accelerated,[16] thereby diminishing the requisite concentration of the active catalyst-substrate iminium complex, and 2) the resulting stabilized pyrrolium species will be a weaker acid and hence require

[16] Alkyl substitution at the C(2)-position is known to acceleration electrophilic addition at the C(5)-position of pyrroles by factors of up to 10^4. Substitution at the C(3) position tends to favor alkylation at the C(2)-position and can result in rate accelerations in the range of 100x. see reference 8.

a stronger base for facile deprotonation. These changes would tend to favor co-catalysts of higher pK_A in the interest of reaction rate and selectivity, a trend that is consistent with the empirical data. Optimal co-catalyst appears to vary with the pyrrole component irrespective of the nature of the electrophile; this relationship further supports the proposed interaction between the counterion and the pyrrolium intermediate.

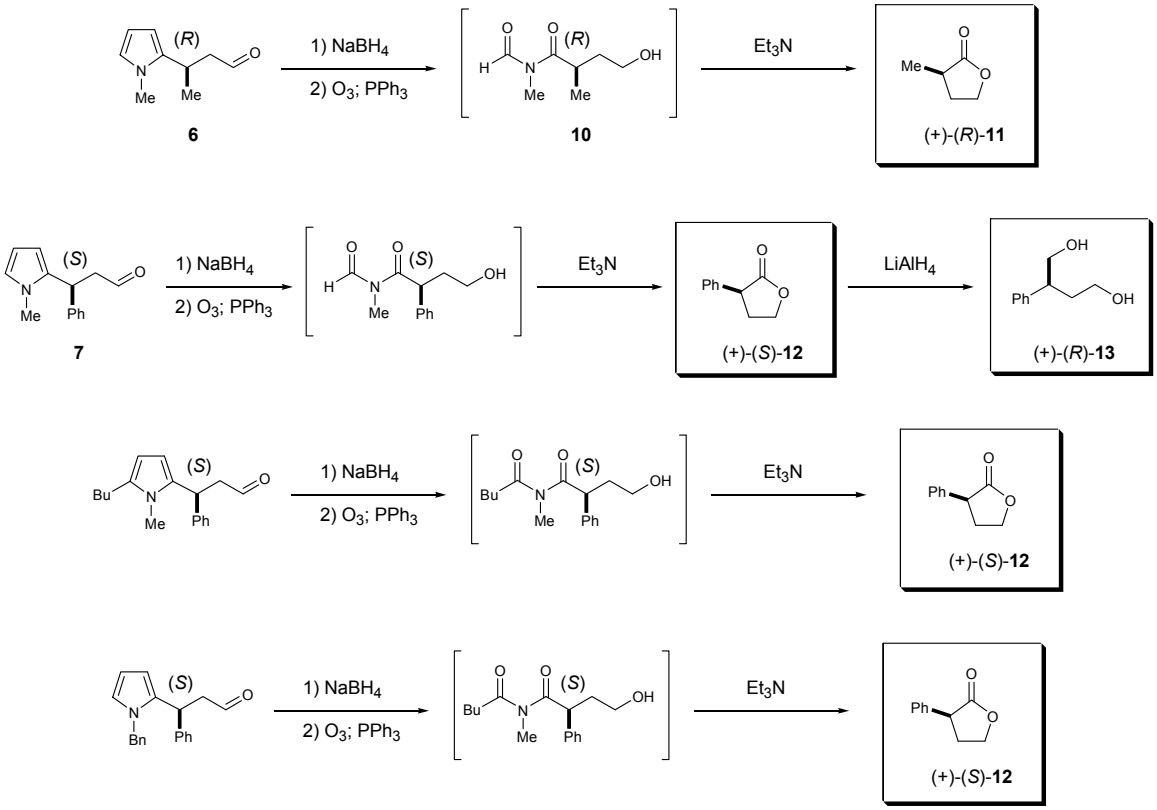
Investigation of transition state topology

The absolute sense of asymmetric induction in the *β*-pyrrolyl aldehyde products was determined by chemical correlation to compounds with known chiroptical properties. Adduct **6**, arising from asymmetric addition of *N*-methylpyrrole to crotonaldehyde in the presence of catalyst (*5S*)-**1** was reduced to the corresponding alcohol and then ozonized. Treatment of the crude ozonide with triphenylphosphine overnight followed by a catalytic amount of triethylamine afforded (*R*)-**11**, presumably through the intermediacy of imide **10** (Scheme 5). Comparison of the optical rotation exhibited by our synthetic material to that of reported (*S*)-**11** confirmed that we had indeed accessed the opposite stereoisomer. Product from the reaction of *N*-methylpyrrole and cinnamaldehyde (**7**) mediated by (*5S*)-**1** was converted to (+)-**12** using the same procedure. Subsequent reduction of the lactone with $LiAlH_4$ afforded (*R*)-2-phenyl-butan-1,4-diol (**13**), the optical rotation of which was compared to that reported for (*S*)-**13**[17] to unambiguously confirm a consistent sense of asymmetric induction for both of these products (Scheme 5). The *β*-pyrrolyl-dihydrocinnamaldehyde products isolated from the alkylations of 2-

[17] Krause, et al, *J. Organomet. Chem.* **1992**, *423*, 271-279.

butyl-1-methylpyrrole and 1-benzylpyrrole were also converted to (+)-**12** using a similar one-pot procedure.

Scheme 5



The same three-dimensional model of unsaturated iminium ion **2** that was used to predict the stereochemical outcome of our asymmetric cycloadditions explains the observed sense of induction in these conjugate additions.[2] As illustrated in the molecular mechanics-minimized structure MM3-**2**, we propose an (*E*, *E*) conformation for the unsaturated iminium ion (Figure 1). This conformation minimizes repulsive steric interactions between the pendant alkene and the *gem*-dimethyl center at the C(2)-position of the catalyst. We also suggest that the preferred orientation of the benzyl substituent at

C(5) is, as shown, directly above the extended electron-deficient π-system, a hypothesis which is supported by ^{1}H-NMR NOE experiments.[18] Such an orientation may be rationalized by a cation-π interaction in which the quadrupole of the aromatic ring is attracted to the positively charged iminium ion.[19] In this overall conformation of the reactive intermediate, the *re*-face of the electrophile is entirely shielded while leaving the *si*-face open to nucleophilic attack.

Further insight into the orientation of reaction partners in the transition state of an enantioselective reaction can often be obtained through identification of matched-mismatched cases in reactions of chiral substrates. In this context, the effects of pre-existing nucleophile stereogenicity on the catalyzed bond formation were examined in our asymmetric conjugate addition. Excess crotonaldehyde reacted smoothly with *N*-methylpyrrole in the presence of (*S*)-**1**·TFA, resulting in complete conversion of the starting material to a 1,2,5-trialkyl pyrrole on reductive work-up (equation 5). The expected C_2-symmetric product of bisalkylation, (*R,R*)-**14**, was formed in 98% ee and in a 90:10 ratio to the *meso* diastereomer. On treatment with cinnamaldehyde, mono-adduct **6** also participated in a facile alkylation in the presence of (*S*)-**1**·TFA to afford the *anti*-bisalkylated pyrrole **15** in similarly high enantio- and diastereoselectivity (equation 6). These figures suggest that the second addition event proceeds without influence from the existing chiral center to give the statistically expected product ratio.

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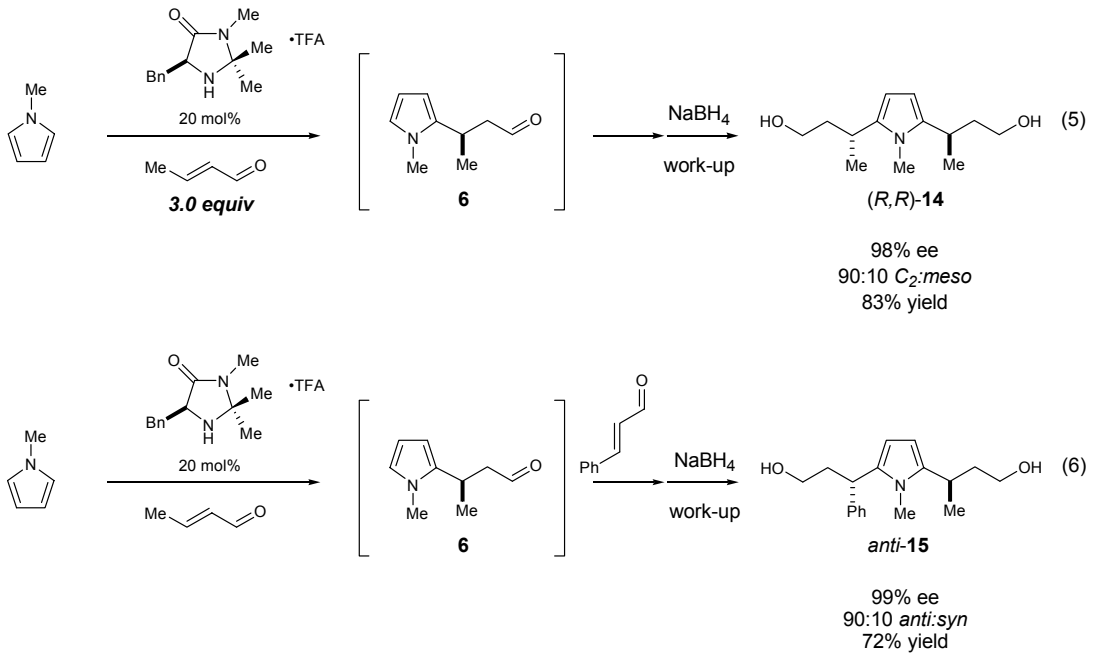
[18] Unpublished results of Julie Park and Catharine Larsen.

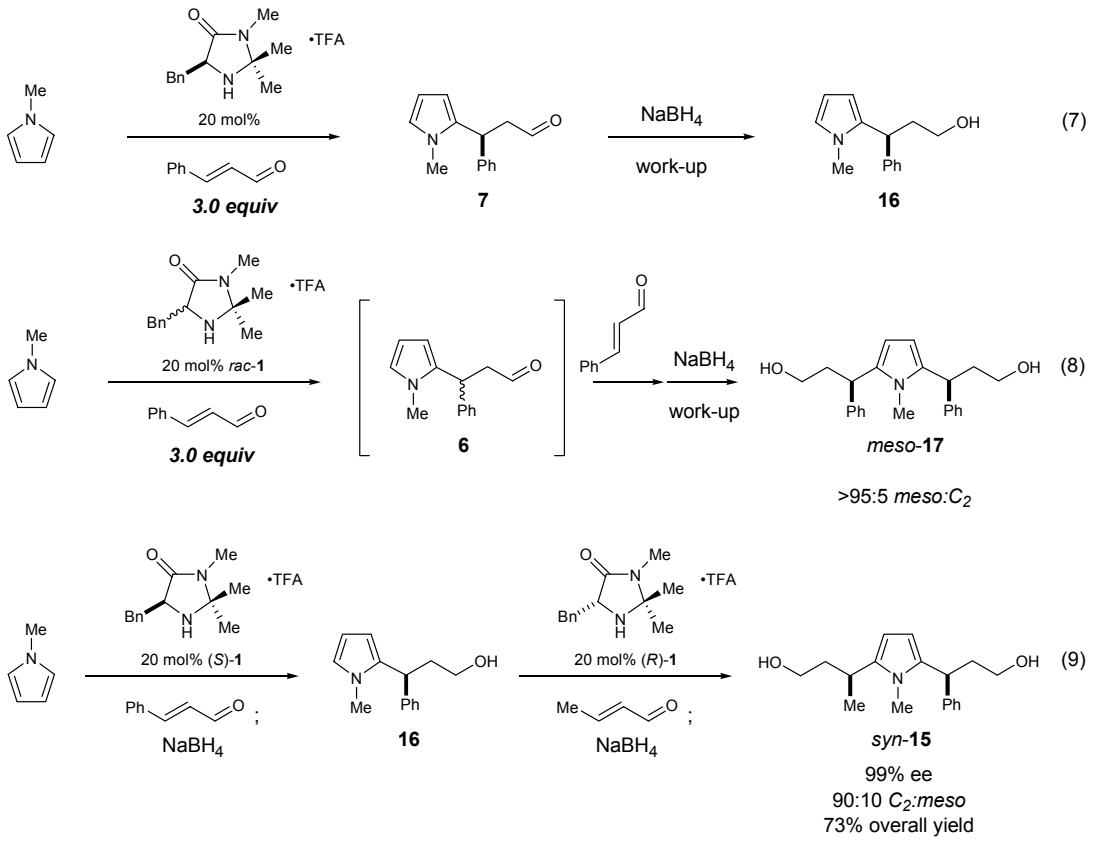
[19] For reviews on the cation-p interaction, see: a) Dougherty, D. A. *Science*, **1996**, *271*, 163; b) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.



In contrast to the above examples, *N*-methylpyrrole failed to participate in a double alkylation with cinnamaldehyde mediated by homochiral **1**·TFA, even in the presence of several equivalents of the electrophile at room temperature (equation 7). However, when methyl pyrrole was treated with cinnamaldehyde in the presence of *rac*-**1**·TFA facile bis-aslkylation afforded *meso*-diol **17,** after reductive work-up, in greater than 95:5 diastereoselectivity (equation 8).[20] Mono-adduct derivative **16** could also be easily alkylated with a second equivalent of enal using the other antipode of our optically pure amine catalyst, (*R*)-**1**·TFA. When crotonaldehyde was used as the electrophile in this case, trisubstituted pyrrole **15** could be isolated, this time as the *syn*-diastereomer, in good yield and selectivity (equation 9). This situation represents a case of matched *versus* mismatched substrates: the pyrrole products from mono-addition to cinnamaldehyde are unfavorable substrates for a second alkylation using the same

[20] Diastereomer ratio of **18** determined by ^{1}H-NMR.

enantiomeric series of catalyst, but readily participate in a second event catalyzed by the other antipode of the imidazolidinone.



Our rationale for the above observations begins with an analysis of the ground state conformation of mono-alkylated pyrrole **17**. In this species, the relationship of the tertiary carbon center to the N(1)-methyl substituent is analogous to that found in (*Z*)-4-methyl-2-butene (Figure 2). In the simple alkene, the rotamer that features a coplanar arrangement between the proton of the tertiary carbon and the allylic methyl is favored by approximately 4.5 kcal/mol, in order to minimize disfavorable non-bonding interactions. In the case of **17** as depicted below, a coplanar arrangement of the proton at the chiral center with the *N*-methyl would project the phenyl substituent above the plane of the

heterocycle and the alkyl chain below the plain. The relative size of the aryl substituent should then disfavor electrophilic attack from the top face of the pyrrole ring. Taken along with our model for iminium ion structures derived from **1** and the assumption of a staggered conformation about the forming bond, this line of reasoning would lead to three reasonable models for the approach of the nucleophile (Figure 3).

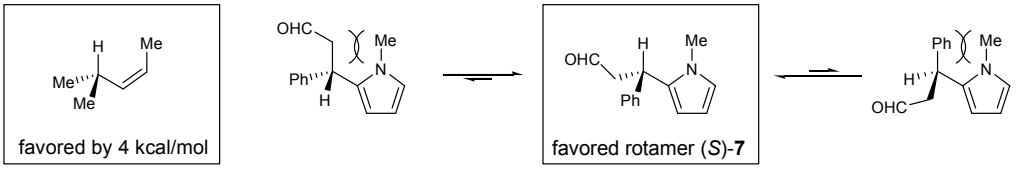


Figure 2

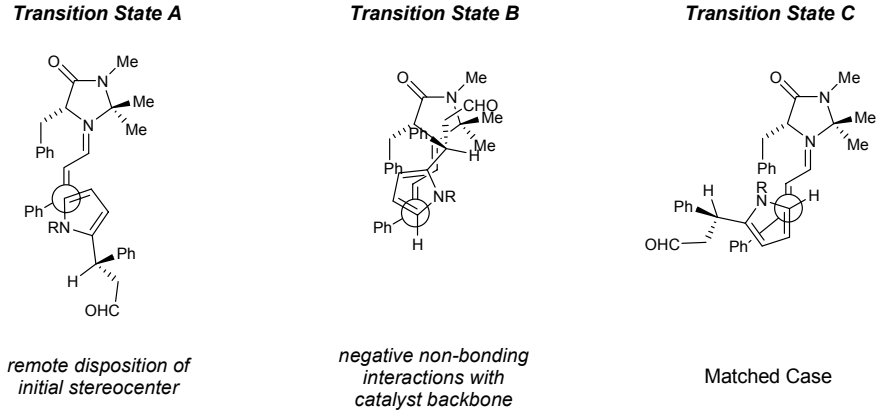


Figure 3

In each of the first three models above (*S*)-**7**, monoalkylation product arising from reaction of 1-methylpyrrole and cinnamaldehyde in the presence of catalyst (*S*)-**1** is paired with a drawing of the iminium derived from cinnamaldehyde and (*R*)-**1**– a scenario which would lead to a second alkylation. In transition state model A for the second alkylation of pyrrole with cinnamaldehyde, the chiral side-chain of the nucleophile is completely segregated from the bond-forming event and the rest of the catalyst architecture. It is difficult to justify any communication of stereochemical information between the substrate and the catalyst-bound iminium ion, so the probability of this model being accurate is small. The second case, model B, describes a transition state in which the bulky C(2)-substituent on the nucleophile is thrust into the core of the catalyst architecture. Such a geometry should be disfavored by steric clash between the large tertiary center and the inflexible 5-membered ring. This approach would also imply that the nitrogen substituent is oriented toward solvent, a conclusion that runs counter to the negative relationship previously established between increasing bulk in N(1)-substitution and reactivity as described above (Table 5, entries 5 & 6). Finally, transition state model B, orients the π-bond between C(4) and C(5) of the nucleophile anti-periplanar to the enal acceptor in the approach. This arrangement brings the pyrrole substituent at the C(2) position into the proximity of the β-position of the unsaturated iminium. In the matched case, this results in an interaction between a flexible two carbon chain on the nucleophile and a flat arene. In the mismatched case, the outcome is that two, nearly orthogonal arenes share the same space. When crotonaldehyde mono-adduct

6 is the electrophile, the difference between the matched and mismatched scenarios are virtually eliminated as both methyl and methylene can be considered small in steric size.

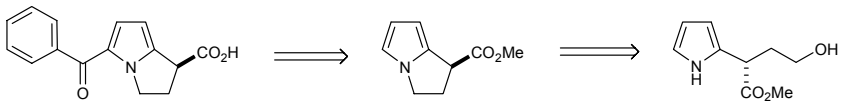
Application: enantioselective synthesis of (*R*)-Ketorolac (18)

The *β*-pyrrolyl aldehyde products generated by our enantioselective conjugate addition methodology are potentially useful synthons in the construction of a variety of biologically active compounds.[21] Ketorolac is a non-steroidal anti-inflamatory drug marketed in racemic form for use as an analgesic. In early biological testing, it was discovered that (*S*)-Ketorolac (**18**) is both more active and less toxic than its enantiomer.[21b] As such a direct, enantioselective route to this dihydropyrrolizine would seem an attractive target, we believe our new enantioselective pyrrole alkylation methodology presents an interesting avenue of opportunity by which to attack this synthetic challenge.

In our retrosynthesis (Scheme 6), **18** would arise from benzoylation and hydrolysis of the bicyclic ester **19**. This dihydropyrrolizine ring would be closed by intramolecular alkylation of the pyrrole nitrogen with a suitably-activated form of the carbinol in open chain alcohol **20**.

[21] A) Kleeman, A.; Engel, J.; Kutscher, B.; Riechert, D. *Pharmaceutical Substances 4 Ed*; Thieme: New York, 2001. b) (*S*)-Ketorolac: Guzman, A.; Yuste, F.; Toscano, R. A.; Young, J. M.; Vanhorn, A. R.; Muchowski, J. M. *J. Med Chem,* **1986**, *29*, 589.

Scheme 6



(*S*)-**18** (*S*)-**19** (*S*)-**20**

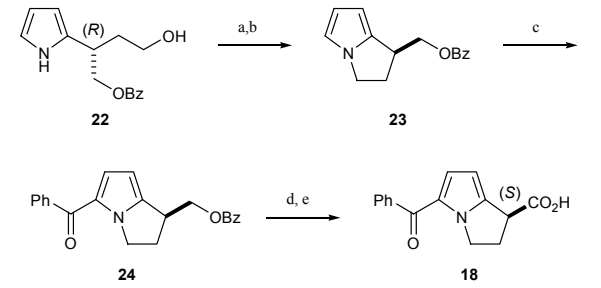
We began our first synthetic attempt with a preparative scale alkylation of pyrrole with methyl 4-oxo-crotonate **21** using (*R*)-**1**·NCAcOH, followed by *in situ* reduction with $NaBH_4$ which afforded the α-pyrrolyl-γ-hydroxy ester in 74% yield and 90% ee (Scheme 7). Selective tosylation of the primary hydroxyl in the presence of the pyrrole nitrogen was readily accomplished with *p*-tolylsulfonyl chloride in pyridine, but attempts to form the fused 5-membered ring by intramolecular alkylation of were unsuccesful. Even with mild bases, such as K_2CO_3, the only product observed arose from alkylation of the ester enolate. Direct intramolecular cyclization of the pyrrolyl propanol using Mitsunobu conditions on **20** gave similar results. Given the acidity of this α-pyrrolyl ester functionality and the concommitant potential for racemization, we decided to carry the acid through the synthesis in the alcohol oxidation state. This would supply a more robust stereocenter which we could unmask as the desired acid in the last step (Scheme 8).

Pyrrole added to γ-benzoyloxy-crotonaldehyde in the presence of catalyst (*R*)-**1**·DCA with an enantiomeric excess of 74% and alcohol **22** was isolated in after a reductive work-up with $NaBH_4$ in 86% yield (Scheme 7). Tosylation and ring-closing alkylation both proceeded cleanly and in high yield to give dihydropyrrolizine **23** (88% over 2 steps). Benzoylation of the pyrrole ring could be accomplished using Wilsmeier-Haack conditions to afford heterocycle **24** in 72% yield. Removal of the benzoyl

protective group from the hydroxyl was accomplished in near quantitative yield with NaOH in MeOH:THF (2:1) and, finally, oxidation of the alcohol to the corresponding alcohol proceeded in the presence of platinum under an oxygen atmosphere to give (*R*)-Ketorolac (97% yield, based on recovered starting material). The entire sequence is carried out in 5 steps and 64% overall yield from **22**. Further optimization of the pyrrole alkylation and reversing order of the cyclization and acylation steps allowed access to **18** in 91% ee and 69% overall yield from **22**.[22]

[22] Unpublished results of Brian Kwan and Craig Countryman.

Scheme 7



a) TosCl, Et_3N, CH_2Cl_2, 94% yield; b) ^tBuOK, ^tBuOH/THF, 94% yield; c) i. 4-Bz-morpholine, $POCl_3$,1,2-dichloroethane; ii. aq. NaOAc, 76% yield; d) 2% NaOH, MeOH/THF, 99% yield; e) PtO_2, O_2, H_2O/^{i}PrOH/EtOAc, 41% yield (56% recovered SM after 40h).

Conclusion

This report describes the successful extension of enantioselective iminium catalysis to conjugate addition reactions. We have demonstrated that substituted acetate salts of chiral imidazolidinone **1** are useful catalysts for asymmetric alkylation reactions of electron-rich heterocycles with α,β–unsaturated aldehydes.[23] These reactions proceed with exquisite regioselectivity favoring the 1,4- over the 1,2-addition pathway, a reaction mode which is unprecedented in reactions of pyrroles and indoles with enals. These studies have also highlighted the significance of the Bronsted acid co-catalyst in our organocatalytic methodology and given some insight into transition state geometries in the alkylation reaction. And finally, we have demonstrated the synthetic utility of asymmetric pyrrole allkylations in the context of a highly enantioselective synthesis of the drug (*S*)-Ketorolac.

[23] This technology has since been successfully optimized for highly selective alkylation of indoles and furans as well. For indoles see: Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2002**, *124*, 1172. for furans see: Sean Brown, unpublished results.

Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[24] Imidazolidinones were synthesized according to published procedures.[25] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[26] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHz and 125 MHz, respectively), AMX-400 (400 MHz and 100 MHz), AMX-300 (300 MHz and 75 MHz), Varian I500 (500 MHz and 125 MHz), or Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid

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[24]Perrin, D. D.; Armarego, W. L. F. *Purificaion of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

[25] See reference 2a in body of text.

[26]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex γ-TA (30 m x 0.25 mm) column. High-performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using Chiralpak AD column (25 cm) and AD guard (5 cm).

General Procedure (A: excess pyrrole): A 10 mL round-bottom flask equipped with a magnetic stir bar and containing a 2,2-dimethylimidazolidin-5-one salt was charged with THF and H_2O, then placed in a bath of the appropriate temperature. The solution/suspension was stirred for 5 min before addition of the pyrrole. Then, the α,β-unsaturated aldehyde was added over the course of 1 min with swirling of the reaction mixture by hand. The resulting suspension was stirred at constant temperature until complete consumption of the α,β-unsaturated aldehyde was observed as determined by TLC/GLC. The reaction mixture was then transferred cold into a flask containing an excess of sodium borohydride and an equal volume of absolute ethanol. After 15 min, the remaining sodium borohydride was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The organic layers were separated and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were then dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel chromatography (15–50% ethyl acetate/hexanes) to afford substituted 3-(2-pyrrolyl)-propanols.

General Procedure (B: excess aldehyde): A 10 mL round-bottom flask equipped with a magnetic stir bar and containing a 2,2-dimethylimidazolidin-5-one salt was charged with THF and H_2O and the α,β-unsaturated aldehyde. The solution was

stirred at room temperature for 5 min before being placed in a bath of the appropriate temperature. The solution/suspension was stirred for 5 min before addition of the pyrrole. The resulting suspension was stirred at constant temperature until complete consumption of the α,β-unsaturated aldehyde was observed as determined by TLC/GLC. Reactions worked-up and purified as in procedure A.

Alternate Work-up Procedure: Direct Isolation of Aldehydes. Reaction mixture was diluted with several volumes of Et_2O and washed with H_2O, $NaHCO_3$, and brine. The organics were then dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel chromatography (15–35% ethyl acetate/hexanes) to afford the title compounds.

(*R*)-3-(1-Methyl-1*H*-pyrrol-2-yl)-butanal (6). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.61 (t, *J* = 1.8 Hz, 1H, CHO), 6.56 (t, *J* = 2.2 Hz, 1H, ArH), 5.85 (t, *J* = 3.2 Hz, 1H, ArH), 5.75 (dd, *J* = 1.6, 3.2 Hz, 1H, ArH), 3.53 (s, 3H, NCH_3), 2.72 (ddd, *J* = 2.0, 6.8, 17.2 Hz, 1H, C**H**$_2$CO), 2.56 (ddd, *J* = 2.0, 7.6, 17.2 Hz, 1H, C**H**$_2$CO), 1.15 (d, *J* = 6.8 Hz, 3H, CCH_3); ^{13}C NMR (100 MHz, d_6-DMSO) δ 202.8, 136.3, 121.3, 106.1, 103.8, 49.7, 33.0, 24.7, 21.2. Product ratio was determined by GLC analysis (70 °C, 5 °C/min gradient, 23 psi); *S* isomer t_r = 16.1 min and *R* isomer t_r = 17.0 min.

(*S*)-3-Phenyl-3-(1-methyl-1*H*-pyrrol-2-yl)-propanal (7). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.61 (t, *J* = 1.6 Hz, 1H, CHO), 7.29-7.15 (m, 5H, ArH), 6.59 (t, *J* = 2.0 Hz, 1H, ArH), 5.99-5.98 (m, 1H, ArH), 5.92 (t, *J* = 3.0, 1H, ArH), 4.63 (t, *J* = 7.6 Hz, 1H, ArCH), 3.30 (s, 3H, NCH_3), 3.09 (ddd, *J* = 2.0, 8.4, 16.8 Hz, 1H, C**H**$_2$CO), 2.89 (ddd, *J* = 1.6, 6.8, 16.8 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (100 MHz, d_6-DMSO) δ 201.9, 143.0, 133.4, 128.5, 127.5, 126.3, 122.1, 106.1, 106.0, 49.3, 36.5, 33.3. Product ratio was determined

by GLC analysis (70 °C, 5 °/min gradient to 170 °C isotherm, 23 psi); *R* isomer t_r = 26.6 min and *S* isomer t_r = 27.4 min.

(*R*)-3-(1-Methyl-1*H*-pyrrol-2-yl)-butanol (Table 4, entry 1). Prepared according to general procedure A from crotonaldehyde (83 μL, 1.0 mmol), 1-methyl-1*H*-pyrrole (0.45 mL, 5.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (33 mg, 0.10 mmol) in THF (2.0 mL) and H_2O (0.30 mL) at -60 °C for 72 h and then –20 °C for 12 h to provide the pure product as a colorless oil in 83% yield (0.13 g, 0.83 mmol); 91% ee. IR (film) 3368, 3105, 2958, 2935, 2881, 1699, 1630, 1491, 1460, 1421, 1375, 1298, 1244, 1050, 1004, 857.3,772.4, 702.9 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.28 (dd, *J* = 1.9, 2.7 Hz, 1H, ArH), 6.20 (t, *J* = 3.6 Hz, 1H, ArH), 5.96 (dd, *J* = 1.7, 3.0 Hz, 1H, ArH), 3.39 (dt, *J* = 2.5, 6.3 Hz, 2H, C**H$_2$**OH), 2.98 (s, 3H, NCH_3), 2.75 (dt, *J* = 6.9, 6.9 Hz, 1H, ArCH), 2.22 (br s, 1H, OH), 1.77-1.65 (m, 1H, CH C**H**$_2$), 1.63 (m, 1H, CHC**H**$_2$), 1.08 (d, *J* = 7.1 Hz, 3H, CCH_3); ^{13}C NMR (100 MHz, C_6D_6) δ 137.8, 128.9, 107.1, 104.0, 60.4, 40.4, 33.0, 27.3, 21.5; LRMS (CI) *m/z* 154.1 $(M+H)^+$; HRMS (CI) exact mass calcd for ($C_9H_{15}NO$) requires *m/z* 153.1154, found *m/z* 153.1151. $[\alpha]_D$ = –29.2 (c = 1.0, $CHCl_3$). Product ratio was determined by GLC analysis of corresponding aldehyde (70 °C, 5 °C/min gradient, 23 psi); *S* isomer t_r = 16.1 min and *R* isomer t_r = 17.0 min.

(*R*)-3-(1-Methyl-1*H*-pyrrol-2-yl)-hexanol (Table 4, entry 2). Prepared according to general procedure A from 2-hexenal (117 μL, 1.00 mmol), 1-methyl-1*H*-pyrrole (0.45 mL, 5.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (66 mg, 0.20 mmol) in THF (2.00 mL) and H_2O (0.30 mL) at -50 °C for 72 h and then –20 °C for 8 h to provide the pure product as a colorless oil in 81% yield (147 mg, 0.811

mmol); 90% ee. IR (film) 3360, 3105, 2935, 2873, 1622, 1491, 1460, 1375, 1298, 1244, 1089, 1043, 903.7, 772.4, 702.9 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.35 (t, *J* = 2.0 Hz, 1H, ArH), 6.28 (t, *J* = 3.2 Hz, 1H, ArH), 6.00 (dd, *J* = 1.5, 3.6 Hz, 1H, ArH), 3.48-3.36 (m, 2H, C**H$_2$**OH). 3.13 (s, 3H, NCH_3), 2.79-2.74 (m, 1H, ArCH), 2.24 (br s, 1H, OH), 1.79-1.69 (m, 2H, C**H$_2$**CH_2OH), 1.55-1.47 (m, 2H, CHC**H$_2$**CH_2CH_3), 1.28-1.20 (m, 2H, $CHCH_2$C**H$_2$**CH_3), 0.81 (t, *J* = 7.2 Hz, 3H, CCH_3); ^{13}C NMR (100 MHz, C_6D_6) δ 136.7, 120.9, 107.3, 104.7, 60.6, 39.4, 39.2, 33.3, 30.5, 20.8, 14.4; LRMS (CI) *m/z* 181.1 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{11}H_{19}NO$) requires *m/z* 181.1467, found *m/z* 181.1470. $[\alpha]_D$ = – 15.8 (c = 1.0, MeOH). Product ratio was determined by GLC analysis of corresponding aldehyde; *S* isomer t_r = 16.4 min and *R* isomer t_r = 17.3 min.

(*R*)-3-(1-Methyl-1*H*-pyrrol-2-yl)-hexanal . ^1H NMR (300 MHz, C_6D_6) δ 9.23 (t, *J* = 1.6 Hz, 1H, CHO), 6.23 (t, *J* = 2.6 Hz, 1H, ArH), 6.18 (t, *J* = 3.3 Hz, 1H, ArH), 5.85 (dd, *J* = 1.7, 3.6 Hz, 1H, ArH), 2.94 (s, 3H, NCH_3), 2.93-2.86 (m, 1H, ArCH), 2.24 (ddd, *J* = 1.9, 8.2, 17.3 Hz, 1H, C**H**$_2$CO), 2.06 (ddd, *J* = 1.4, 6.1, 17.0 Hz, 1H, C**H**$_2$CO), 1.38-1.17 (m, 2H, CHC**H$_2$**CH_2), 1.10-0.96 (m, 2H, CH_2C**H$_2$**CH_3), 0.69 (t, J = 7.1 Hz, 3H, CH_2C**H$_3$**).

(*S*)-4-Methyl-3-(1-methyl-1*H*-pyrrol-2-yl)-pentanol (Table 4, entry 3). Prepared according to general procedure A from 4-methyl-2-pentenal (117 μL, 1.00 mmol), 1-methyl-1*H*-pyrrole (0.45 mL, 5.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (66 mg, 0.20 mmol) in THF (2.00 mL) and H_2O (0.30 mL) at –50 °C for 72 h and then -20 °C for 8 h to provide the pure product as a colorless oil in 80% yield (145 mg, 0.800 mmol); 91% ee. IR (film) 3368, 3105, 2958, 2873, 1722, 1692, 1622, 1483, 1367, 1298, 1236, 1174, 1089, 1043, 888.2, 772.4, 702.9 cm^{-1}; ^1H

NMR (400 MHz, C_6D_6) δ 6.36 (t, *J* = 2.0 Hz, 1H, ArH), 6.28 (t, *J* = 3.2 Hz, 1H, ArH), 5.97 (dd, *J* = 1.8, 3.5 Hz, 1H, ArH), 3.47 (ddd, *J* = 4.6, 6.5, 10.5 Hz, 1H, C**H**$_2$OH), 3.33 (ddd, *J* = 5.7, 8.6, 10.2 Hz, 1H, C**H**$_2$OH), 3.12 (s, 3H, NCH_3), 2.58 (ddd, *J* = 3.7, 6.6, 10.8, 1H, ArCH), 2.37 (br s, 1H, OH), 1.90-1.85 (m, 1H, C**H**$(CH_3)_2$), 1.73-1.65 (m, 2H, C**H$_2$**CH_2OH), 0.87 (t, *J* = 7.2 Hz, 6H, CH(C**H$_3$**)**$_2$**); ^{13}C NMR (100 MHz, C_6D_6) δ 135.4, 120.9, 107.2, 105.5, 61.0, 39.4, 35.9, 33.9, 33.5, 20.5, 20.3; LRMS (CI) *m/z* 181.1 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{11}H_{19}NO$) requires *m/z* 181.1467, found *m/z* 181.1463. $[\alpha]_D$ = – 20.0 (c = 1.0, MeOH). Product ratio was determined by GLC analysis of corresponding aldehyde (130 °C isotherm, 23 psi); *R* isomer t_r = 14.2 min and *S* isomer t_r = 15.0 min.

(*S*)-4-Methyl-3-(1-methyl-1*H*-pyrrol-2-yl)-pentanal. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.50 (t, *J* = 2.0 Hz, 1H, CHO), 6.54 (t, *J* = 2.0 Hz, 1H, ArH), 5.85 (t, *J* = 2.8 Hz, 1H, ArH), 5.72 (dd, *J* = 2.0, 3.6 Hz, 1H, ArH), 3.53 (s, 3H, NCH_3), 3.13 (td, *J* = 6.0, 8.4 Hz, 1H, ArCH), 2.67-2.63 (m, 2H, CH_2CO), 1.74 (8-tet, *J* = 6.4 Hz, 1H, C**H**$(CH_3)_2$), 0.81 (d, *J* = 6.8 Hz, 3H, CCH_3), 0.78 (d, *J* = 6.8 Hz, 3H, CCH_3); ^{13}C NMR (100 MHz, d_6-DMSO) δ 203.2, 134.1, 121.1, 106.1, 105.3, 45.1, 35.9, 33.4, 32.4, 20.0, 19.0.

(*S*)-3-Phenyl-3-(1-methyl-1*H*-pyrrol-2-yl)-propanol (Table 4, entry 4). Prepared according to general procedure A from cinnamaldehyde (3.15 mL, 25.0 mmol), 1-methyl-1*H*-pyrrole (11.1 mL, 125.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (1.66 g, 5.00 mmol) in THF (50.0 mL) and H_2O (7.50 mL) at –30 °C for 42 h to provide the pure product as a white glass in 87% yield (4.67 g, 21.7 mmol); 93% ee. IR (film) 3352, 3105, 3066, 3028, 2943, 2881, 1599, 1491, 1452, 1413, 1298, 1089, 1035, 756.9, 702.9 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.28-7.19 (m,

4H, ArH), 7.13 (tt, *J* = 1.6, 8.7 Hz, 1H, ArH), 6.42 (d, *J* = 2.8 Hz, 2H, ArH), 6.36 (t, *J* = 2.8 Hz, 1H, ArH), 4.18 (t, *J* = 7.6 Hz, 1H, ArCH), 3.62-3.49 (m, 2H, C**H**$_2$OH), 2.90 (s, 3H, CH_3), 2.39-2.32 (m, 1H, C**H**$_2$$CH_2$OH), 2.20 (br s, 1H, OH), 2.11-2.03 (m, 1H, C**H**$_2$$CH_2$OH); ^{13}C NMR (100 MHz, C_6D_6) δ 144.5, 134.9, 128.3, 127.8, 121.9, 110.8, 106.9, 106.3, 60.2, 39.5, 33.3; LRMS (CI) *m/z* 215.0 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{14}H_{17}NO$) requires *m/z* 215.1310, found *m/z* 215.1311. $[\alpha]_D$ = + 98.3 (c = 1.0, MeOH). Product ratio was determined by GLC analysis of corrseponding aldehyde (70 °C, 5 °/min gradient to 170 °C isotherm, 23 psi); *R* isomer t_r = 26.6 min and *S* isomer t_r = 27.4 min.

(*S*)-3-(4-Methoxyphenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)-propanol (Table 4, entry 5). Prepared according to general procedure A from 4-methoxycinnamaldehyde (162 mg, 1.00 mmol), 1-methyl-1*H*-pyrrole (0.45 mL, 5.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (66 mg, 0.20 mmol) in THF (2.00 mL) and H_2O (0.30 mL) at –30 °C for 105 h to provide the pure product as a low-melting white glass in 79% yield (193 mg, 0.787 mmol); 91% ee. IR (film) 3368, 3105, 3066, 2943, 2889, 2841, 1699, 1614, 1506, 1468, 1336, 1298, 1244, 1174, 1089, 1035, 896.0, 834.2, 780.1, 710.6 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.08 (d, *J* = 8.6 Hz, 2H, ArH), 6.75 (d, *J* = 8.7 Hz, 2H, ArH), 6.38-6.34 (m, 2H, ArH), 6.29-6.28 (m, 1H, ArH), 4.09 (t, *J* = 7.8 Hz, 1H, ArCHAr), 3.57-3.48 (m, 2H, C**H**$_2$OH), 3.34 (s, 3H, OCH_3), 2.87 (s, 3H, NCH_3), 2.32-2.27 (m, 1H, C**H**$_2$$CH_2$OH), 2.11 (br s, 1H, OH), 2.13-1.99 (m, 1H, C**H**$_2$$CH_2$OH); ^{13}C NMR (100 MHz, C_6D_6) δ 158.2, 136.3, 135.4, 129.2, 121.8, 114.2, 106.9, 106.1, 60.3, 54.8, 39.7, 38.7, 33.3; LRMS (CI) *m/z* 245.0 (M)+; HRMS (CI) exact mass calcd for ($C_{15}H_{19}NO_2$) requires *m/z* 245.1416, found *m/z* 245.1420. $[\alpha]_D$ = + 100.3 (c = 1.0, $CHCl_3$)

Product ratio was determined by GLC analysis of corrseponding aldehyde (70 °C, 5 °/min gradient to 170 °C isotherm, 23 psi); *R* isomer t_r = 49.1 min and *S* isomer t_r = 51.5 min.

(*S*)-3-(4-Methoxyphenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)-propanal. ^{1}H NMR (400 MHz, C_6D_6) δ 9.59 (d, *J* = 1.1 Hz, 1H, CHO), 7.06 (d, *J* = 8.6 Hz, 2H, ArH), 6.83 (d, *J* = 8.6 Hz, 2H, ArH), 6.56 (t, *J* = 1.1 Hz, 1H, ArH), 5.96-5.94 (m, 1H, ArH), 5.90 (t, *J* = 3.1, 1H, ArH), 4.57 (t, *J* = 7.8 Hz, 1H, ArCH), 3.69 (s, 3H, OCH_3), 3.30 (s, 3H, NCH_3), 3.04 (ddd, *J* = 2.2, 8.5, 16.8 Hz, 1H, C**H**$_2$CO), 2.85 (ddd, *J* = 1.5, 7.8, 16.8 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (100 MHz, d_6-DMSO) δ 201.9, 157.7, 134.9, 133.7, 128.5, 122.0, 113.9, 106.0, 105.7, 55.0, 49.4, 35.7, 33.3.

(*R*)-3-(2-furyl)-3-(1-methyl-1*H*-pyrrol-2-yl)-propanol (Table 4, entry 6). Prepared according to general procedure from 3-(2-furyl)-acrolein (122 mg, 1.0 mmol), 1-methyl-1*H*-pyrrole (0.45 mL, 5.0 mmol), and (*S*)-4-Benzyl-2,2-dimethylimidazolidin-5-one • TFA (66 mg, 0.2 mmol) in THF (2.00 mL) and water (0.30 mL) at -30 °C for 42 h to provide the pure product as a colorless oil in 49% yield (101 mg, 0.492 mmol); 84% ee. IR (film) 3368, 3113, 2950, 2889, 1591, 1498, 1298, 1244, 1043, 1003, 926.9, 888.2, 710.6 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.08 (dd, J = 0.9, 1.8 Hz, 1H, ArH), 6.34 (t, *J* = 1.9 Hz, 1H, ArH), 6.26 (t, *J* = 3.5 Hz, 1H, ArH), 6.20 (dd, *J* = 1.4, 3.2 Hz, 1H, ArH), 6.07 (dd, *J* = 1.9, 3.1 Hz, 1H, ArH), 5.86 (d, *J* = 3.2 Hz, 1H, ArH), 4.27 (t, *J* = 7.2 Hz, 1H, ArCHAr), 3.49 (t, *J* = 6.1 Hz, 2H, C**H**$_2$OH), 3.02 (s, 3H, NCH_3), 2.28-2.20 (m, 1H, C**H**$_2$$CH_2$OH), 2.19-2.04 (m, 2H, C**H**$_2$$CH_2$OH, OH); ^{13}C NMR (100 MHz, C_6D_6) δ 157.6, 141.3, 132.5, 121.9, 110.4, 107.2, 106.6, 105.7, 60.1, 37.2, 33.2, 33.1; LRMS (CI) *m/z* 205.0 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{12}H_{15}NO_2$) requires *m/z* 205.1103, found

m/z 205.1102. Product ratio was determined by GLC as corrseponding aldehyde (70 °C, 5 °/min gradient to 170 °C isotherm, 23 psi); *S* isomer t_r = 18.5 min and *R* isomer t_r = 20.4 min.

(*R*)-3-(2-furyl)-3-(1-methyl-1*H*-pyrrol-2-yl)-propanal. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.61 (t, *J* = 1.6 Hz, 1H, CHO), 7.50 (t, *J* = 0.9 Hz, 1H, ArH), 6.60 (t, *J* = 2.0 Hz, 1H, ArH), 6.32 (dd, *J* = 2.0, 2.8 Hz, 1H, ArH), 6.02 (d, *J* = 2.8Hz, 1H, ArH), 5.87 (t, *J* = 3.2, 1H, ArH), 5.84-5.82 (m, 1H, ArH), 4.70 (t, *J* = 7.6 Hz, 1H, ArCH), 3.50 (s, 3H, NCH_3), 3.04 (dd, *J* = 1.6, 7.6 Hz, 2H, CH_2CO; ^{13}C NMR (100 MHz, d_6-DMSO) δ 201.5, 155.4, 141.9, 131.3, 122.1, 110.3, 106.3, 105.9, 105.5, 46.4, 33.3, 30.0.

(*S*)-4-Benzyloxy-3-(1-methyl-1*H*-pyrrol-2-yl)-butanol (Table 4, entry 7). Prepared according to general procedure A from 4-benzyloxy-but-2-enal (171 μL, 1.00 mmol), 1-methyl-1*H*-pyrrole (0.45 mL, 5.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (33 mg, 0.10 mmol) in THF (2.00 mL) and H_2O (0.30 mL) at –60 °C for 60 h and then -20 °C for 12 h to provide the pure product as a colorless oil in 80% yield (208 mg, 0.802 mmol); 87% ee. IR (film) 3398, 3097, 3066, 3035, 2935, 2866, 1630, 1545, 1491, 1452, 1359, 1298, 1244, 1205, 1074, 950.0, 849.6, 702.9 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.33-7.23 (m, 4H, ArH), 7.20 (t, *J* = 6.8 Hz, 1H, ArH), 6.44 (t, *J* = 2.0 Hz, 1H, ArH), 6.38 (t, *J* = 3.2 Hz, 1H, ArH), 6.13 (dd, *J* = 1.5, 3.6 Hz, 1H, ArH), 4.36 (dd, *J* = 12.0, 15.4 Hz, 2H, $ArCH_2O$), 3.66 (dt, *J* = 5.6, 5.6 Hz, 1H, C**H**$_2$OH), 3.60-3.55 (m, 1H, C**H**$_2$OH), 3.53-3.50 (m, 2H, CHC**H**$_2$OBn), 3.31-3.24 (m, 1H, ArCH), 3.19 (s, 3H, NCH_3), 2.36 (br s, 1H, OH), 2.18-2.09 (m, 1H, C**H**$_2$$CH_2$OH), 1.90-1.81 (m, 1H, C**H**$_2$$CH_2$OH); ^{13}C NMR (100 MHz, C_6D_6) δ 138.6, 133.6, 130.0, 128.2, 127.3, 121.0, 106.9, 104.9, 74.9, 72.8, 60.1, 35.9, 32.7, 32.9; LRMS (CI) *m/z* 259.1 $(M)^+$; HRMS (CI)

exact mass calcd for ($C_{16}H_{21}NO_2$) requires *m/z* 259.1572, found *m/z* 259.1578. $[\alpha]_D$ = – 29.1 (c = 1.0, $CHCl_3$). Product ratio was determined by GLC analysis of corresponding aldehyde (70 °C, 5 °C/min gradient to 170 °C isotherm, 23 psi); *S* isomer t_r = 53.8 min and *R* isomer t_r = 56.1 min.

(*R*)-4-Hydroxy-2-(1-methyl-1*H*-pyrrol-2-yl)-butyric acid methyl ester (Table 4, entry 8). Prepared according to general procedure A from methyl 4-oxo-butenoate (114 mg, 1.00 mmol), 1-methyl-1*H*-pyrrole (0.27 mL, 3.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • cyanoacetic acid (CNAcOH) (61 mg, 0.20 mmol) in THF (4.00 mL) and H_2O (0.20 mL) at -60 °C for 104 h before warming to –50 °C for 14 h to provide the pure product as a colorless oil in 72 % yield (141 mg, 0.715 mmol); 90% ee. IR (film) 3406, 3113, 2950, 2889, 1730, 1491, 1437, 12$_9$8, 1213, 1166, 1050, 903.7, 849.6, 780.1, 710.6 cm^{-1}; 1H NMR (300 MHz, CDCl3) δ 6.55 (dd, *J* = 1.9, 1.8 Hz, 1H, ArH), 6.07 (t, *J* = 3.6 Hz, 1H, ArH), 6.04-6.02 (m, 1H, ArH), 3.90 (t, *J* = 7.5 Hz, 1H, ArCHAr), 3.70-3.56 (m, 2H, C**H$_2$**OH), 3.67 (s, 3H, OCH_3), 3.60 (s, 3H, NCH_3), 2.37-2.25 (m, 1H, C**H**$_2$$CH_2OH$), 2.11 (br s, 1H, OH), 2.10-1.99 (m, 1H, C**H**$_2$$CH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 129.6, 122.6, 107.3, 106.9, 60.5, 52.6, 39.8, 35.0, 34.3; LRMS (CI) *m/z* 197.1 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{10}H_{15}NO_3$) requires *m/z* 197.1052, found *m/z* 197.1047 $[\alpha]_D$ = – 72.9 (c = 1.0, $CHCl_3$). Product ratio was determined by GLC as the corresponding aldehyde (140 °C isotherm 20 minutes, 10 °/min gradient to 170 °C isotherm, 23 psi); *R* isomer t_r = 20.9 min and *S* isomer t_r = 21.1 min.

(*S*)-3-Phenyl-3-(1-allyl-1*H*-pyrrol-2-yl)-propanol (Table 5, entry 3). Prepared according to general procedure A from cinnamaldehyde (126 μL, 1.00 mmol), 1-allyl-

1*H*-pyrrole (0.59 mL, 5.0 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TCA (76 mg, 0.20 mmol) in THF (2.00 mL) and H_2O (0.30 mL) at –30 °C for 72 h to provide the pure product as a clear oil in 83% yield (201 mg, 0.83 mmol); 91% ee. IR (film) 3337, 3082, 3028, 2935, 2881,1645, 1599, 1483, 1352, 1290, 1174, 1035, 926.9, 841.9, 756.9, 702.9 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.12-7.01 (m, 4H, ArH), 6.96 (tt, *J* = 1.6, 6.0 Hz, 1H, ArH), 6.40 (dd, *J* = 1.6, 3.7 Hz, 1H, ArH), 6.31 (t, *J* = 2.8 Hz, 1H, ArH), 6.23 (ddd, *J* = 0.5, 1.6, 3.0 Hz, 1H, ArH), 5.42-5.29 (m, 1H, $NCH_2C\mathbf{H}$), 4.74 (dq, *J* = 10.4, 1.6 Hz, $CH_2CHC\mathbf{H}_2$), 4.60 (dq, *J* = 17.0, 1.6 Hz, $CH_2CHC\mathbf{H}_2$), 4.18 (t, *J* = 7.7 Hz, 1H, ArCHAr), 3.88 (tdd, *J* = 1.6, 5.4, 17.5 Hz, 1H, $NC\mathbf{H}_2$), 3.75 (tdd, *J* = 1.9, 4.7, 16.5 Hz, 1H, $NC\mathbf{H}_2$), 3.46-3.32 (m, 2H, $C\mathbf{H}_2OH$), 2.25-2.14 (m, 1H, $C\mathbf{H}_2CH_2OH$), 1.97-1.86 (m, 1H, $C\mathbf{H}_2CH_2OH$), 1.88 (br s, 1H, OH); ^{13}C NMR (100 MHz, C_6D_6) δ 161.2,144.5, 134.9, 134.5, 128.6, 128.2, 126.3, 120.9, 115.8, 107.4, 106.4, 60.2, 48.8, 39.7, 39.4; LRMS (CI) *m/z* 242.2 $(M+H)^+$; HRMS (CI) exact mass calcd for ($C_{16}H_{19}NO$) requires *m/z* 241.1467, found *m/z* 241.1467. $[\alpha]_D$ = + 76.9 (c = 1.0, $CHCl_3$). Product ratio was determined by GLC as corresponding aldehyde (70 °C, 5 °/min gradient to 170 °C isotherm, 23 psi); *R* isomer t_r = 28.4 min and *S* isomer t_r = 28.7 min.

(*S*)-3-Phenyl-3-(1-benzyl-1*H*-pyrrol-2-yl)-propanol (Table 5, entry 4). Prepared according to general procedure A from cinnamaldehyde (126 μL, 1.00 mmol), 1-benzyl-1*H*-pyrrole (0.46 mL, 3.0 mmol), and (*S*)-4-Benzyl-2,2-dimethylimidazolidin-5-one • trichloroacetic acid (TCA) (76 mg, 0.20 mmol) in THF (2.00 mL) and H_2O (0.30 mL) at –30 °C for 120 h to provide the pure product as a clear oil in 80% yield (232 mg, 0.796 mmol); 89% ee. IR (film) 3352, 3066, 3028, 2935, 2881, 1715, 1607, 1491, 1452, 1359, 1298, 1182, 1027, 702.9 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.60-7.31 (m, 8H,

ArH), 7.05 (d, *J* = 6.6 Hz, 2H, ArH), 6.80-6.78 (m, 1H, ArH), 6.72 (t, *J* = 2.3 Hz, 1H, ArH), 6.68-6.63 (m, 1H, ArH), 4.88 (d, *J* = 16.5 Hz, 1H, NC**H**$_2$), 4.76 (d, *J* = 16.2 Hz, 1H, NC**H**$_2$), 4.33 (t, J = 7.6 Hz, 1H, ArCHAr), 3.69-3.60 (m, 2H, C**H**$_2$OH), 2.59-2.46 (m, 1H, CHC**H**H), 2.31-2.19 (m, 1H, CHC**H**$_2$) 1.90 (br s, 1H, OH); ^{13}C NMR (75 MHz, C_6D_6) δ 144.4, 138.9, 128.6, 128.2, 127.5, 127.2, 126.6, 126.4, 126.3, 121.8, 107.5, 106.9, 60.2, 50.2, 39.8, 39.5; LRMS (CI) *m/z* 292.2 $(M+H)^+$; HRMS (CI) exact mass calcd for ($C_{20}H_{21}NO$) requires *m/z* 291.1623, found *m/z* 291.1625. $[\alpha]_D$ = + 24.4 (c = 1.0, $CHCl_3$). Product ratio was determined by HPLC (6% ethanol in hexanes, 1 mL/min); *R* isomer t_r = 10.3 min and *S* isomer t_r = 13.4 min.

(*S*)-3-Phenyl-3-(1-*i*-Pr-1*H*-pyrrol-2-yl)-propanal. Prepared according to general procedure A from cinnamaldehyde and 1-isopropyl-1*H*-pyrrole at – 10 °C with (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA. ^{1}H NMR (300 MHz, C_6D_6) δ 9.32 (dd, *J* = 1.4, 1.9 Hz, 1H, CHO), 6.75-7.06 (m, 5H, ArH), 6.55 (dd, *J* = 1.6, 2.8 Hz), 6.36 (t, *J* = 3.0 Hz, 1H, ArH), 6.06-6.08 (m, 1H, ArH), 4.42 (t, *J* = 7.4 Hz, ArCH), 3.92 (dq, *J* = 6.6, 6.6 Hz, 1H, NCH), 2.78 (ddd, *J* = 1.9, 8.2, 17.0 Hz, 1H C**H**$_2$CO), 2.47 (ddd, *J* = 1.0, 6.9, 17.0 Hz, 1H C**H**$_2$CO), 1.02 (d, J = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 0.62 (d, J = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$). Product ratio determined by GC analysis (140 °C isotherm, 23 psi); *R* isomer t_r = 87.3 min and *S* isomer t_r = 88.3 min.

(*R*)-3-(1-*t*-Bu-1*H*-pyrrol-2-yl)-butanal (Table 5, entry 5). Prepared according to general procedure A from crotonaldehyde and 1-isopropyl-1*H*-pyrrole at 20 °C with (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA. Not isolated from crude product mixture. Product ratio determined by GC analysis (70 °C, 5 °/min gradient, 23 psi); *S* isomer t_r = 16.2 min and *R* isomer t_r = 17.0 min.

(*R*)-4-Hydroxy-2-(1*H*-pyrrol-2-yl)-butyric acid methyl ester (Table 5, entry 6). Prepared according to general procedure A from methyl 4-oxo-butenoate (0.500 g, 4.38 mmol), 1*H*-pyrrole (0.920 mL, 13.1 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • CNAcOH (0.27 g, 0.88 mmol) in THF (17.5 mL) and H_2O (0.88 mL) at –60 °C for 42 h provide the pure product as a colorless oil in 74 % yield (592 mg, 3.23 mmol); 90% ee. IR (film) 3368, 3113, 2950, 2889, 1591, 1498, 1298, 1244, 1043, 1003, 926.9, 888.2, 710.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (br s, 1H, NH), 6.76-6.73 (m, 1H, ArH), 6.14 (q, *J* = 3.3 Hz, 1H, ArH), 6.06-6.03 (m, 1H, ArH), 3.92 (t, *J* = 7.7 Hz, 1H, ArCH), 3.71 (s, 3H, OCH_3), 3.71-3.57 (m, 2H, C**H**$_2$OH), 2.28-2.16 (m, 1H, C**H**$_2$$CH_2OH$), 2.10-2.00 (m, 2H, C**H**$_2$$CH_2OH$, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ174.6, 127.8, 118.1, 108.5, 106.8, 60.5, 52.7, 41.7, 36.0; LRMS (CI) *m/z* 184.1 $(M+H)^+$; HRMS (CI) exact mass calcd for ($C_9H_{14}NO_3$) requires *m/z* 184.0973, found *m/z* 184.0976. $[\alpha]_D$ = – 36.6 (c = 1.0, $CHCl_3$). Product ratio was determined by GLC analysis of the corresponding aldehyde (110 °C isotherm for 96 min, 10 °/min gradient to 170 °C isotherm, 23 psi); *R* isomer t_r = 100.1 min and *S* isomer t_r = 100.4 min.

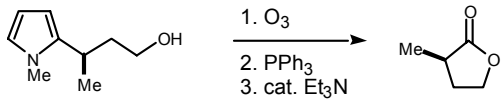
(*S*)-3-Phenyl-3-(2-butyl-1-methyl-1*H*-pyrrol-2-yl)-propanol (Table 5, entry 7). Prepared according to general procedure B from cinnamaldehyde (378 μL, 3.00 mmol), 2-butyl-1-methyl-1*H*-pyrrole (0.155 mL, 1.00 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • dichloroacetic acid (DCA) (69 mg, 0.20 mmol) in THF (4.00 mL) and H_2O (0.20 mL) at –60 °C for 120 h to provide the pure product as a clear oil in 87% yield (236 mg, 0.88 mmol); 90% ee. IR (film) 3344, 3105, 3059, 3028, 2935, 2862, 1954, 1885, 1815, 1676, 1599, 1452, 1413, 1336, 1228, 1174, 1027, 880.5, 826.4, 749.2, 702.9 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.20-7.08 (m, 5H, ArH), 6.18 (d, *J* = 3.6

Hz, 1H, ArH), 6.06 (d, *J* = 3.3 Hz, 1H, ArH), 4.09 (t, *J* = 4.8 Hz, 1H, ArCHAr), 3.50-3.36 (m, 2H, C**H**$_2$OH), 2.75 (s, 3H, NCH_3), 2.28-2.17 (m, 3H, $ArCH_2$ & C**H**$_2$COH), 1.98-1.89 (m, 1H, C**H**$_2$COH), 1.78 (br s, 1H, OH), 1.49-1.39 (m, 2H, CH_2C**H**$_2$$CH_2$), 1.31-1.19 (m, 2H, C**H**$_2$$CH_3$), 0.80 (t, *J* = 6.9 Hz, 3H, CCH_3); ^{13}C NMR (75 MHz, C_6D_6) δ 144.9, 128.8, 128.5, 128.4, 126.4, 105.0, 104.6, 60.4, 40.1, 39.7, 31.3, 30.0, 26.8, 23.0, 14.3; LRMS (CI) *m/z* 271.1 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{18}H_{25}NO$) requires *m/z* 271.1936, found *m/z* 271.1933. $[\alpha]_D$ = 72.2. Product ratio was determined by HPLC (6% ethanol in hexanes, 1 mL/min); *R* isomer t_r = 7.35 min and *S* isomer t_r = 8.65 min.

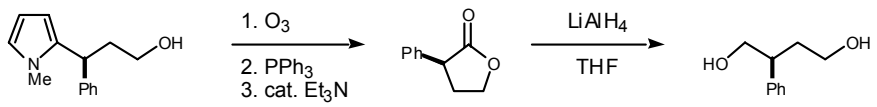
(*S*)-3-Phenyl-3-(2-butyl-1-methyl-1*H*-pyrrol-2-yl)-propanal. ^{1}H NMR (300 MHz, C_6D_6) δ 9.30 (dd, *J* = 1.5, 2.4 Hz, 1H, CHO), 7.05-6.90 (m, 5H, ArH), 6.03 (t, *J* = 4.2 Hz, 1H, ArH), 6.01 (d, *J* = 4.2 Hz, 1H, ArH), 4.25 (dd, *J* = 6.9, 8.7 Hz, 1H, ArCH), 2.73 (ddd, *J* = 2.1, 8.4, 17.1 Hz, 1H, C**H**$_2$CO), 2.65 (s, 3H, NCH_3), 2.40 (ddd, *J* = 1.8, 6.6, 16.8 Hz, 1H, C**H**$_2$CO), 2.15 (td, *J* = 2.7, 7.2 Hz, $ArCH_2$), 1.47-1.36 (m, 2H, CH_2C**H**$_2$ CH_2), 1.20 (6-tet, *J* = 7.5 Hz, 2H, C**H**$_2$$CH_3$), 0.79 (t, *J* = 7.1 Hz, 3H, CCH_3); ^{13}C NMR (100 MHz, d_6-DMSO) δ 199.2, 166.2, 143.6, 132.1, 128.7, 126.6, 105.8, 104.6, 50.2, 38.2, 31.1, 29.8, 26.7, 22.8, 14.1.

(*S*)-3-Phenyl-3-(1-methyl-3-propyl-1*H*-pyrrol-2-yl)-propanol (Table 5, entry 8). Prepared according to general procedure A from cinnamaldehyde (63 μL, 0.50 mmol), 1-methyl-3-propyl-1*H*-pyrrole (0.205 mL, 1.50 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • DCA (35 mg, 0.10 mmol) in THF (2.00 mL) and H_2O (0.10 mL) at –60 °C for 120 h to provide the pure product as a clear oil in 68% yield (87 mg, 0.34 mmol); 97% ee, 84:1 regioslectivity. IR (film) 3337, 3090, 3059, 3028, 2958, 2873, 1498, 1452, 1328, 1220, 1027, 695.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.12 (m,

5H, ArH), 6.43 (d, J = 2.8 Hz, 1H, ArH), 5.99 (d, J = 3.0 Hz, 1H, ArH), 4.41 (dd, J = 5.8, 10.4 Hz, 1H, ArCHAr), 3.74-3.60 (m, 2H, C**H**$_2$OH), 3.28 (s, 3H, NCH_3), 2.47-2.39 (m, 3H, $ArCH_2$ & C**H**$_2$COH), 1.63-1.48 (m, 1H, C**H**$_2$COH), 1.42 (br s, 1H, OH), 0.94 (t, J = 7.4 Hz, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 136.8, 128.8, 128.5, 128.5, 127.5, 126.6, 126.2, 121.6, 107.4, 64.1, 62.0, 37.7, 35.7, 29.3, 25.0, 14.7; LRMS (CI) *m/z* 257.2 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{17}H_{23}NO$) requires *m/z* 257.1780, found *m/z* 257.1770. $[\alpha]_D$ = –54.5 (c = 1.0, $CHCl_3$). Product ratio was determined by HPLC analysis (6% iPrOH/hexanes, 1 mL/min); *R* isomer t_r = 11.4 min and *S* isomer t_r = 17.6 min, t_r= 10.3 and 12.3 for regioisomers.

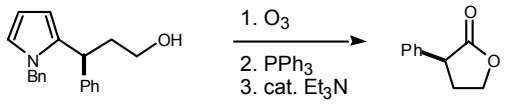


Determination of the absolute stereochemistry of (*R*)-3-(1-methyl-1*H*-pyrrol-2-yl)-butanol by correlation with (*S*)-3-methyl-dihydro-furan-2-one (*ent*-11). (*R*)-3-(1-methyl-1*H*-pyrrol-2-yl)-butanol was converted to the corresponding (*R*)-lactone according to the ozonolysis procedure described below. $[\alpha]_D$ = + 5.7 (c = 1.0, EtOH); reported rotation for the (*S*)-lactone, $[\alpha]_D$ = – 13 ° (c = 1.6, EtOH).

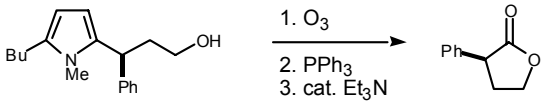


Determination of the absolute stereochemistry of (*S*)-3-phenyl-3-(1-methyl-1*H*-pyrrol-2-yl)-propanol (17) by correleation with (*S*)-2-phenyl-butan-1,4-diol (13)

***via* (*S*)-5-3-phenyl-dihydro-furan-2-one (12).** General procedure for conversion of 3-(2-pyrrolyl)-propanols to corresponding dihydrofuranones: O_3/O_2 was bubbled through a solution of **3** (460 mg, 2.14 mmol) in CH_2Cl_2 (125 mL) at –78 °C for 10 min, until the solution turned blue. The reaction mixture was treated with an excess of PPh_3 and stirred at ambient temperature overnight. A catalytic quantity of triethylamine was added and after 15 min the solution was concentrated and triturated with Et_2O to remove PPh_3 and its oxide. The solution was concentrated and resulting residue purified by chromatography to give (*S*)-3-phenyl-dihydro-furan-2-one (49 mg). $[\alpha]_D$ = + 2.4 (c = 1.0, $CHCl_3$). A solution of the lactone was treated with an $LiAlH_4$ in THF at ambient temperature. The reaction was diluted with Et_2O and quenched with aqueous Rochelle's salts at 0 °C. The mixture was stirred until biphasic and clear, then extracted several times and purified by chromatography to give (*R*)-2-phenyl-butan-1,4-diol, $[\alpha]_D$ = + 6.4 (c = 1.0, $CHCl_3$); reported rotation for (*S*)-2-phenyl-butan-1,4-diol, $[\alpha]_D$ = – 39 (c = 3.0, $CHCl_3$).



Determination of the absolute stereochemistry of (*S*)-2-Phenyl-3-(1-benzyl-1*H*-pyrrol-2-yl)-propanol by correlation with (*R*)-3-phenyl-dihydro-furan-2-one. (*S*)-2-phenyl-3-(1-benzyl-1*H*-pyrrol-2-yl)-propanol was converted to the corresponding (*S*)-3-phenyl-dihydro-furan-2-one according to the ozonolysis procedure above. $[\alpha]_D$ = + 2.2 (c = 1.0, $CHCl_3$).



Determination of the absolute stereochemistry of (*S*)-3-Phenyl-3-(2-butyl-1-methyl-1*H*-pyrrol-2-yl)-propanol. (*S*)-2-phenyl-3-(1-benzyl-1*H*-pyrrol-2-yl)-propanol was converted to (*S*)-3-phenyl-dihydro-furan-2-one according to the ozonolysis procedure above. $[\alpha]_D$ = + 3.1 (c = 1.0, $CHCl_3$).

(*R,R*)-3-[5-(3-Hydroxy-1-methyl-propyl)-1-methyl-1H-pyrrol-2-yl]-butan-1-ol (14). To a solution of (S)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (33 mg, 0.10 mmol) in THF (1.50 mL) and H_2O (0.150 mL) at –50 °C were added crotonaldehyde (124 μL, 1.50 mmol) and 1-methyl-1*H*-pyrrole (.044 ml, 0.50 mmol). The reaction was stirred at –50 °C for 72 h after which time the mixture was transferred directly into a round-bottom flask containing an excess of $NaBH_4$ (100 mg) in EtOH. After stirring for 5 min at ambient temperature, the mixture was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$ solution. The organic layer was washed with additional saturated $NaHCO_3$ solution and with brine, before drying (Na_2SO_4) and concentrating *in vacuo*. The residue was purified via silica gel chromatography with a gradient of 50% ethyl acetate/hexanes–100% ethyl acetate, affording the product and its diastereomer as a pale yellow oil in 83% yield (187 mg, 0.420 mmol). 91:9 C_2 : *meso* selectivity, 98% ee of C_2. IR (film) 3337, 3105, 3059, 2966, 2873, 1676, 1444, 1375, 1298, 1174, 1120, 1043, 996.4, 857.3, 749.2, 695.1 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 5.82 (s, 2H, ArH), 3.64 (t, *J* = 6.3 Hz, 4H, C**H$_2$**OH), 3.47 (s, 3H, NCH_3), 2.95 (dq, *J* = 6.8, 6.9 Hz, 2H, ArCH), 1.70-1.91 (m, 6H, OH and CHC**H$_2$**), 1.22 (d, *J* = 6.9 Hz, 6H, CCH_3); ^{13}C-NMR (75 MHz,

$CDCl_3$) δ 137.7, 102.4, 61.0, 39.9, 30.4, 27.9, 21.1. $[\alpha]_D$ = – 15.3 (c = 1.0, $CHCl_3$). Diastereomer ratio determined by HPLC with Sil-RX column (5% iPrOH/hexanes, 1 mL/min); *meso* isomer t_r = 32.1 min and C_2 isomer t_r = 35.8 min. Enantiomer ratio determined by HPLC analysis (8% EtOH/hexanes, 1mL/min)); (*S, S*) isomer t_r = 13.2 min and (*R, R*) isomer t_r = 17.0 min.

(3*R*, 1′*S*)-3-[5-(3-Hydroxy-1-phenyl-propyl)-1-methyl-1H-pyrrol-2-yl]-butan-1-ol (15). (*R*)-3-(1-Methyl-1*H*-pyrrol-2-yl)-butanol (38 mg, 0.25 mmol) was added to a solution of cinnamaldehyde (.095 mL, 0.75 mmol) and (S)-4-benzyl-2,2-dimethylimidazolidin-5-one • TFA (17 mg, 0.10 mmol) in THF (1.00 mL) and H_20 (50 □L) at –50 °C. The mixture was stirred at that temperature for 36 h at which time it was transferred to a flask containing excess $NaBH_4$ (40 mg) in EtOH. After stirring for 5 min at ambient temperature, the mixture was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$ solution. The organic layer was washed with additional saturated $NaHCO_3$ solution and with brine, before drying (Na_2SO_4) and concentrating *in vacuo*. The residue was purified via silica gel chromatography with a gradient of 50-75% ethyl acetate/hexanes. The product was isolated in 81% yield (58 mg, 0.40 mmol). 90:10 *anti* : *syn* selectivity, >99% ee of *anti*. IR (film) 3337, 3105, 3028, 2935, 2881, 1607, 1452, 1413, 1375, 1298, 1220, 1035, 911.4, 749.2, 702.9 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.03-7.25 (m, 5H, ArH), 6.08 (d, *J* = 3.6 Hz, 1H, ArH), 5.90 (d, *J* = 3.6 Hz, 1H, ArH), 4.09 (dd, *J* = 7.4, 7.6 Hz, 1H, ArCHAr), 3.52-3.73 (m, 4H, C**H**$_2$OH), 3.19 (s, 3H, NCH_3), 2.82 (dq, *J* = 6.8, 6.9 Hz, ArC**H**CH_3), 2.24-2.39 (m, 1H, $(Ar)_2CHCH_2$), 1.99-2.12 (m, 1H, $(Ar)_2CHCH_2$), 1.66-1.87 (m, 2H, CH_3CHCH_2), 1.23 (d, *J* = 7.0 Hz, 3H, CCH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.9, 138.4, 134.5, 128.7, 128.1, 126.5, 104.8, 102.2, 61.1,

61.0, 40.3, 40.0, 39.2, 30.6, 27.9, 21.1. $[\alpha]_D$ = + 46.5 (c = 1.0, $CHCl_3$). Diastereomer and enantiomer ratios determined by HPLC AD column (5% EtOH/hexanes, 1 mL/min); (*S, R*) isomer t_r = 37.3 min, *syn*- isomer t_rs = 41.7, 53.2 min, (*R, S*) isomer t_r = 45.6 min.

(*S*)-4-Benzoyloxy-3-(1*H*-pyrrol-2-yl)-butanol (22). Prepared according to general procedure A from 4-benzoyloxy-but-2-enal (9.37 g, 49.2 mmol), pyrrole (17.2 mL, 246 mmol), and (*S*)-4-benzyl-2,2-dimethylimidazolidin-5-one • DCA (3.42 g, 9.84 mmol) in THF (100 mL) and H_2O (5.0 mL) at –60 °C for 96 h to provide the pure product as a white solid 86% yield (208 mg, 0.802 mmol); 74% ee. ^{1}H-NMR (500MHz, $CDCl_3$) δ 8.44 (br s, 1H, NH), 8.04 (dd, *J* = 1.4, 8.3 Hz, 2H, ArH), 7.60 (tt, *J* = 1.0, 7.8 Hz, 1H, ArH), 7.47 (t, *J* = 7.8 Hz, 2H, ArH), 6.74-6.76 (m, 1H, ArH), 6.19 (dd, *J* = 2.9, 5.9 Hz, ArH), 6.08-6.09 (m, 1H, ArH), 4.56 (dd, *J* = 5.8, 10.7 Hz, 1H, C**H**$_2$OBz), 4.49 (dd, *J* = 6.4, 10.8 Hz, 1H, C**H**$_2$OBz), 3.76-3.80 (m, 1H, C**H**$_2$OH), 3.66-3.73 (m, 1H, CH), 3.38-3.43 (m, 1H, C**H**$_2$OH), 2.06-2.14 (m, 1H, CHC**H**$_2$CH$_2$), 1.93-2.00 (m, 1H, CHC**H**$_2$CH$_2$), 1.43 (br s, 1H, OH). Product ratio was determined by HPLC analysis (6% EtOH/hexanes, 1 mL/min); *R* isomer t_r = 18.4 min and *S* isomer t_r = 20.2 min.

(*S*)-4-Benzoyloxy-3-(1*H*-pyrrol-2-yl)-butane *p*-toluenesulfonate. A dry 100 mL round-bottom flask equipped with a stirbar was charged with 6 (5.76 g, 22.2 mmol) and CH_2Cl_2 (44 mL). The efficiently stirring solution was treated with Et_3N (3.71 mL, 26.6 mmol) and then *p*-toluenesulfonyl chloride (5.08 g, 26.6 mmol) was added as a solid in one portion. The reaction was stirred for 24 h at ambient temperature. The mixture was then concentrated the residue was treated with Et_2O. The ammonium salts were filtered away and the resulting organics were purified via flash chromatography (gradient elution: 25-50% ethyl acetate/hexanes) to afford 8.63 grams of tosylate **7**. ^{1}H-NMR

(300MHz, $CDCl_3$) δ 8.31 (br s, 1H, NH), 7.97-8.10 (m, 2H, ArH), 7.74 (d, *J* = 7.60, 2H, ArH), 7.57 (tt, *J* = 2.2, 7.4 Hz, 1H, ArH), 7.45 (t, *J* = 8.0 Hz, 2H, ArH), 7.31 (d, J = 2.5, 2H, ArH), 6.65-6.67 (m, 1H, ArH), 6.11 (q, *J* = 3.0 Hz, ArH), 5.92-5.94 (m, 1H, ArH), 4.47 (dd, *J* = 5.5, 10.7 Hz, 1H, C**H**$_2$OBz), 4.36 (dd, *J* = 6.6, 11.0 Hz, 1H, C**H**$_2$OBz), 3.95-4.13 (m, 2H, C**H$_2$**OTs), 3.22-3.34 (m, 1H, ArCH), 2.43 (s, 3H, CH_3), 2.16-2.28 (m, 1H, CHC**H**$_2$CH$_2$), 1.88-2.00 (m, 1H, CHC**H**$_2$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ. 166.5, 145.1, 133.4, 132.9, 130.1, 129.7, 128.7, 128.1, 117.4, 107.8, 105.7, 68.6, 67.9, 34.8, 32.3, 22.0.

(*S*)-1-Benzoyloxymethyl-2,3-dihydro-1*H*-pyrrolizine (23). A dry 25-mL round-bottomed flask equipped with a magnetic stirbar was charged with *t*-BuOK (0.27 g, 2.4 mmol), *t*-BuOH (6.7 mL), and THF (3.3 mL). A solution of (*R*)-4-benzoyloxy-3-(1*H*-pyrrol-2-yl)-butane *p*-toluenesulfonate (0.770 g) in THF (3.0 mL) was added dropwise to the stirring suspension of base over a period of 10 min. The reaction was stirred for an additional 15 min before quenching of residual base with AcOH. The mixture was diluted with Et_2O and H_2O, and the layers were separated. The aqueous layer was extracted 2x with Et_2O and the combind organics were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel chromatography (gradient elution 20–30% ethyl acetate/hexanes) to afford **7** in 94% yield. ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.01-8.05 (m, 2H, ArH), 7.59 (tt, *J* = 1.2, 7.8 Hz, 1H, ArH), 7.47 (t, *J* = 6.9 Hz, 2H, ArH), 6.63-6.65 (m, 1H, ArH), 6.25 (t, *J* = 4.5 Hz, ArH), 5.95-5.97 (m, 1H, ArH), 4.47 (dd, *J* = 6.9, 10.7 Hz, 1H, C**H**$_2$OBz), 4.38 (dd, *J* = 7.4, 10.7 Hz, 1H, C**H**$_2$OBz), 3.94-4.12 (m, 2H, NCH_2), 3.64 (apparent quintet, *J* = 6.9, 1H, ArCH), 2.70-2.82 (m, 1H, CHC**H**$_2$CH$_2$), 2.31-2.43 (m, 1H, CHC**H**$_2$CH$_2$); ^{13}C NMR

(75 MHz, $CDCl_3$) δ179.1, 166.6, 133.2, 130.3, 129.8, 128.6, 114.4, 112.6, 100.2, 67.5, 45.7, 37.2, 32.3.

(*S*)-4-Benzoyl-1-benzoyloxymethyl-2,3-dihydro-1*H*-pyrrolizine (24). A dry 3-necked 250-mL round-bottom flask equipped with a magnetic stirbar and a reflux condenser under N_2 was charged with 4-benzoyl-morpholine (1.58 g, 8.28 mmol) and 1,2-dichloroethane (56 mL). $POCl_3$ (0.776 mL, 8.28 mmol) was added to the rapidly stirring solution via syringe. The solution was heated to reflux in an oil bath and maintained at that temperature for 1 h prior to the addition of a solution of **7** (1.00 g, 4.14 mmol) in 1,2-dichloroethane (17 mL). The reaction was stirred at reflux for 25 h before careful addition of aqueous sodium acetate (2.5 M, 35 mL) to the hot solution. The reaction was stirred for an additional 25 min as it was allowed to cool to ambient temperature. The layers were separated and the aqueous extracted with CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by chromatography to give 8 in 77% yield (1.10 g, 3.19 mmol) and 4% of recovered 7 (42 mg, 0.17 mmol). ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.03-8.06 (m, 2H, ArH), 7.81-7.84 (m, 2H, ArH), 7.58 (tt, *J* = 1.6, 7.7 Hz, 1H, ArH), 7.41-7.52 (m, 5H, ArH), 6.82 (d, *J* = 3.7 Hz, 1H, ArH), 6.06 (dd, *J* = 0.5, 3.8 Hz, ArH), 4.58-4.64 (m, 1H, NC**H**$_2$), 4.48 (d, J = 7.9 Hz, 2H, C**H**$_2$OBz), 4.40-4.49 (m, 1H, NC**H**$_2$), 3.69 (dq, *J* = 6.6, 6.9 Hz, 1H, ArCH), 2.76-2.88 (m, 1H, CHC**H**$_2$CH$_2$), 2.38-2.50 (m, 1H, CHC**H**$_2$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 166.5, 145.9, 139.5, 133.4, 131.5, 129.8, 129.1, 128.7, 128.3, 125.3, 125.2, 102.8, 66.6, 47.9, 37.4, 31.6.

(*S*)-4-Benzoyl-2,3-dihydro-1-hydroxymethyl-1*H*-pyrrolizine. In a 50 mL round-bottomed flask equipped with a magnetic stirbar, benzoyl ester **8** (0.990 g, 2.87

mmol) was treated with 20 mL of 1:1 MeOH/THF. To this stirring suspension was added a solution of NaOH in MeOH (4% w/v, 11.5 mL). After 30 minutes, the ester cleavage was complete by TLC analysis. The reaction was diluted with Et_2O and H_2O. The aqueous layer was extracted twice with Et_2O and the combined organics were dried (Na_2SO_4) and concentrated to give a 99% yield of the hydroxymethyl pyrrolizine (684 mg, 2.87 mmol). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.81 (dd, *J* = 1.2, 6.9 Hz, 2H, ArH), 7.42-7.55 (m, 3H, ArH), 6.82 (d, *J* = 3.8 Hz, 1H, ArH), 6.02 (dd, *J* = 0.8, 4.1 Hz, 1H, ArH), 4.48-4.59 (m, 1H, NC**H**$_2$), 4.35-4.45 (m, 1H, NC**H**$_2$), 3.76-3.88 (m, 2H, C**H**$_2$OH), 3.38-3.46 (m, 1H, ArCH), 2.67-2.76 (m, 1H, CH_2C**H**$_2$CH), 2.35-2.47 (m, 1H, CH_2C**H**$_2$CH).

(*R*)-4-Benzoyl-2,3-dihydro-1-carboxy-1*H*-pyrrolizine (Ketorolac, 18). A suspension of PtO_2 (0.25 g, 0.10 mmol) in *i*-PrOH/H_2O (0.4 mL : 0.7 mL) was agitated under H_2 atmosphere for 20 minutes until the platinum species was observed to change color from brown to black. The reaction chamber was then purged with N_2 before addition of alcohol substrate (50 mg, 0.21 mmol) as a solution in ethyl acetate (3.4 mL). The reaction vessel was then purged with O_2 and stirred under oxygen atmosphere for 40 hours. The reaction mixture was filtered through Celite and concentrated to give 50 mg of a mixture consisting of 56 % alcohol, 41% acid, and 3% of another unknown pyrrole compound by NMR.

Chapter 3

Development of an Asymmetric Organocatalytic Friedel-Crafts Alkylation[1]

Reaction Design

The benzyllic carbon stereocenter represents one of the most important structural elements found in organic chemistry. This stereochemical motif is common to over 5000 natural product isolates spanning the biosphere.[2] Benzyllic stereogenicity has also been heavily exploited in the chemical synthesis of a range of biologically active compounds, becoming a staple of small-molecule therapeutics in recent years (e.g., Zoloft,[3] Paxil,[4] Detrol[5]). While access to optically active synthons bearing benzyllic stereogenicity has been accomplished using transition metal catalysis in hydrogenations[6], metallobenzene additions,[7] and enolate arylations,[8] an organocatalytic enantioselective alkylation of benzene rings with electron-deficient alkenes would constitute a valuable complement to

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[1] Parts of this work have been published previously: Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894-7895.

[2] This number is based on a survey of the Beilstein database.

[3] McRae, A. L.; Brady, K. T.; *Expert Opin. Pharmacotherapy* **2001**, *2*, 883.

[4] Heydorn, W. E. Expert Opin. Invest. Drugs **1999**, *8*, 417.

[5] Hills, C. J.; Winter, S. A.; Balfour, J. A.; *Drugs* **1998**, *55*, 813-820.

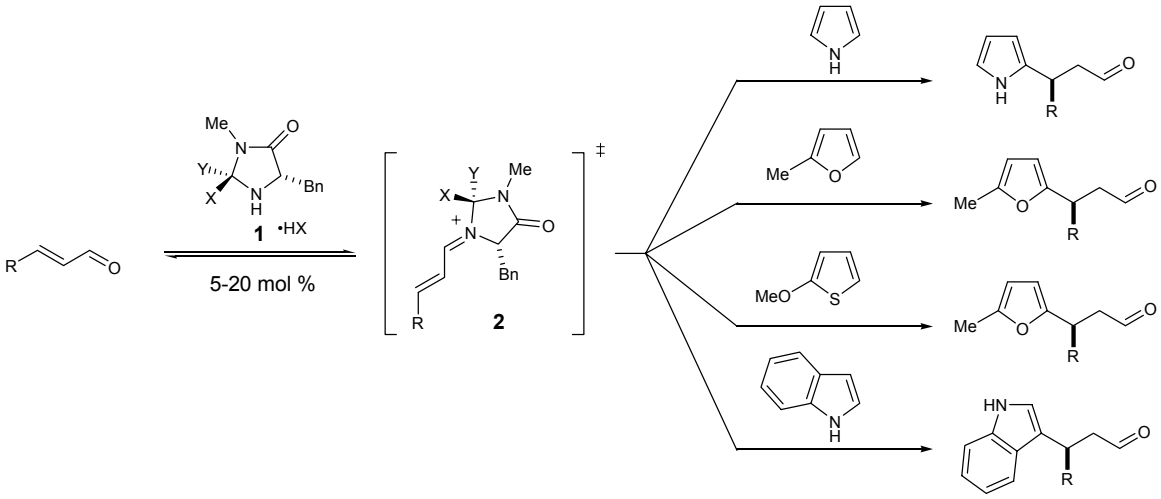
[6] For lead references, see: *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds; Springer: Heidelberg, Germany, 1999, Ch. 5, p. 121.

[7] Hayashi, T. *Synlett*, **2001**, 879, and references therein.

[8] Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2002**, *124*, 15168-15169, and references therein.

existing technologies.[9] As described in the previous chapters, LUMO-lowering activation of α,β-unsaturated aldehydes via reversible formation of iminium ions has been established as a valuable platform for asymmetric cycloadditions[10] and heteroaromatic substitution reactions (Scheme 1).[11] Alkylation of electron-rich benzenes would be the logical extension of these methodologies (equation 1).

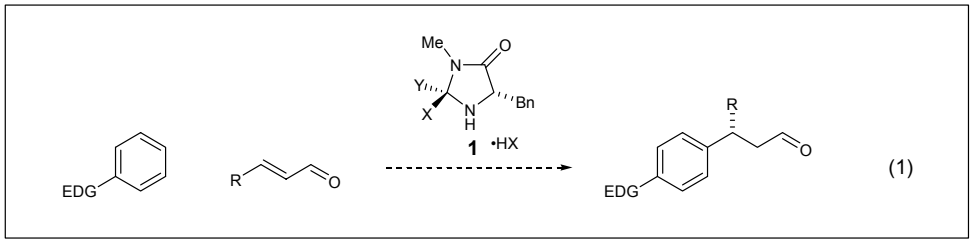
Scheme 1



[9] For the Lewis acid-catalyzed enantioselective additions of electron-rich benzenes to carbonyls and imines, see: a) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. b) Saaby, S.; Fang, X. M.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. For the enantioselective conjugate addition of heteroaromatic rings and 1,3-dimethoxy benzene to β,γ-unsaturated-α-keto esters see: c) Jensen, K. M.; Thorhauge, J.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.

[10] For Diels-Alder, see: a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244; for nitrones cycloaddition, see: b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122,* 9874-9875.

[11] For pyrrole alkylations, see: a) Paras, N. A., MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371. For indole alkylations, see: b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2002**, *124*, 1172. For furans and thiophene alkylations, see: c) unpublished results, Sean Brown.



Results and Discussion

Initial results

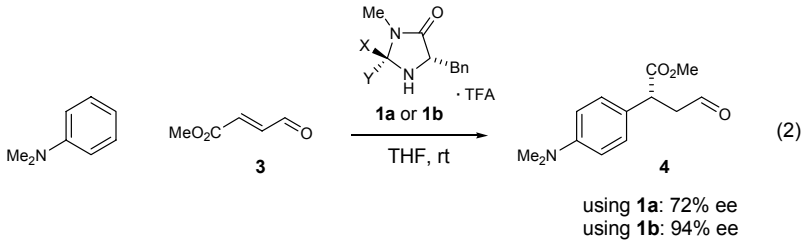
The first step in the development of organocatalytic benzene alkylations was sought to identify an electron-donating group (EDG) that might impart sufficient nucleophilicity to the aromatic ring. Toluene and benzene had proven inert to the conditions of our organocatalytic reactions, having been examined as solvents for these reactions on several occasions with no incidence of alkylation. We were encouraged by reports that amino-benzenes were "as reactive as pyrroles" toward a variety of electrophilic aromatic substitution reactions.[12] The prospect of using anilines as nucleophiles also provided an interesting opportunity for determining if iminium ion formation could proceed at a useful rate in the presence of a moderate base.[13]

In order to rapidly ascertain the feasibility of aniline alkylations under our organocatalytic conditions, we subjected *N,N*-dimethylaniline to a highly reactive enal,

[12] Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*; Springer-Verlag: Heidelberg, Germany 1999, Vol. 3.

[13] The pK_B *N,N*-dimethyl aniline has been reported at 5.20 in aqueous solution. Pyridine ($pK_B = 5.21$) was found to suppress all reactivity in organocatalytic alkylations of pyrrole in THF-H_2O. All pK_A and pK_B values referenced in aqueous solution, see: Albert, A.; Serjeant, E.P. *The Determination of Ionization Constants 3 Ed*; Chapman and Hall: New York 1984.

methyl 4-oxo-butenoate (**3**), in the presence of imidazolidinone catalysts **1a** (X = Y = Me) and **1b**[14] (X = H, Y = *tert*-butyl) in THF at ambient temperature (equation 2). Both of these catalysts promoted formation of mandellate derivative **4** as the exclusive regioisomeric product. Gratifyingly, reaction in the presence of 0.20 equivalents of **1b** · TFA proceeded to completion within five hours and afforded the product in 94% ee and 78% yield. Further investigations based on this model reaction revealed that HCl is generally superior to TFA as a co-catalyst and $CHCl_3$ is the optimal medium for additions to **3**.



(2)

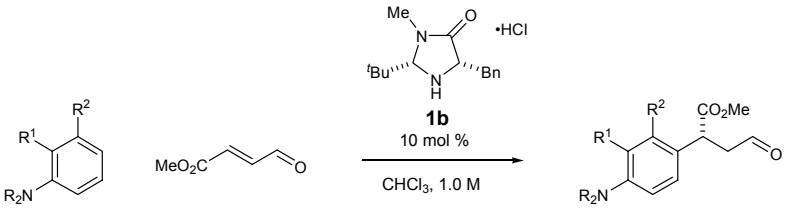
Scope and limitations

Significant structural variation in the aniline component of this reaction can be realized without loss of reaction efficiency or selectivity (Table 1). The dimethylamino function can be replaced with the readily deprotected dibenzyl equivalent or constrained into various rings (entries 1–8, NMe_2, NBn_2, 1-pyrrolidino, indoline, 65–97% yield 93–99% ee). A variety of alkyl, aryl, and heteroatom substituents can be incorporated on the aniline ring at either the *ortho* or *meta* positions (entries 6–8, R^1 = Ph, CH_2, 93–94%

[14] **1b** had been identified as a substantially more reactive and selective catalyst than **1a** in asymmetric conjugate addition reactions. For development and rationale see: reference 11b and unpublished results: Christopher Borths in these laboratories.

yield, 93–99% ee; entries 10–15, R_2 = Me, OMe, SMe, 73–90% yield, 84–93% ee). The arene component can also consist of a bicyclic structure without compromise of yield or optical purity (entry 9, 89% yield, 93% ee). We have also utilized relatively electron-deficient anilines in the context of a *meta*-chloro system (entry 14, 73% yield, 93% ee). As expected, subambient temperatures provided the highest levels of asymmetric induction (91–98% ee); however, alkylations conducted at room temperature provide operationally convenient reaction times without significant loss in enantioselectivity (entries 2, 3, 5, 6, 8, 9, 12, and 15, reaction time: 0.1 to 24 h).

Table 1



entry	NR_2	R^1	R^2	temp(°C)	time(h)	% yield	% ee[a]
1	NMe_2	H	H	–10	48	86	96[b]
2	NMe_2	H	H	+20	5	77	94[b]
3	NBn_2	H	H	+20	24	65	96[b]
4	1-pyrrolidino	H	H	–20	8	97	97[b]
5	1-pyrrolidino	H	H	+20	0.3	96	95[b]
6	1-pyrrolidino	Ph	H	+20	12	94	99
7	$–N(Me)CH_2CH_2^–$		H	–20	8	94	98
8	$–N(Me)CH_2CH_2^–$		H	+20	0.3	93	93
9	NMe_2	$–CH=CH-CH=CH^–$		+20	36	89	93
10	NMe_2	H	Me	–10	10	89	84[b]
11	NMe_2	H	OMe	–20	8	90	92[b]
12	NMe_2	H	OMe	+20	0.1	73	91[b]
13	NMe_2	H	SMe	–20	8	92	91
14	NMe_2	H	Cl	–20	80	73	93[b,c]
15	NMe_2	H	Cl	+20	12	66	86[b]

[a]Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b]Absolute configuration assigned by chemical correlation. [c]Using catalyst 1b (20 mol % amine, 15 mol % HCl).

In the course of exploring the effect of differential benzene substitution patterns in these arene conjugate additions, a dramatically enhanced reactivity was observed in the case of cyclically constrained anilines. Particularly, aniline nitrogens constrained in five-membered rings[15] provided substantially more nucleophilic arenes than the *N,N*-dimethyl or *N,N*-dibenzyl substrates (cf. entries 2, 3, 4, 5, and 8, k_{rel} pyrrolidino : indoline : NMe_2: NBn_2 ~ 48:48:4:1). This observation is consistent with the known geometric requirements for activation of π-systems pendant amine: as the contribution of the amine lone pair to the arene increases, hybridization at nitrogen develops sp^2 character.[16] In the limiting case of a full double-bond between the nitrogen and the aryl carbon, N-Ar bond length is decreased and the dihedral angle between the nitrogen alkyl groups (R^N) and the *ortho* substitutents of the ring (R^O) approaches zero (Figure 1). The energetic cost of adopting such a conformation would be reflected in the activation barrier for ring alkylation. Cyclic constraints in the *N*-phenylpyrrolidine case ameliorate these effects by encouraging a 120° R^N-N-R^N bond angle. Furthermore, constraint of the nitrogen substituents away from the aromatic ring also alleviates non-bonding interactions between R^N and R^O in the trigonal planar geometry. Alternatively, when indoline structures are considered, one of the two disfavorable R^N-R^O interactions is absent entirely as the substituents are connected through a covalent bond.

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[15] The ring size of the cyclic amino functionality is crucial. *N*-Ph-piperidine (6-membered ring) is completely inert to alkylation with **3** under standard conditions while alkylation of *N*-Ph-pyrrolidine is complete in 20 minutes.

[16] For a detailed discussion of the conformation requirements for electron donation of dialkylamine substituents into aromatic rings, supported by calculations at the Becke3LYP/6-311+G(d,p) level of theory, see: Heinrich, M. R; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4826 – 4828.

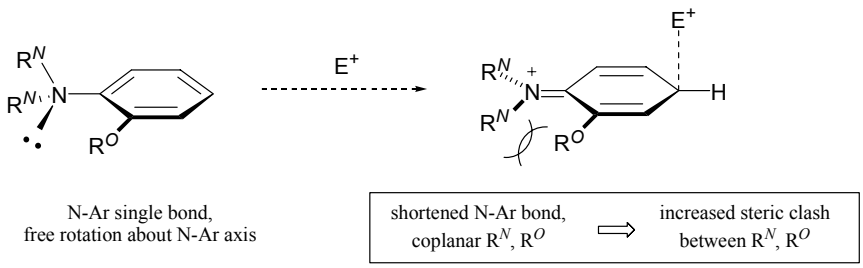


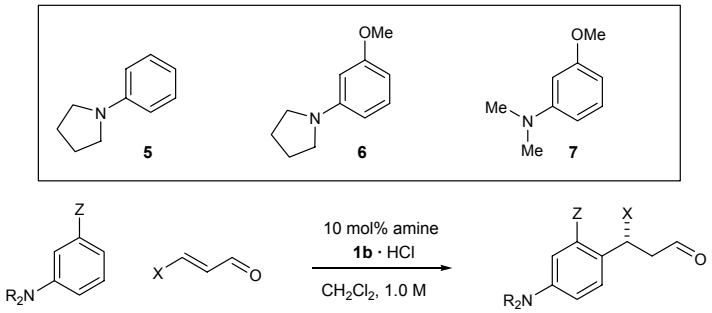
Figure 1

Beyond an intriguing illustration of hybridization effects, these highly nucleophilic, cyclically constrained anilines provided a window of reactivity that would help to expand the scope of the aldehyde component of this reaction.[17] Further investigations of various enal substrates were conducted using *N*-phenylpyrrolidines **5** and **6** as well as *N,N*-dimethyl-*m*-anisidine (**7**) (Table 2). Crotonaldehyde was found to be an adequate electrophile in reactions with either **5** or **7**, providing the conjugate adducts with good levels of enantioselectivity (entries 1–2, 70–86% yield, 87–89% ee). Some variation in the steric size of the β-substituent of the enal is tolerated without compromise of reaction efficiency (entries 1–5, R = Me, Et, CH_2OBz, 68–89% yield, 87–92% ee); however, treatment of either **5** or **7** with 4-methyl-2-pentenal (R = ^{i}Pr) failed to produce a significant amount of the conjugate adduct even after 48 hours at room temperature (<5% conversion). On the other hand, cinnamaldehyde derivatives react smoothly to furnish bis-benzyllic stereocenters which are not readily accessible via asymmetric hydrogenation (entries 7–10, 80–85% yield, 84–92% ee). Notably, cinnamate derivatives are frequently among the most recalcitrant substrates for

[17] Under typical conditions, *N,N*-dimethylaniline did not react with crotonaldehyde in the presence of amine catalysts **1a** or **1b**. When the nucleophile was used as a solvent, 83% conversion of the aldehyde was observed in 24 hours, but the product exhibited only 72% ee.

enantioselective conjugate additions, but serve as competent electrophiles in this transformation.

Table 2



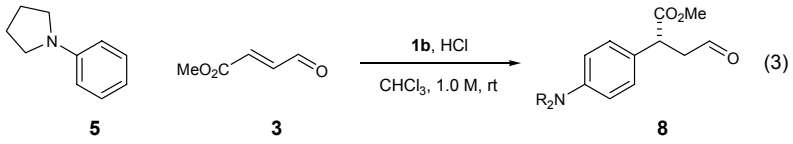
entry	aniline	X	temp(°C)	time(h)	% yield	% ee[a]
1	**7**	Me	–40	36	86	89[d]
2	**5**	Me	–20	48	70[b]	87[d]
3	**5**	Et	–50	48	68	88
4	**7**	CH_2OBz[c]	–20	24	89	92[d]
5	**5**	CH_2OBz[c]	+20	24	73	90[d]
6	**7**	CO_2Me[c]	–20	8	90	92[d]
7	**6**	Ph	–50	36	82[b]	84
8	**6**	*p*-Cl-Ph	–50	30	80[b]	92
9	**7**	*p*-NO_2-Ph	–10	48	87	92
10	**5**	*p*-NO_2-Ph	+20	48	82	90

[a]Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction. [b]Using 20 mol % catalyst. [c]1.0 M in $CHCl_3$. [d]Absolute configuration assigned by chemical correlation.

The remarkable efficiency with which imidazolidinone salt **1b**·HCl catalyzes the conjugate addition of some tertiary anilines (e.g., 96% yield, 95% ee, 20 min at 20 ºC; Table 1, entry 5) prompted us to investigate the effect of catalyst loading on the *para*-alkylation of *N*-phenylpyrrolidine (**5**) with enal **3** (Table 3). While 10 mol % of imidazolidinone **1b** was routinely employed in these studies, it appears that catalyst loadings as low as 0.01 mol equivalents provide useful levels of enantioselectivity (entry 1, 10 mol %, 95% ee; entry 2, 1 mol %, 88% ee). To demonstrate preparative utility, the addition of aniline **5** to enal **3** was performed on a 50 mmol scale using 2 mol % of

catalyst **1b** (240 mg) to afford 12.2 g (97% yield) of aniline adduct (*R*)-**8** in 92% ee (87% yield, 96% ee after recrystallization). With regard to operational simplicity it is important to note that all of the reactions discussed herein, including this preparative scale example, were performed under aerobic atmosphere using "wet" solvents[18] and a bench-stable catalyst.

Table 3



5 **3** **8**

entry	mol% **1b**	mol% HCl	time	% yield	% ee[a]
1	10	10	20 min	96	95
2	5.0	5.0	2 h	92	94
3	2.0	2.0	12 h	92	92
4	1.0	1.0	40 h	87	88

[a]Ratios determined by chiral HPLC analysis of corresponding alcohol after $NaBH_4$ reduction.

Kinetics studies

In an attempt to further elucidate the mechanism of enantioselective aniline alkylations catalyzed by imidazolidinone salt **1b**·HCl, a preliminary study was undertaken to quantify reaction kinetics using the addition of *N*-phenylpyrrolidine (**5**) to methyl 4-oxobutenoate (**3**) as a model (equation 3).[19] Notably, additions to **3** are particularly amenable to study in this context, as reaction mixtures are not complicated by

[18] $CHCl_3$ stirred with $NaHCO_3$ prior to use to minimize accumulated HCl from photolytic decomposition.

[19] Real-time conversion measurements based on integration of ester CH_3 or pyrrolidine $N(CH_2)_2$ peaks in proton-NMR. Reactions conducted in $CDCl_3$ at 35 ºC on Varian Mercury 300 spectrometer; elevated temperature employed in order to eliminate random fluctuations. Unless otherwise noted, catalyst loadings of 5 mol % were employed to maintain reaction times in a range suitable to this mode of analysis.

appreciable concentrations of iminium intermediates, thereby allowing reasonable assumption of a constant concentration of catalyst over time.[20]

In studies conducted with initial concentrations of aldehyde and aniline standardized at 0.077 M (1.0 equiv) and 0.155 M (2.0 equiv), respectively, and in the presence of 0.05 equivalents of **1b**·HCl, a plot of ln [aldehyde]/[aniline] against time exhibits a clear linear correlation (Figure 2). This behavior is consistent with a reaction that is first order with respect to each of two reagents, and that is second order overall.[21]

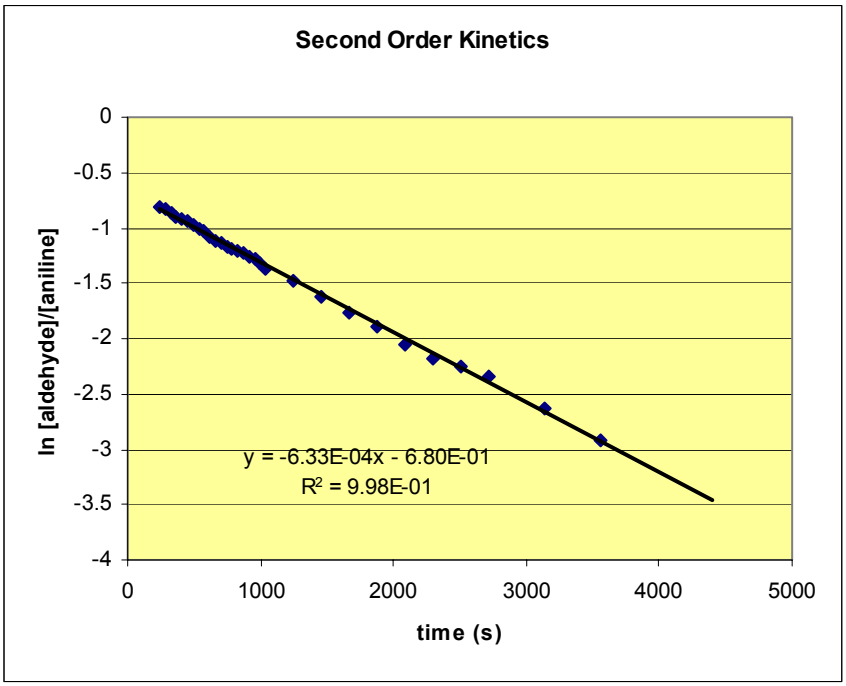


Figure 2

[20] Iminium ions (**2**) derived from other unsaturated aldehydes and imidazolidinone salts form in detectable amounts and have been observed by NMR under standard reaction conditions.

[21] This data represents an average of six experiments.

Independent confirmation of the order of the reaction with respect to both the electrophile and the aniline component was also obtained. In order to ascertain the order of the reaction specifically with respect to enal **3**, initial concentration of aniline was maintained at 0.155 M while the initial concentration of aldehyde was reduced to 0.0077 M. Not surprisingly, under these pseudo-first-order conditions, ln [**3**] also appeared be linearly related to time (Figure 3), as was ln [**5**] when the situation was reversed (Figure 4).

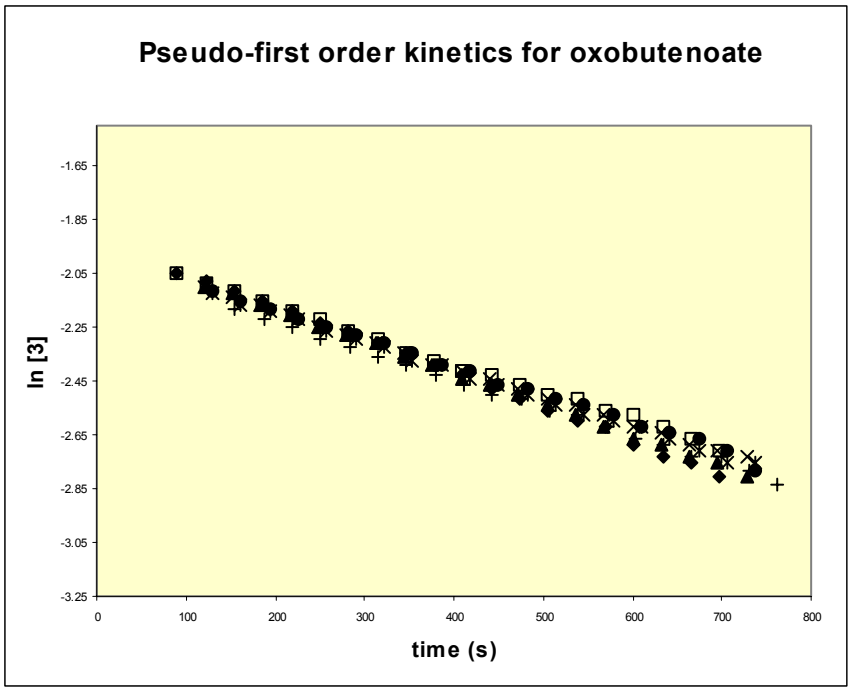


Figure 3

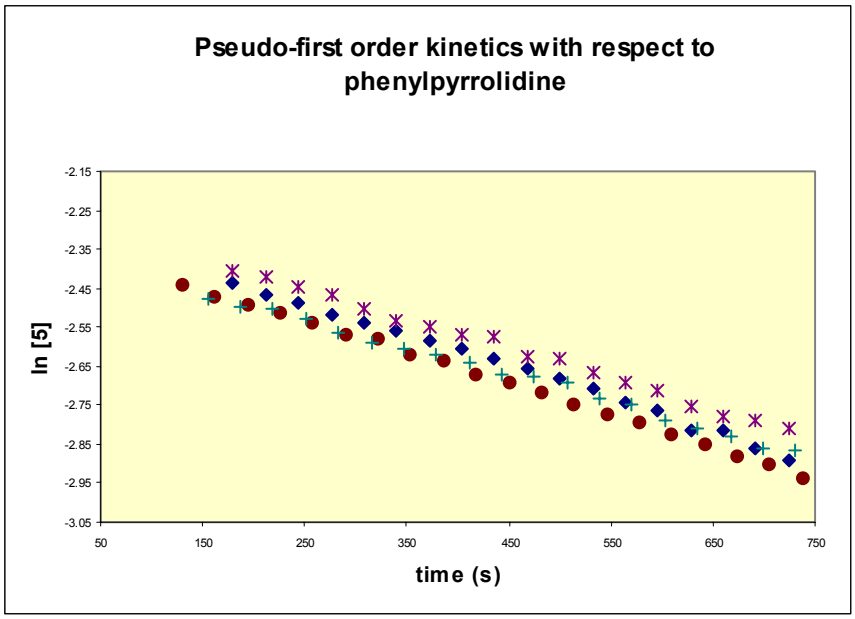


Figure 4

The reaction appears to be second order with regard to the catalyst salt. Observed rate constants derived from experiments conducted with 2.5 mol % catalyst loading exhibited approximately a fourfold reduction as compared to comparable results from 5 mol % reactions (k_{obs} = 2.3 x 10^{-4}, 2.5 mol % vs. k_{obs} = 1.1 x 10^{-3}, 5 mol %).[22] To a first approximation, a similar increase is observed as catalyst loading is increased to 10 mol % as well (k_{obs} = 1.1 x 10^{-3}, 5 mol % vs. k_{obs} = 3.7 x 10^{-3}, 10 mol %). Given that the concentration of the catalyst salt is constant over the course of each reaction and that increase of catalyst loading by a factor of two results in twice that increase in k_{obs}, the most likely scenario would seem to be a first order dependence on both the amine and acid components of **1b**·HCl. In combination with the determinations made above

[22] k_{obs} derived from m = k_{obs} x ([**3**]^{i}-[**5**]^{i}) where m is the slope of the plot of ln ([**3**]/[**5**]) vs. time.

regarding the reaction order in the two substrates, these data provide a rate law of the general form:

$$\text{rate} = k\,[\mathbf{3}][\mathbf{5}][\,\mathbf{1b}\cdot\text{HCl}]^2$$

Unfortunately, this equation does not distinguish between any of a number of mechanistic hypotheses regarding the role of the amine and acid co-catalyst in these organocatalytic alkylation reactions. Further studies to evaluate the effects of varying concentrations of **1b**, HCl, and chloride anions independently may be beneficial.

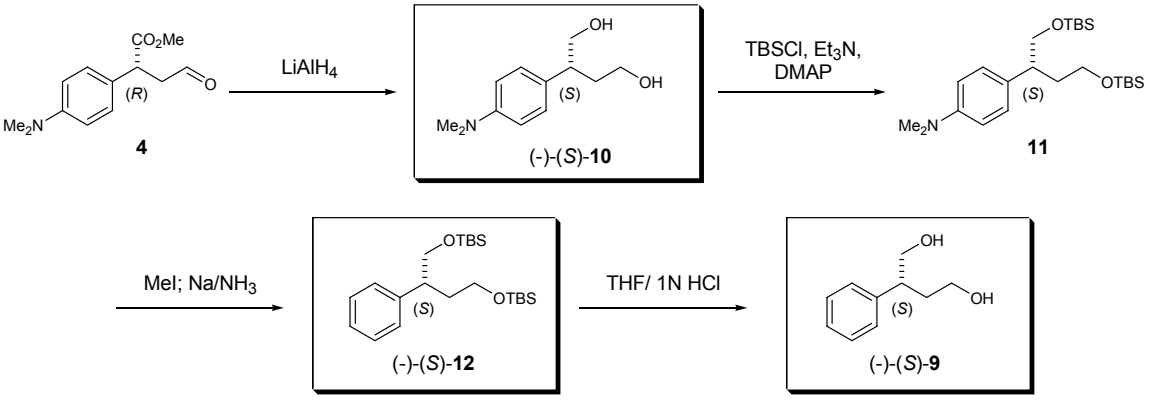
Determination of absolute stereochemical configuration of products

The absolute configurations of these substituted dihydrocinnamaldehydes were determined by chemical correlation to compounds with known chiroptical properties. Aldehyde **4** was converted to known 2-phenyl-butane-1,4-diol (**9**) in a five-step sequence (Scheme 2). The conjugate addition product arising from *N,N*-dimethylaniline and γ-oxo-ester **3** in the presence of (*S,S*)-**1b** hydrochloride was first reduced to the corresponding diol, (-)-(*S*)-**10**, using $LiAlH_4$ in Et_2O. Silylation of both primary hydroxyls proceeded smoothly with *tert*-butyldimethylsilyl chloride, triethylamine, and DMAP. The dimethylamino group was then removed using a new quaternization-reduction procedure to afford bis-siyl ether (-)-(*S*)-**12**.[23] Deprotection was effected using

[23] This novel method for the cleavage of dialkylamines from arenes is discussed at length in Chapter 4 (*vide infra*).

aqueous HCl in THF to afford (-)-(*S*)-**9** which was spectroscopically identical to the literature compound in all respects.[24]

Scheme 2

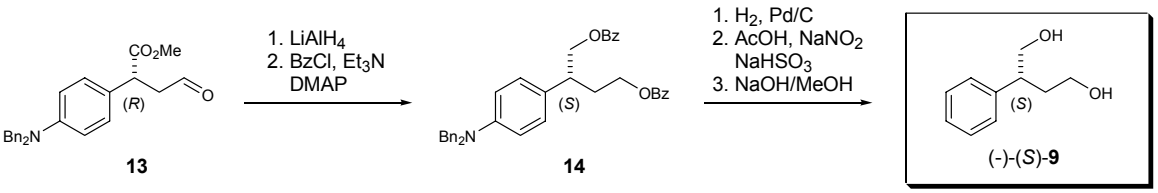


The absolute configuration of the adduct of *N,N*-dibenzylaniline and oxo-ester **3** was also determined by correlation to (*S*)-**9** (Scheme 3). To accomplish this correlation, alkylation product **13** was also reduced to the diol using $LiAlH_4$ and esterified with benzoylchloride to afford dibenzoate **14**. The aniline nitrogen was debenzylated under hydrogenolysis conditions to reveal a primary amine which was removed using a conventional one-step diazotization and reduction procedure.[25] Hydrolysis of the benzoyl esters in basic methanol completed the sequence and furnished diol **9**, which was spectroscopically identical to that derived from adduct **4**.

[24] Krause, et al, *J. Organomet. Chem.* **1992**, *423*, 271-279.

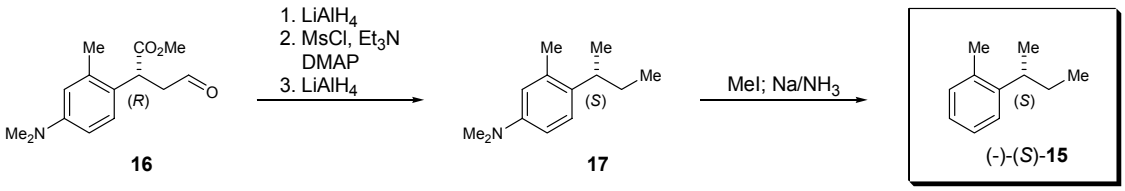
[25] Geoffroy, O. J.; Morinelli, T. A.; Meier, G. P. *Tet. Lett.* **2001**, *42*, 5367-5369.

Scheme 3



The configuration of the product from the conjugate addition of *N,N*-dimethyl-*meta*-toluidine to **3** was confirmed by chemical correlation to (-)-(*R*)-*ortho*-(*sec*-butyl)-toluene (**15**) (Scheme 4). Global reduction of γ-oxo-ester **16** was performed in a three step sequence to provide access to deoxygenated aniline **17**. Reductive deamination *via* the aryl-trialkylammonium salt afforded (+)-(*S*)-**15** which was spectroscopically identical to the literature reports for (-)-(*R*)-**15** except with respect to the direction of its optical rotation.[24]

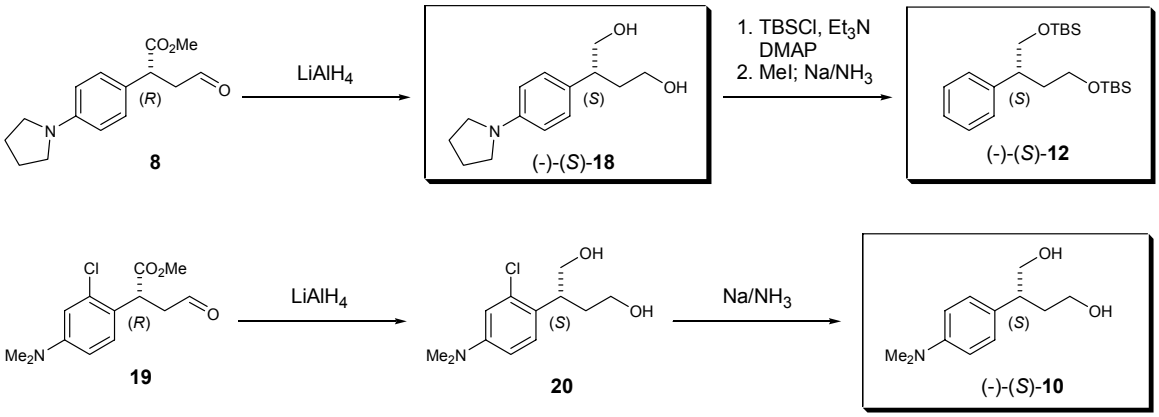
Scheme 4



Correlation to intermediates in the derivation of aldehyde **4** to the known 2-phenyl-butane-1,4-diol allowed for straightforward assignment of absolute stereochemistry of two more adducts (Scheme 5). Substituted phenylpyrrolidine **8** was converted to bis-siyl ether (-)-(*S*)-**12** following an identical sequence of functional group manipulations to that described above. Reduction of *meta*-chloro product **19** with $LiAlH_4$

followed by dehalogenation of the phenyl ring by dissolving metal reduction intercepted (dimethylaminophenyl)-diol (-)-(*S*)-**10**. In both of these cases, the orientation of the optical rotation of the second-generation materials matched that from the original derivation of **4**, confirming a consistent sense of asymmetric induction in all of the additions to methyl 4-oxobutenoate.

Scheme 5



In total, absolute configurations of twelve products were assigned by chemical correlation.[26] In each of these cases, the result was predicted by a simple model of a reactive iminium intermediates resulting from condensation of 5-benzylimidazolidinones with α,β-unsaturated aldehydes.[10,11]

[26] For details regarding stereochemical correlations of conjugate additions to cinnamaldehyde, crotonaldehyde, 4-benzoyloxycrotonaldehyde, and pentenal, see experimental section at end of chapter.

Conclusion

This report describes the first enantioselective organocatalytic Friedel-Crafts alkylation of anilines using unsaturated aldehydes as electrophiles. The hydrochloride salt of imidazolidinone **1b** was identified as an effective catalyst for this reaction, providing a range of substituted hydrocinnamaldehyde derivatives in good to excellent yield and optical purity. The capability of this methodology to access biologically relevant benzyllic stereogenicity, particularly *gem*-diaryl carbon stereocenters, from readily accessible starting materials constitutes a useful complement to existing asymmetric technologies.

Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Armarego and Perrin.[27] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Methylene chloride was distilled from calcium hydride prior to use. $CHCl_3$ was distilled from calcium sulfate and potassium carbonate and passed through an alumina plug prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[28] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching, anisaldehyde stain, potassium permanganate stain or dinitrophenylhydrazine stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 spectrometers (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. High-performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series

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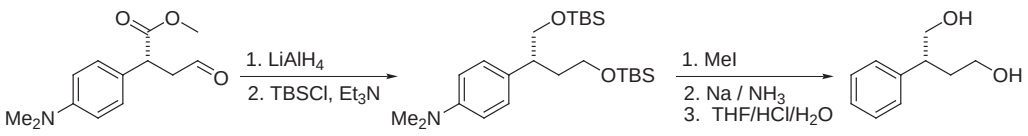
[27] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals;* 4th ed., Butterworth-Heinemann: Oxford, 1996.

[28] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

chromatographs using Chiralpak AD column (0.46 x 25 cm) and AD guard (0.46 x 5 cm). Optical rotations were taken using a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C).

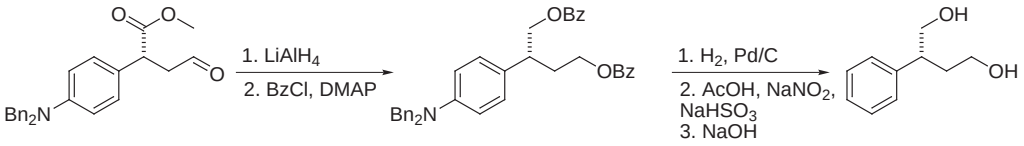
(*R*)-4-Oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester (4) (Table 1, entries 1 & 2). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.0500 mmol, 0.100 equiv), and *N,N*-dimethylaniline (76 μL, 0.60 mmol, 1.2 equiv). The solution was stirred for 5.5 h at ambient temperature and loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 77% yield (90.0 mg, 0.383 mmol); 94% ee. The same reaction conducted at –10 °C was complete after 48 h and purified in identical fashion to give the product in 86% yield (101 mg, 0.429 mmol) and 96% ee. IR (film) 2950, 2902, 2844, 2809, 2728, 1732, 1614, 1523, 1437, 1353, 1230, 1166, 947.3, 818.8, 777.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 7.14 (d, *J* = 7.1 Hz, 2H, ArH), 6.68 (d, *J* = 7.6 Hz, 2H, ArH), 4.03 (dd, *J* = 4.7, 9.9 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.35 (dd, *J* = 9.9, 18.7 Hz, 1H, C**H**$_2$CO), 2.93 (s, 6H, $N(CH_3)_2$), 2.77 (dd, *J* = 4.8, 18.3 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 174.0, 150.1, 128.5, 125.2, 112.9, 52.7, 47.8, 44.2, 40.8. HRMS (CI) exact mass calcd for ($C_{13}H_{17}NO_3$) requires *m/z* 236.1286, found *m/z* 236.1285. $[\alpha]_D$ = – 152.3 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 27.3 min, *R* isomer t_r = 29.4 min.



Determination of the absolute configuration (*R*)-4-oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester by correlation to (*S*)-2-phenyl-butan-1,4,-diol. (*R*)-4-Oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester was treated with lithium aluminum hydride to give the (*S*)-diol ($[\alpha]_D$ = – 23.1; c = 0.975, $CHCl_3$) which was then protected as the bis-*tert*-butyldimethylsilyl ether ($[\alpha]_D$ = – 28.7; c = 1.01, $CHCl_3$). The aryldialkyl amine was alkylated with methyl iodide as described below and removed via dissolving metal reduction (for bis-silyl ether $[\alpha]_D$ = – 22.0; c = 1.08, $CHCl_3$). The silyl ethers were cleaved with THF/HCl/H_2O to give the corresponding diol; $[\alpha]_D$ = – 29.8 (c = 0.50, $CHCl_3$). For (*S*)-diol lit. $[\alpha]_D$ = - 13 (c = 3.0 , $CHCl_3$).[24]

(*R*)-4-Oxo-2-(4-dibenzylamino-phenyl)-butyric acid methyl ester (Table 2, entry 3). To an amber 2-dram vial under an argon atmosphere and equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 µL, 0.0500 mmol, 0.100 equiv), and *N,N*-dibenzylaniline (273 mg, 1.00 mmol, 2.00 equiv). The solution was stirred for 24 h at ambient temperature and loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 65% yield (126 mg, 0.325 mmol); 96% ee. IR (film) 3028, 2949, 2904, 2844, 2725, 1729, 1717, 1613, 1520, 1434, 1451, 1360, 1231, 1166,

956.2, 816.0, 733.7, 696.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 7.22-7.36 (m, 10H, ArH), 7.05 (d, *J* = 9.0 Hz, 2H, ArH), 6.68 (d, *J* = 8.7 Hz, 2H, ArH), 4.64 (s, 4H, $ArCH_2$), 4.01 (dd, *J* = 4.7, 9.9 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.33 (ddd, *J* = 0.9, 9.9, 18.7 Hz, 1H, C**H**$_2$CO), 2.76 (ddd, *J* = 0.8, 4.7, 18.4 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 173.9, 148.8, 135.5, 128.9, 128.7, 127.2, 126.8, 125.4, 112.8, 54.6, 52.7, 47.8, 44.1. HRMS (CI) exact mass calcd for ($C_{25}H_{25}NO_3$) requires *m/z* 387.1834, found *m/z* 387.1834. $[\alpha]_D$ = – 91.2 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 25.5 min, *R* isomer t_r = 28.4 min.

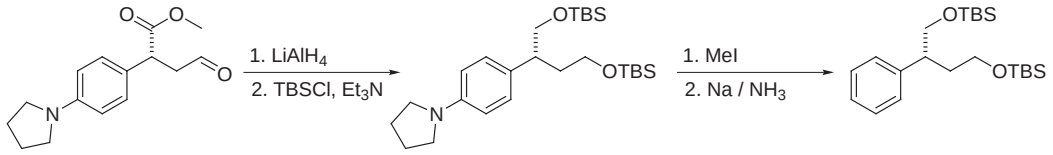


Determination of the absolute configuration of (*R*)-4-oxo-2-(4-dibenzylamino-phenyl)-butyric acid methyl ester by correlation to (*S*)-2-phenyl-butan-1,4,-diol. (*R*)-4-Oxo-2-(4-dibenzylamino-phenyl)-butyric acid methyl ester was treated with lithium aluminum hydride to give the diol which was then protected as the bis-benzoate ester. The benzyl groups were cleaved from the aniline with 10% palladium on carbon under hydrogen at atmospheric pressure (free aniline: $[\alpha]_D$ = – 29.9; c = 1.92, $CHCl_3$). Deamination was accomplished again using acetic acid, sodium nitrite, and sodium bisulfite in aqueous ethanol. The benzoates were cleaved with sodium hydroxide in

methanol to give the diol; $[\alpha]_D = -32.3$ (c = 0.96, $CHCl_3$). For (*S*)-diol lit. $[\alpha]_D = -13$ (c = 3.0 , $CHCl_3$).[5]

(*R*)-4-Oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester (8) (Table 2, entries 4 & 5). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.0500 mmol, 0.100 equiv), and 1-phenylpyrrolidine (144 μL, 1.00 mmol, 2.00 equiv). The solution was stirred for 20 min at ambient temperature and loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a white powder in 96% yield (126 mg, 0.480 mmol); 95% ee. IR (film) 2974, 2959, 2899, 2827, 2726, 1730, 1718, 1614, 1522, 1488, 1435, 1374, 1229, 1164, 1091, 814, 771, 531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 7.12 (d, *J* = 8.8 Hz, 2H, ArH), 6.51 (d, *J* = 8.8 Hz, 2H, ArH), 4.02 (dd, *J* = 4.7, 9.6 Hz, 1H, ArCH), 3.65 (s, 3H, OCH_3), 3.33 (dd, *J* = 9.9, 18.4 Hz, 1H, C**H**$_2$CO), 3.28-3.23 (m, 4H, $N(CH_2)_2$), 2.76 (dd, *J* = 5.0, 18.4 Hz, 1H, C**H**$_2$CO), 2.01-1.96 (m, 4H, CH_2**$(CH_2)_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 174.2, 147.6, 128.7, 124.1, 112.1, 52.5, 47.8, 47.7, 44.2, 25.7. HRMS (CI) exact mass calcd for ($C_{15}H_{19}NO_3$) requires *m/z* 261.1443, found *m/z* 262.1439. $[\alpha]_D = -147.8$ (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 20.9 min, *R* isomer t_r = 24.4 min. The same reaction conducted at –20 °C was complete after 8h and purified in identical fashion to give the product as a white powder in 97% yield (127 mg, 0.487

mmol); 97% ee. On a 50-mmol scale using 2 mol% amine and 2 mol% HCl at ambient temperature, the reaction afforded the product in 93% yield (12.21 g, 46.7 mmol); 91% ee. A recrystallization of this product from ethyl acetate provided 10.56 g (86% yield) of material in 96% ee.



Determination of the absolute configuration of (*R*)-4-oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester by correlation to (*S*)-2-phenyl-butan-1,4,-diol bis-*tert*-butyldimethylsilyl ether. (*R*)-4-Oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester was treated with lithium aluminum hydride to give the diol which was then protected as the bis-*tert*-butyldimethylsilyl ether. The aryldialkyl amine was alkylated with methyl iodide as described below and removed via dissolving metal reduction. This compound gives an optical rotation of $[\alpha]_D$ = – 22.8 (c = 0.92, $CHCl_3$) intercepts an intermediate in the proof above which has a rotation of $[\alpha]_D$ = – 22.0 (c = 1.08, $CHCl_3$).

(*R*)-4-Oxo-2-(6-pyrrolidin-1-yl-biphenyl-3-yl)-butyric acid methyl ester (Table 1, entry 6). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.500 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.0500 mmol, 0.100 equiv), and 2-(pyrrolidin-1-yl)-biphenyl (223 mg, 1.00 mmol, 2.00 equiv). The solution was stirred for 12 h at ambient temperature and loaded directly on a column of silica gel for

purification. Gradient elution with 10–40% EtOAc in hexanes afforded the product as a white powder in 94% yield (158.4 mg, 0.469 mmol); 99% ee. IR (film) 2949, 2871, 2820, 2721, 1734, 1719, 1606, 1505, 1482, 1354, 1329, 1229, 1164, 769.9, 701.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.44-7.24 (m, 5H, ArH), 7.13 (dd, *J* = 2.5, 8.5 Hz, 1H, ArH), 7.05 (d, *J* = 2.2 Hz, 1H, ArH), 6.82 (d, *J* = 8.2 Hz, 1H, ArH), 4.07 (dd, *J* = 4.7, 9.9 Hz, 1H, ArCH), 3.67 (s, 3H, OCH_3), 3.38 (dd, *J* = 9.9, 18.4 Hz, 1H, C**H**$_2$CO), 2.94 (m, 4H, $N(CH_2)_2$), 2.81 (dd, *J* = 4.7, 18.4 Hz, 1H, C**H**$_2$CO), 1.79-1.72 (m, 4H, CH_2**(CH$_2$)$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 173.9, 147.5, 142.9, 131.8, 130.3, 129.3, 128.1, 127.1, 126.7, 126.5, 114.9, 52.7, 51.3, 47.8, 44.3, 25.8. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 337.1679, found *m/z* 337.1678. $[\alpha]_D$ = –110.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 13.9 min, *R* isomer t_r = 16.5 min.

(*R*)-2-(1-Methyl-2,3-dihydro-1*H*-indol-5-yl)-4-oxobutyric acid methyl ester (Table 1, entries 7 & 8). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.050 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.500 ml), and HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.050 mmol, 0.100 equiv). The reaction vessel was cooled to –20 °C before the addition of 1-methylindoline (133 μL, 1.00 mmol, 2.00 equiv). The solution was stirred for 8 h at –20 °C and then loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 94% yield (116.6 mg, 0.471

mmol); 98% ee. IR (film) 2952, 2923, 2847, 2812, 2728, 1732, 1616, 1499, 1436, 1381, 1276, 1232, 1170, 1086, 1045, 988.7, 815.8, 585.2. cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 6.97 (s, 1H, ArH), 6.94 (d, *J* = 8.0 Hz, 1H, ArH), 6.39 (d, J = 8.0 Hz, 1H, ArH), 4.00 (dd, *J* = 4.7, 9.7 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.32 (ddd, *J* = 0.8, 9.9, 15.7 Hz, 1H, C**H**$_2$CO), 3.29 (t, *J* = 8.2 Hz, 2H, NCH_2), 2.91 (t, *J* = 8.2 Hz, 2H, $ArCH_2$), 2.75 (ddd, *J* = 0.6, 4.9, 18.3 Hz, 1H, C**H**$_2$CO), 2.73 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 174.2, 153.2, 131.4, 127.1, 126.7, 123.8, 107.3, 56.3, 52.6, 47.9, 44.5, 36.3, 28.8. . HRMS (CI) exact mass calcd for ($C_{14}H_{17}NO_3$) requires *m/z* 248.1286 for $[M+H]^+$, found *m/z* 248.1282. $[\alpha]_D$ = – 128.9 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 13.9 min, *R* isomer t_r = 16.5 min. The same reaction conducted on 0.25–mmol scale at ambient temperature over 20 min and purified in identical fashion afforded the product in 93% yield (57.5 mg, 0.233 mmol) and 93% ee.

(*R*)-2-(4-Dimethylaminonaphthalen-1-yl)-4-oxobutyric acid methyl ester (Table 1, entry 9). To an amber 2-dram vial under an argon atmosphere and equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.1 mg, 0.025 mmol, 0.10 equiv), 4-oxobuteneoic acid methyl ester (28.5 mg, 0.250 mmol, 1.00 equiv), $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.2 μL, 0.025 mmol, 0.10 equiv), and *N,N*-dimethyl-1-naphthylamine (82.0 μL, 0.500 mmol, 2.00 equiv). The solution was stirred for 36 h at ambient temperature and loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes

afforded the product as a colorless oil in 89% yield (63.8 mg, 0.224 mmol); 93% ee. IR (film) 2940, 2832, 2783, 2724, 1731, 1582, 1455, 1436, 1391, 1214, 1185, 1087, 1043, 767.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H, CHO), 8.29-8.34 (m, 1H, ArH), 7.99-8.04 (m, 1H, ArH), 748-7.58 (m, 2H, ArH), 7.28 (d, *J* = 8.0 Hz, 1H, ArH), 7.02 (d, *J* = 7.7 Hz, 2H, ArH), 4.91 (dd, *J* = 5.2, 9.9 Hz, 1H, ArCH), 3.68 (s, 3H, OCH_3), 3.54 (dd, *J* = 9.9, 18.7 Hz, 1H, C**H**$_2$CO), 2.89 (s, 6H, $N(CH_3)_2$), 2.86 (dd, *J* = 4.2, 18.6 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 174.1, 151.0, 132.3, 129.5, 128.5, 126.7, 125.5, 125.4, 125.3, 1234, 113.9, 52.8, 47.4, 45.5, 40.7. HRMS (CI) exact mass calcd for ($C_{17}H_{19}NO_3$) requires *m/z* 285.1365, found *m/z* 285.1365. $[\alpha]_D$ = – 200.7 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 14.9 min, *R* isomer t_r = 16.9 min.

(*R*)- 2-(4-Dimethylamino-2-methylphenyl)-4-oxobutyric acid methyl ester (Table 1, entry 10). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 25.0 μL, 0.100 mmol, 0.200 equiv), and *N,N*-dimethyl-*m*-toluidine (145 μL, 1.00 mmol, 2.00 equiv). The solution was stirred for 10 h at –10 °C temperature and loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 89% yield (112 mg, 0.447 mmol); 84% ee. IR (film) 2949, 2892, 2846, 2797, 2731, 1732, 1723, 1611, 1565, 1513, 1482, 1435, 1354, 1295, 1218, 1169, 1109,

1013, 968.6, 902.1, 840.9, 805.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H, CHO), 7.04 (dd, *J* = 2.4, 7.0 Hz, 1H, ArH), 6.55 (dd, *J* = 2.7, 7.5 Hz, 1H, ArH), 6.54 (s, 1H, ArH), 4.31 (dd, *J* = 5.4, 9.9 Hz, 1H, ArCH), 3.65 (s, 3H, OCH_3), 3.35 (ddd, *J* = 0.8, 9.9, 18.7 Hz, 1H, C**H**$_2$CO), 2.92 (s, 6H, $N(CH_3)_2$), 2.70 (dd, *J* = 0.6, 4.4, 18.4 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 174.3, 149.9, 136.8, 127.7, 124.1, 114.7, 110.9, 52.6, 47.4, 40.8, 40.1, 20.7. HRMS (CI) exact mass calcd for ($C_{14}H_{19}NO_3$) requires *m/z* 250.1443 for $[M+H]^+$, found *m/z* 250.1446. $[\alpha]_D$ = – 129.8 (c = 1.14, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 13.8 min, *R* isomer t_r = 15.4 min.

(*R*)-4-Oxo-2-(4-dimethylamino-2-methoxyphenyl)-butyric acid methyl ester (Table 1, entries 11 & 12). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.13 mg, 0.0250 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (28.5 mg, 0.250 mmol, 1.00 equiv), $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.25 µL, 0.0250 mmol, 0.100 equiv), and 3-dimethylamino-anisole (44 µL, 0.30 mmol, 1.2 equiv). The solution was stirred for 5 min at ambient temperature and loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 73% yield (48.2 mg, 0.182 mmol); 91% ee. IR (film) 2950, 2903, 2838, 2727, 1730, 1616, 1569, 1519, 1462, 1440, 1356, 1242, 1171, 1114, 1033, 979.4, 814.6, 642.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.1 Hz, 1H, CHO), 6.99 (d, *J* = 8.2 Hz, 1H, ArH), 6.27 (dd, J = 2.5, 8.5 Hz, 1H, ArH), 6.22 (d, *J* = 2.5 Hz, 1H, ArH), 4.38

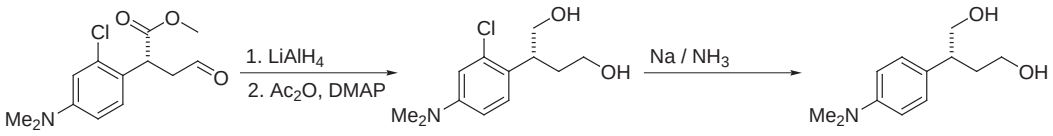
(dd, *J* = 5.2, 9.1 Hz, 1H, ArCH), 3.81 (s, 3H, $ArOCH_3$), 3.66 (s, 3H, CO_2CH_3), 3.52 (ddd, *J* = 1.4, 9.1, 18.1 Hz, 1H, C**H**$_2$CO), 2.94 (s, 6H, $N(CH_3)_2$), 2.67 (ddd, *J* = 0.8, 4.9, 17.8 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 174.4, 157.5, 151.5, 129.3, 114.6, 104.9, 96.2, 55.6, 52.5, 46.7, 40.9, 39.2. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 266.1392 for $[M+H]^+$, found *m/z* 266.1387. $[\alpha]_D$ = – 149.0 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 26.0 min, *R* isomer t_r = 27.8 min. The same reaction conducted at –20 °C on 0.5–mmol scale was complete after 8 h and purified in identical fashion to give the product in 90% yield (119 mg, 0.448 mmol) and 92% ee.

(*R*)-4-Oxo-2-(4-dimethylamino-2-methylthio-phenyl)-butyric acid methyl ester (Table 1, entry 13). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (114.1 mg, 1.00 mmol, 1.00 equiv), $CHCl_3$ (1.00 ml), and HCl (as a 4N solution in 1,4-dioxane, 25.0 μL, 0.100 mmol, 0.100 equiv). The reaction vessel was cooled to –20 °C before the addition of 3-dimethylamino-thioanisole (334 mg, 2.00 mmol, 2.00 equiv). The solution was stirred for 20 h at –20 °C and then loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 92% yield (258.6 mg, 0.920 mmol); 91% ee. IR (film) 2950, 2913, 2845, 2711, 1730, 1600, 1554, 1502, 1437, 1353, 1227, 1170, 958.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 7.02 (d, *J* = 8.5 Hz, 1H, ArH), 6.66 (d, *J* = 2.5 Hz, 1H, ArH), 6.53 (dd, J = 2.8, 8.8 Hz,

1H, ArH), 4.66 (dd, *J* = 4.4, 9.6 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.25 (ddd, *J* = 1.1, 9.6, 18.1 Hz, 1H, C**H**$_2$CO), 2.94 (s, 6H, $N(CH_3)_2$), 2.70 (ddd, *J* = 0.8, 4.7, 18.1 Hz, 1H, C**H**$_2$CO), 2.47 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 173.8, 150.1, 137.3, 128.0, 124.7, 112.3, 110.8, 52.4, 47.1, 41.0, 40.5, 17.6. HRMS (CI) exact mass calcd for ($C_{14}H_{19}NO_3S$) requires *m/z* 281.1086, found *m/z* 281.1086. $[\alpha]_D$ = – 130.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 15.7 min, *R* isomer t_r = 17.4 min.

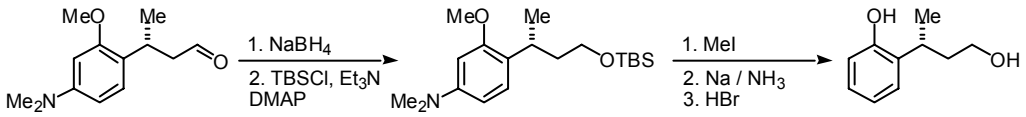
(*R*)-4-Oxo-2-(4-dimethylamino-2-chlorophenyl)-butyric acid methyl ester (Table 1. entries 14 & 15). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.500 ml), and HCl (as a 4N solution in 1,4-dioxane, 18.8 μL, 0.075 mmol, 0.150 equiv). The reaction vessel was cooled to –20 °C before the addition of 3-chloro-*N,N*-dimethylaniline (156 mg, 1.00 mmol, 2.00 equiv). The solution was stirred for 80 h at –20 °C and then loaded directly on a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 73% yield (98.7 mg, 0.366 mmol); 93% ee. IR (film) 2950, 2900, 2817, 2726, 1734, 1724, 1610, 1512, 1437, 1357, 1285, 1228, 1173, 129, 962.4, 818.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 7.06 (d, *J* = 8.8 Hz, 1H, ArH), 6.69 (d, *J* = 2.9 Hz, 1H, ArH), 6.56 (dd, J = 2.8, 8.8 Hz, 1H, ArH), 4.53 (dd, *J* = 4.7, 9.3 Hz, 1H, ArCH), 3.69 (s, 3H, OCH_3), 3.29 (ddd, *J* = 1.1, 9.6, 18.4 Hz, 1H, C**H**$_2$CO), 2.93 (s, 6H, $N(CH_3)_2$), 2.74

(ddd, J = 0.8, 4.9, 18.4 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 173.6, 150.7, 134.4, 129.3, 122.6, 113.2, 111.5, 52.8, 46.7, 41.4, 40.6. HRMS (CI) exact mass calcd for ($C_{13}H_{16}ClNO_3$) requires *m/z* 269.0819, found *m/z* 269.0814. $[\alpha]_D$ = – 156.4 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 23.3 min, *R* isomer t_r = 25.2 min. The same reaction conducted on 0.25–mmol scale at ambient temperature over 12 hours and purified in identical fashion afforded the product in 66% yield (44.4 mg, 0.165 mmol) and 86% ee.



Determination of the absolute configuration of (*R*)-4-oxo-2-(4-dimethylamino-2-chlorophenyl)-butyric acid methyl ester by correlation to (*S*)-2-(4'-dimethylamino-phenyl)-butan-1,4,-diol. (*R*)-4-Oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester was treated with lithium aluminum hydride to give the diol. On exposure to dissolving metal conditions, the aryl chloride was cleanly reduced to (*S*)-2-(4'-dimethylamino-phenyl)-butan-1,4,-diol, $[\alpha]_D$ = – 20.5 (c = 0.555, $CHCl_3$). The same intermediate above was found to have a rotation of ($[\alpha]_D$ = – 23.1; c = 0.975, $CHCl_3$) and chemically correlated to the known, deaminated compound.

(*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-butyraldehyde (Table 1, entry 1). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.050 mmol, 0.100 equiv), dichloromethane (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.050 mmol, 0.100 equiv), and *N,N*-dimethyl-*m*-anisidine (73.3 μL, 0.500 mmol, 1.00 equiv). The solution was cooled to –40 °C before adding crotonaldehyde (124 μL, 1.50 mmol, 3.00 equiv). After 36 h, the reaction mixture was loaded directly on a column of silica gel for purification. Elution with 20% EtOAc in hexanes followed by concentration and removal of residual crotonaldehyde under vacuum afforded the product as a colorless oil in 86% yield (94.9 mg, 0.429 mmol); 89% ee. IR (film) 2958, 2874, 2834, 2719, 1721, 1615, 1568, 1516, 1462, 1441, 1352, 1238, 1133, 1034, 979.6, 814.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (t, *J* = 2.7 Hz, 1H, CHO), 7.03 (d, *J* = 8.2 Hz, 1H, ArH), 6.31 (dd, *J* = 2.5, 8.2 Hz, 1H, ArH), 6.27 (d, *J* = 2.5 Hz, 1H, ArH), 3.83 (s, 3H, OCH_3), 3.63 (dq, *J* = 7.1, 7.1 Hz, 1H, ArCH), 2.94 (s, 6H, $N(CH_3)_2$), 2.68 (ddd, *J* = 2.5, 6.9, 15.9 Hz, 1H, C**H**$_2$CO), 2.55 (ddd, *J* = 2.8, 7.7, 15.9 Hz, 1H, C**H**$_2$CO), 1.27 (d, 3H, CH**CH$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 157.8, 150.9, 127.5, 121.7, 15.1, 96.6, 55.4, 51.2, 41.0, 27.6, 20.9. HRMS (CI) exact mass calcd for ($C_{13}H_{19}NO_2$) requires *m/z* 222.1494 for $[M+H]^+$, found *m/z* 222.1497. $[\alpha]_D$ = – 9.5 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (3.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 21.6 min, *R* isomer t_r = 23.1 min.



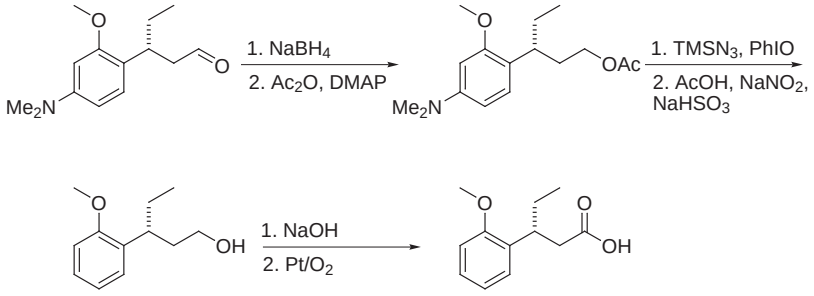
Determination of the absolute configuration (*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-butyraldehyde by correlation to (*S*)-2-phenyl-butanol. (*R)*-3-(4-Dimethylamino-2-methoxy-phenyl)-butyraldehyde was treated with sodium borohydride in ethanol to give the (*R*)-alcohol which was then protected as the *tert*-butyldimethylsilyl ether ($[\alpha]_D$ = – 13.3; c = 1.12, $CHCl_3$) using the corresponding silyl chloride, triethylamine, and DMAP in dichloromethane. The aryldialkyl amine was subsequently alkylated with methyl iodide as described below and removed via dissolving metal reduction. The ethers were cleaved in refluxing HBr to give the corresponding dihydroxy compound; $[\alpha]_D$ = – 6.1 (c = 0.128, acetone). For (*S*)-alcohol lit. [α] = + 16 (c = 25 , acetone).[24]

(*R*)-3-(4-Pyrolidin-1-yl-phenyl)-butyraldehyde (Table 2, entry 2). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (49.3 mg, 0.200 mmol, 0.200 equiv) dichloromethane (0.33 ml), HCl (as a 4N solution in 1,4-dioxane, 50 μL, 0.200 mmol, 0.200 equiv), and 1-phenylpyrrolidine (144 μL, 1.00 mmol, 1.00 equiv). The solution was cooled to –20 °C before adding crotonaldehyde (166 μL, 2.00 mmol, 2.00 equiv). After 48 h, the reaction mixture was loaded directly on a column of silica gel for purification. Elution with 20% EtOAc in hexanes followed by concentration and removal of residual crotonaldehyde under high vacuum afforded the product as a pale yellow oil in 70% yield (147 mg, 0.676 mmol); 87% ee. IR (film) 2962, 2927, 2829, 2717, 1721, 1616, 1522, 1372, 814.0 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.2 Hz, 1H, CHO), 7.10 (d, *J* = 8.8 Hz, 2H, ArH), 6.54 (d, *J* = 8.8 Hz, 2H, ArH), 3.32-3.21 (m, 5H, ArCH, $N(CH_2)_2$), 2.71 (ddd, *J* = 2.2, 7.1, 16.5 Hz, 1H, C**H**$_2$CO), 2.61 (ddd, *J* = 2.2, 7.7, 16.0 Hz, 1H, C**H**$_2$CO), 2.03-1.96 (m, 4H, CH_2**(CH_2)$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 146.7, 132.0, 127.5, 111.8, 52.3, 47.8, 33.8, 25.7, 22.8. HRMS (CI) exact mass calcd for ($C_{14}H_{19}NO$) requires *m/z* 218.1545, found *m/z* 218.1542. $[\alpha]_D$ = – 33.9 (c = 0.539, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 20.9 min, *S* isomer t_r = 24.4 min.

(*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-pentanal (Table 2, entry 3). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), dichloromethane (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 25.0 μL, 0.100 mmol, 0.200 equiv), and *N,N*-dimethyl-*m*-anisidine (73.3 μL, 0.500 mmol, 1.00 equiv). The solution was cooled to –50 °C before adding pentenal (98.0 μL, 1.00 mmol, 2.00 equiv). After 62 h, the reaction mixture was loaded directly on a column of silica gel for purification. Elution with 20% EtOAc in hexanes followed by concentration and removal of residual pentenal under vacuum afforded the product as a colorless oil in 68% yield (79.5 mg, 0.338 mmol); 88% ee. IR (film) 2959, 2926, 2871, 2839, 2800, 2721, 1718, 1616, 1569, 1517, 1351, 1237, 1136, 1034, 979.5, 812.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (t, *J* = 2.8 Hz, 1H, CHO), 6.97 (d, *J* = 8.2 Hz, 1H, ArH), 6.30 (dd, *J* = 2.5, 8.3 Hz, 1H, ArH), 6.26 (d, *J* = 2.5 Hz, 1H, ArH), 3.81 (s, 3H, OCH_3), 3.40 (dt, *J* = 7.3, 7.4 Hz, 1H, ArCH), 2.94 (s, 6H, $N(CH_3)_2$), 2.66 (dd, *J* = 2.7, 7.4 Hz, 2H, CH_2CO), 1.72-1.61 (m, 2H, C**H**$_2$$CH_3$), 0.83 (t, *J*

= 7.4 Hz, 3H, $CH_2\mathbf{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) 203.8, 158.2, 150.6, 128.4, 119.8, 105.0, 96.5, 55.5, 49.7, 1.1, 34.9, 28.4, 12.4. HRMS (CI) exact mass calcd for ($C_{14}H_{21}NO_2$) requires *m/z* 236.1650 for $[M+H]^+$, found *m/z* 236.1649. $[\alpha]_D = -18.9$ (c = 0.970, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (3.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 11.5 min, *R* isomer t_r = 12.4 min.



Determination of the absolute configuration of (*R*)-3-(4-dimethylamino-2-methoxy-phenyl)-pentanal by correlation to (*R*)-3-ethyl-*o*-methoxy-dihydrocinnamic acid. (*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-pentanal was treated with sodium borohydride followed by acetic anhydride to furnish the corresponding acetate. Subsequent dealkylation according to the procedure of Jørgensen[29] and deamination via one-pot diazotization and reduction provide a modest yield of the *ortho*-alkyl anisole. Deprotection of the acetate was accomplished with sodium hydroxide in methanol and finally, the free alcohol was oxidized to the acid using platinum (IV) oxide under an

[29] Jørgensen, et. al. *J. Am. Chem. Soc.* **2000**, *122*, 12517.

atmosphere of oxygen; $[\alpha]_D$ = – 3.1 (c = 1.0, $CHCl_3$). lit. $[\alpha]$ = – 21.3 (c = 11.2, $CHCl_3$).[30]

(*S*)-4-Benzoyloxy-3-(4-dimethylamino-2-methoxy-phenyl)-butyraldehyde

(Table 2, entry 4). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.100 equiv), *N,N*-dimethyl-*m*-anisidine hydrochloride (18.8 mg, 0.100 mmol., 0.100 equiv), $CHCl_3$ (1.00 ml), and *N,N*-dimethyl-*m*-anisidine (132 μL, 0.900 mmol, 0.900 equiv). The solution was cooled to –20 °C before adding 4-benzoyloxy-crotonaldehyde as a solid (0.380, 2.00 mmol, 2.00 equiv). After 24 h, the reaction mixture was loaded directly on a column of silica gel for purification. Gradient elution with 10–25% EtOAc in hexanes followed by concentration and removal of residual pentenal under vacuum afforded the product as a colorless oil in 89% yield (304 mg, 0.889 mmol); 92% ee. IR (film) 2940, 2892, 2836, 2724, 1719, 1615, 1518, 1273, 1240, 1117, 712.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.1 Hz, 1H, CHO), 8.01 (ddd, *J* = 0.6, 1.1, 6.3 Hz., 2H, ArH), 7.58-7.40 (m, 3H, ArH), 7.08 (d, *J* = 8.2 Hz, 1H, ArH), 6.30 (dd, *J* = 2.5, 8.5 Hz, 1H, ArH), 6.25 (d, *J* = 2.4 Hz, 1H, ArH), 4.51 (dd, *J* = 5.5, 10.7 Hz, 1H, C**H**$_2$O), 4.42 (dd, *J* = 8.2, 10.7 Hz, 1H, C**H**$_2$O), 4.08-3.98 (m, 1H, ArCH), 3.83 (s, 3H, OCH_3), 2.98-2.80 (m, 2H, CH_2CO), 2.95 (s, 6H, $N(CH_3)$; ^{13}C NMR (75 MHz, $CDCl_3$) 202.2, 166.6, 158.2, 151.3, 133.1, 130.3, 129.8, 129.0, 128.6, 115.6, 104.9, 96.3, 67.9, 55.4, 46.3, 50.0, 33.5. HRMS (CI) exact mass calcd for ($C_{20}H_{23}NO_4$) requires *m/z* 342.1705 for $[M+H]^+$, found *m/z* 342.1705. $[\alpha]_D$ = – 16.9 (c = 0.751, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$

[30] Meyers, A. I. et al, *J. Org. Chem.* **1979**, *44*, 2250-2256.

reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 15.2 min, *S* isomer t_r = 24.0 min.

(*S*)-4-Benzoyloxy-3-(4-pyrolidin-1-yl-phenyl)-butyraldehyde (Table 2, entry 5). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.13 mg, 0.025 mmol, 0.100 equiv) $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.25 μL, 0.025 mmol, 0.100 equiv), 1-phenylpyrrolidine (36.1 μL, 0.025 mmol, 1.00 equiv). To the stirring solution at room temperature was added 4-benzoyloxy-crotonaldehyde (95.0 mg, 0.5 mmol, 2.00 equiv). After 24 h, the reaction mixture was loaded directly on a column of silica gel for purification. Elution with 20–40% EtOAc in hexanes followed by concentration *in vacuo* afforded the product as a pale yellow oil in 73% yield (61.3 mg, 0.182 mmol); 90% ee. IR (film) 2961, 2888, 2825, 1717, 1715, 1616, 1522, 1487, 1450, 1374, 1271, 1176, 1115, 1069, 1026, 964.1, 812.7, 711.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 7.99 (d, *J* = 7.1 Hz, 2H, ArH), 7.56 (t, *J* = 7.7 Hz, 1H, ArH), 7.44 (t, *J* = 7.7 Hz, 2H, ArH), 7.17 (d, *J* = 8.8 Hz, 2H, ArH), 6.54 (d, *J* = 8.8 Hz, 2H, ArH), 4.49 (dd, *J* = 6.1, 11.0 Hz, 1H, OC**H**$_2$), 4.34 (dd, *J* = 8.2, 10.4 Hz, 1H, OC**H**$_2$), 3.72-3.60 (m, 1H, ArCH), 3.30-3.21 (m, 4H, $N(CH_2)_2$), 2.94 (ddd, *J* = 1.7, 6.6, 16.5 Hz, 1H, C**H**$_2$CO), 2.84 (ddd, *J* = 2.2, 8.3, 17.1 Hz, 1H, C**H**$_2$CO), 2.03-1.95 (m, 4H, CH_2**(CH_2)$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 166.5, 147.3, 133.2, 130.2, 129.8, 128.6, 128.6, 126.1, 112.1, 69.0, 47.9, 47.2, 38.8, 25.8. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 338.1756, found *m/z* 338.1747. $[\alpha]_D$ = – 5.1 (c = 0.50, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding

alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 31.4 min, *S* isomer t_r = 37.8 min.

(*R*)-4-Oxo-2-(4-dimethylamino-2-methoxyphenyl)-butyric acid methyl ester (Table 2, entry 6). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.13 mg, 0.0250 mmol, 0.100 equiv), $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.25 μL, 0.0250 mmol, 0.100 equiv), and 3-dimethylamino-anisole (44 μL, 0.30 mmol, 1.2 equiv). The solution was cooled to –20 °C before oxobuteneoic acid methyl ester (28.5 mg, 0.250 mmol, 1.00 equiv) was added. The resulting solution was maintained at –20 °C for 8 h before being added directly onto a column of silica gel for purification. Gradient elution with 20–40% EtOAc in hexanes afforded the product as a colorless oil in 73% yield (48.2 mg, 0.182 mmol); 91% ee. IR (film) 2950, 2903, 2838, 2727, 1730, 1616, 1569, 1519, 1462, 1440, 1356, 1242, 1171, 1114, 1033, 979.4, 814.6, 642.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.1 Hz, 1H, CHO), 6.99 (d, *J* = 8.2 Hz, 1H, ArH), 6.27 (dd, J = 2.5, 8.5 Hz, 1H, ArH), 6.22 (d, *J* = 2.5 Hz, 1H, ArH), 4.38 (dd, *J* = 5.2, 9.1 Hz, 1H, ArCH), 3.81 (s, 3H, $ArOCH_3$), 3.66 (s, 3H, CO_2CH_3), 3.52 (ddd, *J* = 1.4, 9.1, 18.1 Hz, 1H, C**H**$_2$CO), 2.94 (s, 6H, $N(CH_3)_2$), 2.67 (ddd, *J* = 0.8, 4.9, 17.8 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 174.4, 157.5, 151.5, 129.3, 114.6, 104.9, 96.2, 55.6, 52.5, 46.7, 40.9, 39.2. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 266.1392 for $[M+H]^+$, found *m/z* 266.1387. $[\alpha]_D$ = – 149.0 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 26.0 min, *R* isomer t_r = 27.8 min.

(*S*)-3-(4-pyrolidin-1-yl-2-methoxy-phenyl)-3-phenyl-propanol (Table 2, entry 7). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one hydrochloride (28.2 mg, 0.100 mmol, 0.200 equiv), dichloromethane (0.50 ml), and 1-(3-methoxy-phenyl)-pyrrolidine (83.6 µl, 0.500 mmol, 1.00 equiv). The solution was cooled to –50 °C before addition of cinnamaldehyde (167 µL, 1.00 mmol, 2.00 equiv). After 36 h, the reaction mixture was added drop-wise to a stirring suspension of $NaBH_4$ (41 mg) in ethanol (0.75 mL). After five minutes, the reduction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with dichloromethane. The layers were separated and the organic was washed with saturated aqueous $NaHCO_3$ and brine solutions. The resulting solution was dried over sodium sulfate and concentrated *in vacuo* and the residue was purified by silica gel chromatography. Gradient elution with 25–75% diethyl ether in hexanes afforded the product as a colorless oil in 82% yield (127.4 mg, 0.409 mmol); 84% ee. IR (film) 3356, 2941,2875, 2832, 1615, 1566, 1515, 1488, 1452, 1374, 1224, 1036, 699.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.23 (m, 4H, ArH), 7.18-7.11 (m, 1H, ArH), 6.96 (d, J = 8.8 Hz, 1H, ArH), 6.14 (dd, J = 2.2, 8.2 Hz, 1H, ArH), 6.09 (d, J = 2.2 Hz, 1H, ArH), 4.51 (dd, J = 6.6, 9.3 Hz, 1H, ArCH), 3.83 (s, 3H, OCH_3), 3.70-3.48 (m, 2H, C**H$_2$**OH), 3.32-3.23 (m, 4H, $N(CH_2)_2$), 2.37-2.23 (m, 1H, CHC**H**$_2$), 2.22-2.10 (m, 1H, CHC**H**$_2$), 2.01-1.94 (m, 4H, CH_2**(CH_2)$_2$**CH_2), 1.89 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.8, 145.8, 129.0, 128.3, 128.2, 125.8, 119.9, 104.5, 95.3, 61.7, 55.9, 48.0, 36.6, 38.2, 25.8. $[\alpha]_D$ = – 60.5 (c = 1.07, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 15.1 min, *R* isomer t_r = 28.6 min.

(*S*)-3-(4-Chloro-phenyl)-3-(4-pyrolidin-1-yl-2-methoxy-phenyl)-propanol

(Table 2, entry 8). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), dichloromethane (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 25.0 µL, 0.100 mmol, 0.200 equiv) and 1-(3-methoxy-phenyl)-pyrrolidine (167 µl, 1.00 mmol, 2.00 equiv). The solution was cooled to –50 °C before addition of *p*-chloro-cinnamaldehyde as a solid (83.0 mg, 0.500 mmol, 1.00 equiv). After 80 h, the reaction mixture was added drop-wise to a stirring suspension of $NaBH_4$ (41 mg) in ethanol (0.75 mL). After 5 min, the reduction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with dichloromethane. The layers were separated and the organic was washed with saturated aqueous $NaHCO_3$ and brine solutions. The resulting solution was dried over sodium sulfate and concentrated *in vacuo* and the residue was purified by silica gel chromatography. Gradient elution with 25–75% diethyl ether in hexanes afforded the product as a colorless oil in 80% yield (137.8 mg, 0.399 mmol); 92% ee. IR (film) 3320, 2941, 2879, 2833, 1615, 1566, 1515, 1488, 1454, 1374, 1224, 1036, 1014, 808.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 4H, ArH), 6.93 (d, *J* = 8.3 Hz, 1H, ArH), 6.13 (dd, *J* = 2.1, 8.1 Hz, 1H, ArH), 6.07 (d, *J* = 2.1 Hz, 1H, ArH), 4.45 (dd, *J* = 6.6, 8.8 Hz, 1H, ArCH), 3.80 (s, 3H, OCH_3), 3.70-3.43 (m, 2H, C**H₂**OH), 3.32-3.20 (m, 4H, $N(CH_2)_2$), 2.32-2.03 (m, 2H, CHC**H₂**), 2.02-1.92 (m, 4H, CH_2**(CH_2)₂**CH_2), 1.74 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 147.9, 144.4, 131.4, 129.5, 128.9, 128.7, 128.4, 127.8, 119.2, 104.4, 95.3, 61.4, 55.8, 48.0, 38.2, 38.0, 25.8. $[\alpha]_D$ = – 57.7 (c = 1.90, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis

using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 12.4 min, *R* isomer t_r = 15.3 min.

(*R*)-3-(4-nitro-phenyl)-3-(4-Dimethylamino-2-methoxy-phenyl)-propionaldehyde (Table 2, entry 9). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.100 equiv), *N,N*-dimethyl-*m*-anisidine hydrochloride (18.8 mg, 0.100 mmol, 0.100 equiv), dichloromethane (1.00 ml), and *N,N*-dimethyl-*m*-anisidine (425 µL, 2.90 mmol, 2.90 equiv). The solution was cooled to –10 °C before adding *p*-nitro-cinnamaldehyde as a solid (177 mg, 1.00 mmol, 1.00 equiv). After 48 h, the reaction mixture was loaded directly on a column of silica gel for purification. Gradient elution with 10–50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 87% yield (285 mg, 0.867 mmol); 92% ee. IR (film) 2938, 2894, 2837, 2726, 1722, 1614, 1516, 1345, 1241, 1120, 1033, 980.1, 858.6, 814.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 8.12 (td, *J* = 2.2, 9.3 Hz, 2H, ArH), 7.42 (td, *J* = 1.5, 9.3 Hz, 2H, ArH), 6.97 (d, *J* = 8.3 Hz, 1H, ArH), 6.30 (dd, *J* = 2.5, 8.8 Hz, 1H, ArH), 6.24 (d, *J* = 2.2 Hz, 1H, ArH), 4.98 (t, *J* = 7.8 Hz, 1H, ArCH), 3.79 (s, 3H, OCH_3), 3.21-3.09 (m, 2H, C**H**$_2$CO), 2.96 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 157.8, 152.3, 151.4, 146.5, 128.9, 128.6, 123.8, 118.0, 104.8, 96.4, 55.4, 48.4, 40.8, 38.2. HRMS (CI) exact mass calcd for ($C_{18}H_{20}N_2O_4$) requires *m/z* 328.1423, found *m/z* 328.1422. $[\alpha]_D$ = –58.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction of the aldehyde) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 25.6 min, *S* isomer t_r = 29.5 min.

(*S*)-3-(4-Nitrophenyl)-3-(4-pyrolidin-1-yl-phenyl)-propionaldehyde (Table 2, entry 10). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv) dichloromethane (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 25 μL, 0.200 mmol, 0.200 equiv), and *p*-nitrocinnamaldehyde (88.6 mg, 0.500 mmol, 1.00 equiv). The solution was cooled to –10 °C before addition of 1-phenylpyrrolidine (216 μL, 1.50 mmol, 3.00 equiv). After 48 h, the reaction mixture was loaded directly on a column of silica gel for purification. Gradient elution with 25–50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 82% yield (133 mg, 0.411 mmol); 90% ee. IR (film) 2968, 2894, 2835, 2728, 1723, 1614, 1520, 1375, 1345, 1182, 1110, 859.2, 804.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.4 Hz, 1H, CHO), 8.13 (d, *J* = 8.8 Hz, 2H, ArH), 7.38 (d, *J* = 8.8 Hz, 2H, ArH), 7.05 (d, *J* = 8.8 Hz, 2H, ArH), 6.50 (d, *J* = 8.8 Hz, 2H, ArH), 4.63 (t, *J* = 7.7 Hz, 1H, ArCH), 3.29-3.09 (m, 6H, C**H$_2$**CO, $N(CH_2)_2$), 2.03-1.94 (m, 4H, CH_2**(CH_2)$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 152.2, 147.1, 128.6, 127.9, 124.1, 112.1, 49., 47.9, 44.2, 25.8. HRMS (CI) exact mass calcd for ($C_{19}H_{20}N_2O_3$) requires *m/z* 324.1474, found *m/z* 324.1470. $[\alpha]_D$ = – 3.75 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding acetate (obtained by $NaBH_4$ reduction of aldehyde and subsequent acylation with Ac_2O) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 35.4 min, *R* isomer t_r = 47.0 min.

Chapter 4

Development of a Facile Procedure for the Removal of Dialkylamino- Substituents from Benzene Rings[1]

Reaction Design

Friedel-Crafts alkylations1, hydroxyalkylations[2a], and aminoalkylations2[b] have emerged as new strategies for the enantioselective, catalytic construction of benzyllic stereocenters. These methods and traditional electrophilic aromatic substitution processes benefit with regard to reactivity and regioselectivity when an electron-donating substituent is present on the aryl nucleophile. Dialkylamines, particularly dimethyl and cyclically constrained amines, are among the most powerful electron-donating substituents in the acceleration of electrophilic aromatic substitution reactions; however, exploitation of this readily available functionality has been hampered by an inability to effect its removal after the fact.

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[1] Parts of this work have been reported previously: Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894-7895.

[2] a) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. b) Saaby, S.; Fang, X. M.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114.

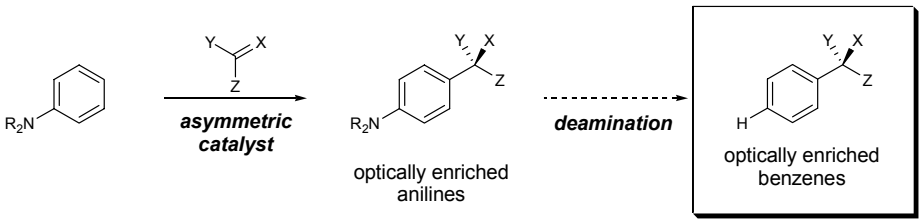
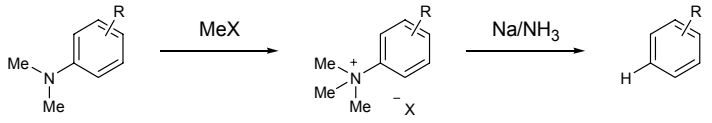


Figure 1

Despite the variety of diazotization protocols that have been developed for the removal or functionalization of primary anilines,[3] a general and reliable method for the cleavage of *N,N*-dialkylamines from benzene rings remains unknown. We became interested in this problem in the course of our studies of asymmetric organocatalytic Friedel-Crafts alkylation of electron-rich benzenes. Here we describe our investigations culminating in a procedure for the general deamination of *N,N*-dialkylamino-arenes. The tertiary amines are *N*-alkylated with either MeI or MeOTf to form the corresponding quaternary ammonium salts and then subjected to a dissolving metal reduction which affords the parent benzene in a net deamination process (Scheme 1).

Scheme 1

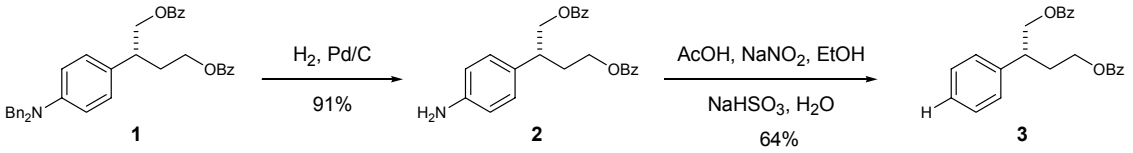


[3] a) Kornblum, N. *Org. React.* **1994**, *2*, 262-339. b) Larock, R. C. *Comprehensive Organic Transformations. A Guide to Functional Group Preparations*, 2nd edition, 1999; pp. 40-41. c) Saunders, K. H. Aromatic Diazo Compounds, 3rd edition; 1985; pp. 537-555.

Results and Discussion

Initially, a conventional strategy toward deamination was investigated (Scheme 2). Chiral *N,N*-dibenzyl aniline **1** was deprotected by hydrogenolysis and the resulting primary aniline **2** was subjected to simultaneous diazotization-reduction conditions,[4] affording the benzene product **3** in 58% overall yield. While this sequence effected the removal of a dialkyl nitrogen from a benzene ring, the scope was limited to anilines with labile nitrogen protective groups. As *N,N*-dibenzyl anilines are among the least reactive in asymmetric Friedel-Crafts alkylations, a general method for the removal of alkyl groups was then sought.

Scheme 2



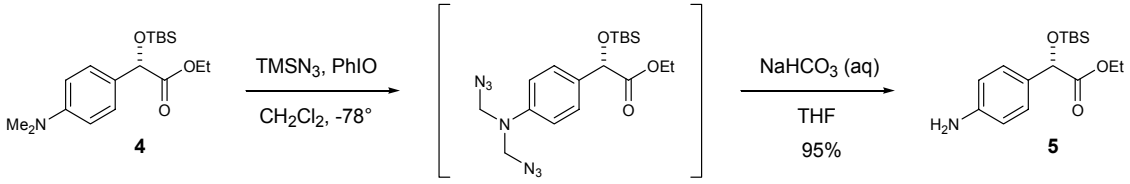
Recent reports outlined a method for oxidative removal of methyl groups from the nitrogen of an aniline under mild conditions. Jorgensen et. al. reported removal of the alkyl substituents from mandelate derivative **4** in 95% overall yield following an oxidative protocol initially described by Magnus (Scheme 3).2[a,5] In this procedure, the amine substituents are selectively oxidized by a hypervalent iodine species and trapped by azide *in situ*. In a second step in the same vessel, treatment of the bis-azidomethylene

[4] Geoffroy, O. J.; Morinelli, T. A.; Meier, G. P. *Tet. Lett.* **2001**, *42*, 5367-5369.

[5] Magnus, P.; Lacour, J.; Weber, W. *Synthesis* **1998**, 547.

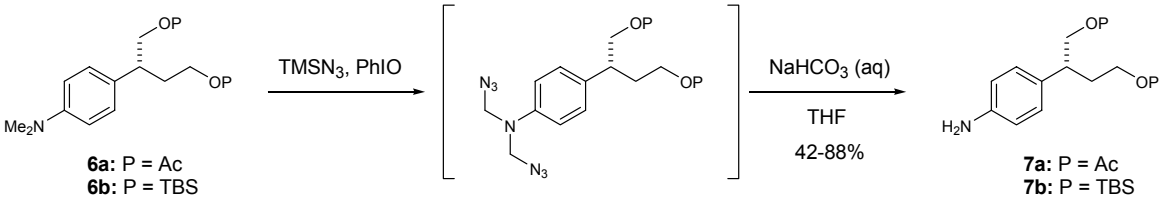
intermediate under mildly basic aqueous conditions reportedly affords primary aniline **5** in excellent yield. Further transformation to (*S*)-mandelic acid ethyl ester was accomplished in a three-step sequence consisting of 1) diazotization with $NOBF_4$, 2) reduction with H_3PO_2, and 3) silyl deprotection with methanolic HCl. This method was particularly attractive to us because the integrity of the benzyllic stereocenter in starting material aniline **4** was reportedly maintained over the three-step deamination protocol.

Scheme 3



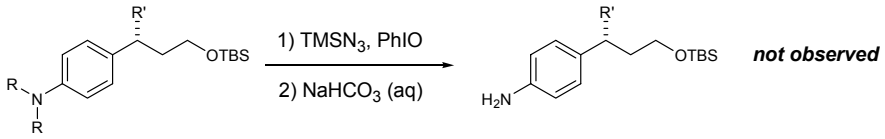
We proceeded to investigate the deamination of optically enriched *N,N*-dialkylanilines according to the published three-step protocol. Subjection of dimethylamino-phenyl diacetate **6** to Jorgensen's modified conditions using freshly prepared iodosobenzene and trimethylsilylazide in either CH_2Cl_2 or $CHCl_3$ at low temperatures produced mixed results (Scheme 4). Purified yields ranging between 42-88% were typical after hydrolytic work-up, though in some attempts complex mixtures containing little or no desired product were obtained. In order to minimize dissimilarities between our substrates and those reported by Jorgensen we varied the protective groups on the 1,4-diol subunit, but saw no improvement in the efficiency or consistency of this reaction.

Scheme 4



Attempts to expand the scope of this protocol proved fruitless in our hands (Scheme 5). Specifically, a pyrrolidine ring such as in substrate **8** was not successfully dealkylated in this fashion, giving rise to a complex mixture including pyrrole and other oxidation products. As the 1-pyrrolidino substituent produces substantial rate accelerations as compared to acyclic amines,[1] inability to effect cleavage of this useful auxiliary represents a significant limitation. Bisbenzyllic stereocenters were also incompatible with the reaction conditions: only decomposition was observed from oxidative treatment of substrate **9**, where R′ is another phenyl ring.

Scheme 5



Design of a new method for direct cleavage of dialkylamines

As attempts at sequential dealkylation–deamination sequences met with limited success, ejection of the dialkylamino substituent intact emerged as an appealing strategy.

A literature search revealed that dialkylamines could be effectively cleaved from benzenes *via* dissolving metal reduction if a carbonyl substituent were present at the *para*-position in the same arene (Figure 2).[6] Presumably, initial single-electron reduction of the benzene ring proceeds with high regioselectivity to produce a 1,4-radical anion stabilized by the electron-withdrawing group.[7] Protonation by solvent and a second reduction/protonation sequence should generate an intermediate which is consistent with the *ipso, para*-reduction product typically associated with the Birch reduction. In the basic reaction medium, this functionalized 1,4-diene is set to further undergo an elimination reaction which ejects the dialkylamine and restores aromaticity to the ring. In the absence of an ester, acid, or other suitable *para*-substituent, anilines are slowly reduced with *ortho,meta*-selectivity to afford 1-amino-1,4-dienes which are not capable of expelling the amine (Figure 2).

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[6] Lindow, A.; Cortez, E.; Harvey, J.; *J. Am. Chem. Soc.* **1972**, *94*, 5406.

[7] For a discussion of regioselectivity in the Birch reduction see: March, J. *Advanced Organic Chemistry: Reactions, Mechanism and Stucture*, 4th ed. Wiley: New York, 1992, pp. 781-782, and references therein.

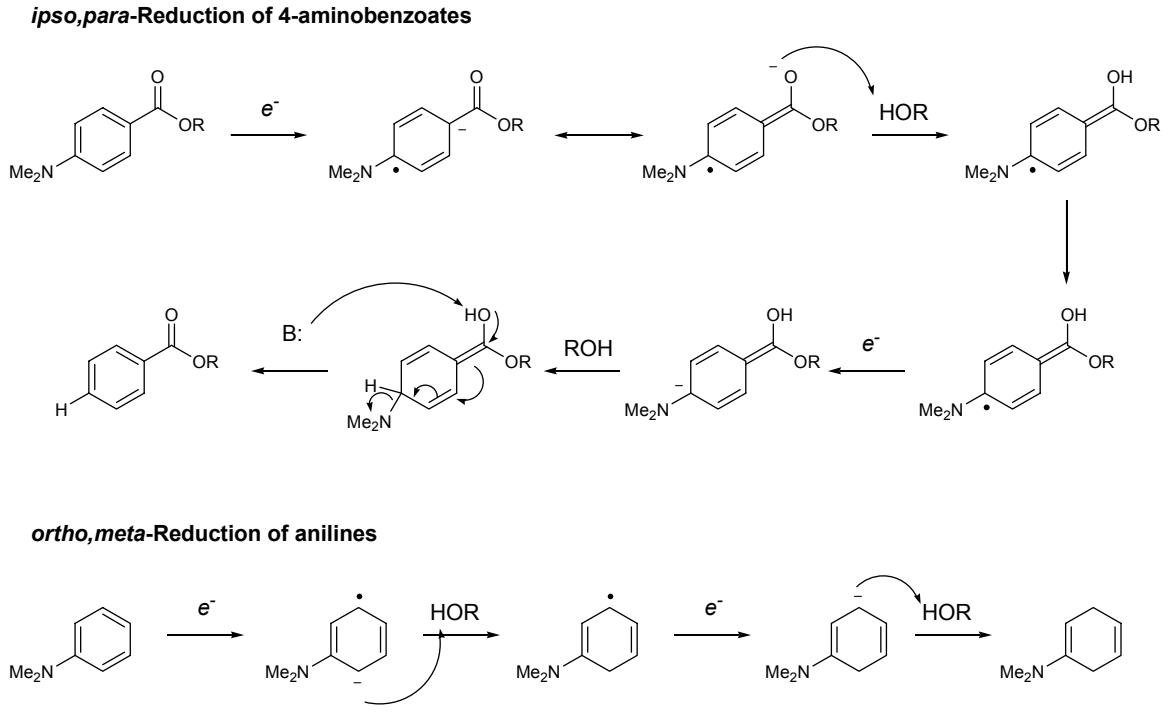


Figure 2

This reductive elimination strategy, while intriguing, was not directly applicable to the optically enriched compounds we were interested in deaminating, as an electron-withdrawing functionality was required precisely at the position occupied by a carbogenic stereocenter in our proposed substrates. In order to circumvent the necessity of this independent electron-withdrawing group we investigated alternate means for direction of reduction regioselectivity (Figure 3). We hypothesized that the 2º amino substituent itself could be converted to an electron-withdrawing group by *N*-alkylation. Reduction of resultant species **12**, directed by the aryl-trialkylammonium substituent might then proceed with the desired regioselectivity to afford 1,4-diene intermediate **13**. Under the basic reaction conditions, such a species would be expected to participate in a

vinylogous Hoffman elimination, ejecting a neutral tertiary amine and regenerating aromaticity.

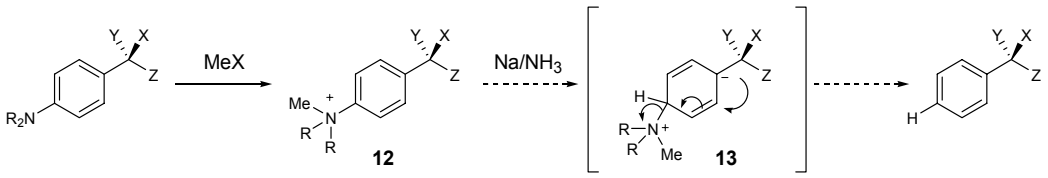
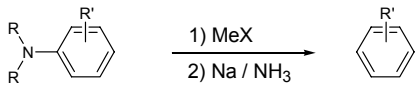


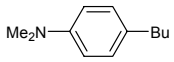
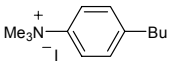
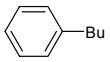
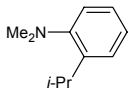
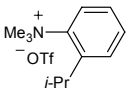
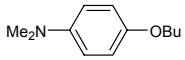
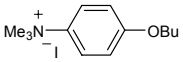
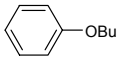
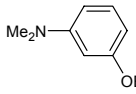
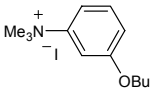
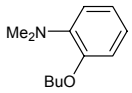
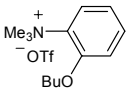
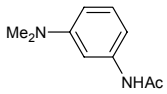
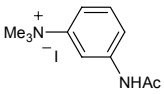
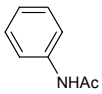
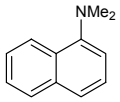
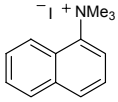
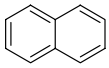
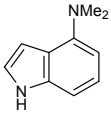
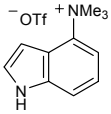
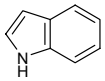
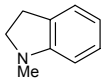
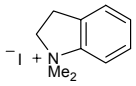
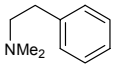
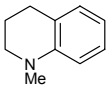
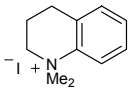
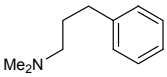
Figure 3

Initial attempts and substrate scope

To test this strategy, *N,N*-dimethyl-4-butylaniline was stirred in MeI overnight to afford the corresponding quaternary ammonium iodide in quantitative yield on evaporation of the alkylating agent. The crystalline solid was then effectively deaminated by treatment with sodium in liquid ammonia at -78 °C, affording butyl benzene in 83% yield (Table 1, entry 1). A bulky *ortho*-substituent did not impede the reduction–elimination reaction (2-*i*-Pr, 86% yield, Table 1, entry 2) nor did electron donating groups at any position on the ring (Table 1, entries 3-6). Dialkyl amines could also be quaternized and reductively removed from indole and naphthalene rings (77-78% yield, Table 1, entry 7-8), and treatment of saturated cyclic salts furnished ring-opened products (Table 1, entries 9-10). While neat MeI (1 mL/200μg) was sufficient for alkylation of several anilines, it was exceedingly slow in sterically demanding cases so MeOTf in CH_2Cl_2 was used instead (Table 1, entries 2, 5, & 8).

Table 1



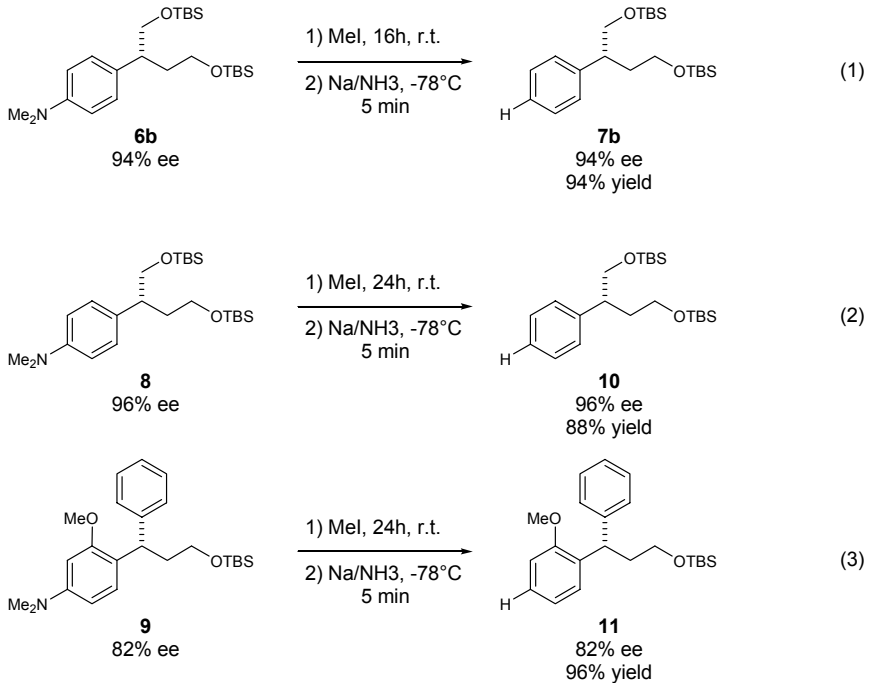
entry	aniline	alkylation method	quaternary aniline	reduction product	% yield[a]
1		MeI			83
2		MeOTf			86[b]
3		MeI			89
4		MeI			90
5		MeOTf			90[b]
6		MeI			74
7		MeI			78
8		MeOTf			77[b]
9		MeI			81[c,d]
10		MeI			78[c]

[a]Unless otherwise noted, yield of reduction of recrystallized quaternary ammonium as determined by GC analysis with internal standard. [b]Overall yield of 2-step quaternization, reduction protocol without intervening purification. [c]Isolated, purified yield. [d]Combined yield of *N,N*-dimethylphenethylamine and 2-ethyl-*N,N*-dimethyl aniline isolated in 3:1 ratio.

Having achieved some degree of success with simple aromatic amines, this new methodology was then applied to the chiral substrates which had initially inspired our

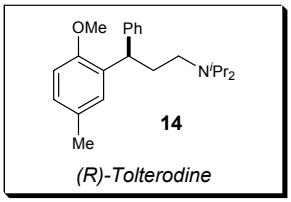
studies (Scheme 6). Aniline **6b** was stirred in neat MeI overnight and then concentrated *in vacuo* to afford the corresponding quaternary ammonium salt. The salt was then treated with sodium metal in THF and liquid NH_3 (~1:12 v:v) solution to furnish the desired benzene derivative **7b** directly in 94% overall yield without intervening purification (Scheme 6, equation 1). Phenyl-pyrrolidine **8** was successfully converted to **10** in 88% overall yield for the two steps (Scheme 6, equation 2). The doubly benzyllic carbon of *N,N*-dialkyl aniline **9** was also tolerated without complication, deamination proceeding in 96% overall yield from the parent aniline (Scheme 6, equation 3). Importantly, in each of these three cases enantiomeric excess of the initial aniline was translated directly to the deaminated product without any deterioration as determined by chiral HPLC analysis.

Scheme 6



Application: enantioselective synthesis of (*R*)-tolterodine (**14**)

This aryl deamination methodology described above provides ready access to optically active dihydrocinnamaldehyde derivatives from the products of enantioselective aniline alkylations described in Chapter 3. For example, with exchange of the ω-silyl ether in substrates **6**, **8** or **9** for an amine functionality the deamination give entry to the 3-phenylpropylamine pharmacophore, known to be crucial in a variety of Ca-agonists, noradrenaline antagonists, and an anti-histamines. Particularly, given the potential for our methodologies to access bisbenzyllic stereocenters, we became interested in their application to the synthesis of the drug (*R*)-tolterodine (**14**).



14

(R)-Tolterodine

Tolterodine is a potent muscarinic receptor antagonist (IC_{50} = 13 nm in isolated guinea pig bladder tissue) first described in 1989 by Jonsson et. al. at Pharmacia.[8] The dextrorotary enantiomer of this chiral 3,3-diphenylpropylamine exhibited 100-fold greater potency than the opposite antipode of the same compound, suggesting that a homochiral formulation would be beneficial in minimizing side-effects. Pharmacia would later launch tolterodine as the enantiopure hydrogen tartrate salt marketed under the name Detrol™, as a treatment for urge incontinence.[9]

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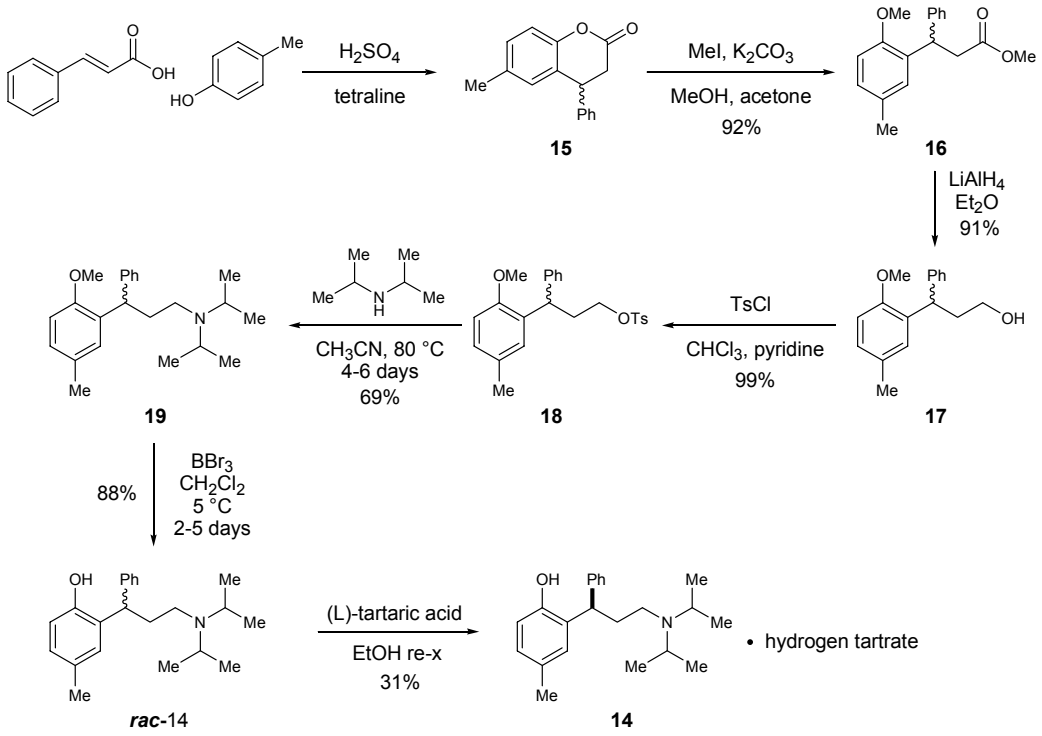
[8] Jonsson, N. A.; Sparf, B. A.; Mikiver, L.; Moses, P.; Nilvebrandt, L.; Glas, G. (Pharmacia & Upjohn Co.) EP 0325571, 1989, U.S. Patent 5,382,600, 1995.

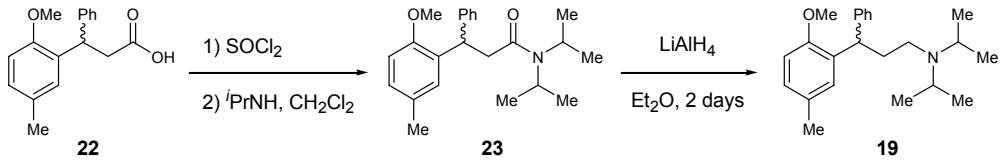
[9] Annual sales of Detrol exceed $900M.

In the initial report, two preparations of enantiopure **14** were described, both terminating in a moderate-yielding resolution *via* the tartrate salt (Schemes 7 & 8).[8] The first synthetic route commences with a condensation of cinnamic acid and *p*-cresol in a refluxing mixture of tetraline and concentrated sulfuric acid to form bicyclic lactone **15**. Ring-opening transesterification in basic methanol and concomitant formation of an aryl methyl ether with methyl iodide was accomplished in 92% yield. Ester **16** was then converted to tosylate **18** in two steps and 90% yield *via* alcohol intermediate **17**. Alkylating agent **18** was subjected to an excess of diisopropylamine at 80 °C in a sealed tube for several days to produce tertiary amine **19** in 69% yield. Deprotection of the phenol was accomplished with BBr_3 in CH_2Cl_2 to afford the target molecule, which readily formed a 1:1 salt with (L)-tartaric acid. Recrystallization of the diastereomeric salts from EtOH produced optically pure tolterodine hydrogen tartrate in 31% yield from the racemic material. Alternatively, intermediate **19** was intercepted in three steps from diphenyl propionic acid derivative **22** (Scheme 8). The overall yield for this sequence with this specific target was not reported, however, related compounds were transformed with efficiencies approaching 85%.

Scheme 7



Scheme 8

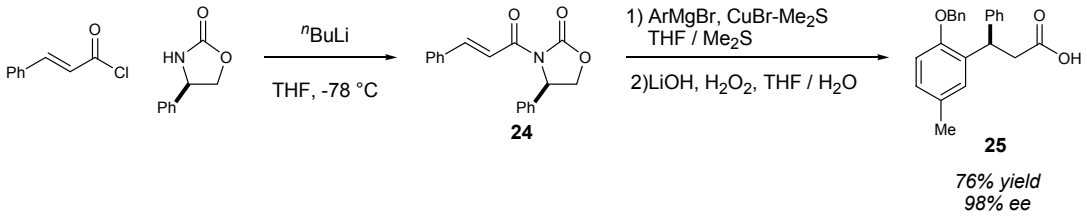


A number of alternative syntheses of **14** have been described since the initial reports from Pharmacia,[10] however, a practical enantioselective synthesis of tolterodine

[10] For examples see: a) *rac*-**12** via 3,6-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-ol as a key intermediate, Gage, J. R.; Cabaj, J. E. (Pharmacia & Upjohn Co.) U.S. Patent 5,922,914, 1999; b) (*R*)-enriched **12**, Andersson, P. G.; Hedberg, Ch. (Pharmacia & Upjohn Co.) WO 0149649, 2001; c) *rac*-**12** via hydroformylation, Botteghi, C.; Corrias, T.; Marchetti, M.; Paganelli, S.; Piccolo, O. *Organic Process Research & Development* **2002**, *6*, 379-383; d) (*R*)-enriched **12** via auxiliary-controlled metallobenzene addition, Andersson, P. G.; Schink, H. E.; Osterlund, K. *J. Org. Chem.* **1998**, *63*, 8067.

remains an elusive goal. In the only enantioselective synthesis of (*R*)-**14**, Andersson and co-workers describe a highly diasteroselective conjugate addition of aryl Grignard reagents to a *N*-cinnamoyl-oxazolidone mediated by CuBr (Scheme 9).[10d] Cleavage of the chiral auxiliary from the adduct in a separate step affords acid **25** in 76% yield from optically pure electrophile **24**. Three additional steps to install the tertiary amine and deprotect the phenol afford the title compound in 60% yield, 46% overall from the imide. While reasonable in the laboratory, use of a costly stoichiometric auxiliary which comprises 1/3 of the mass balance of the C-C bond-forming event and the extra step required to liberate the free acid are unattractive for production scale.

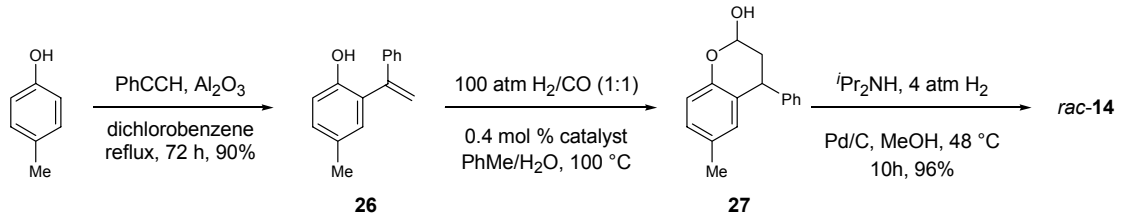
Scheme 9



Another intriguing approach to (*R,S*)-tolterodine highlights the difficulty of controlling formation of bisbenzyllic stereocenters by metal-catalyzed reduction (Scheme 10).[10c] Botteghi and co-workers efficiently access α-aryl-styrene **26** by zeolite-catalyzed condensation of *p*-cresol and phenyl acetylene. Rhodium-catalyzed hydroformylation of the 1,1-diaryl-alkene proceeds in exceptional yield (99%) when $[Rh(COD)Cl]_2$/TPPTS is employed as a catalyst, but none of numerous attempts to effect this transformation asymmetrically achieved a double-digit enantiomeric excess. The authors did, however,

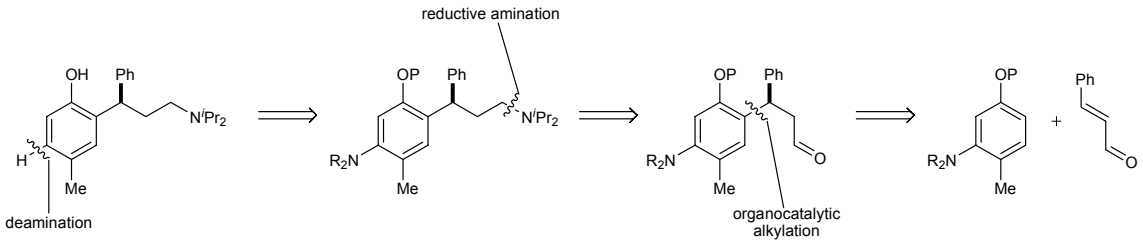
demonstrate the utility of exploiting an aldehyde oxidation state for the installation of the tertiary amine subunit, producing *rac*-**14** in 96% yield in one step from hemiacetal **27**.

Scheme 10

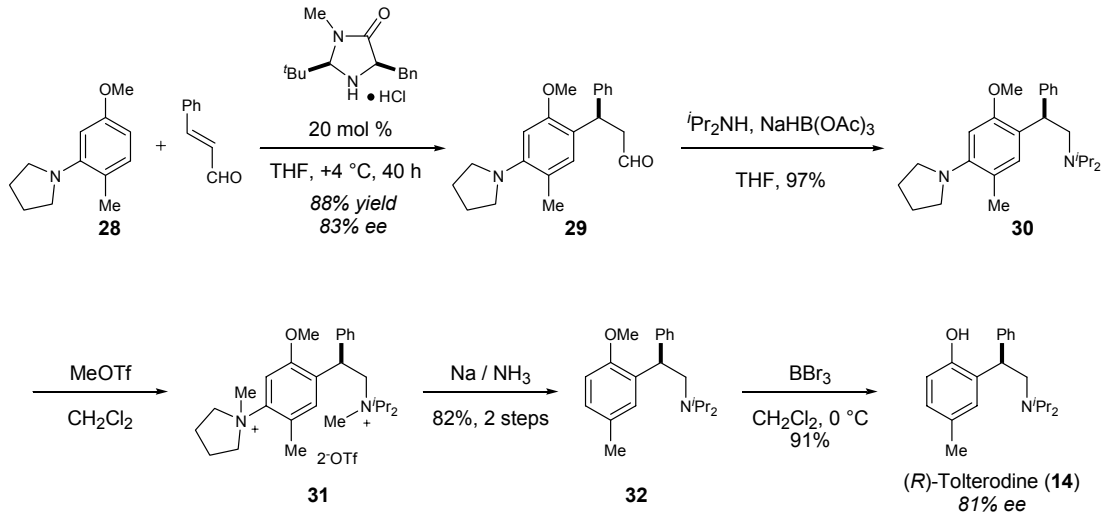


In our approach, retrosynthetic analysis of (*R*)-14 suggested that arene deamination and a reductive amination could link tolterodine to a chiral 3-(4-dialkylaminophenyl)-dihydrocinnamaldehyde (Scheme 11). In turn, such an intermediate might be readily accessed through an organocatalytic conjugate addition of an appropriately substituted anisidine to cinnamaldehyde. Besides the potential practical utility of an economical route to enantiopure tolterodine, this synthetic exercise would serve as a proving ground for the feasibility of our deamination methodology in presence of other tertiary amines.

Scheme 11



Scheme 12



Known 3-(1-pyrrolidino)-anisole **28** is prepared from commercially available 2-bromo-4-methyl-anisole and pyrrolidine (Scheme 12). Alkylation of anisidine 28 with cinnamaldehyde proceeds smoothly at +4 °C in the presence of (*R,R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one hydrochloride to afford the carbon core of tolterodine in good chemical yield and optical purity (88% yield, 91.5:8.5 enantiomer ratio). Direct conversion of the *β*-branched aldehyde to the diisopropylamine was accomplished by a reductive amination using sodium triacetoxyborohydride as the hydride source to afford the tertiary amine **30** in 97% yield. Attempts to selectively methylate the aniline nitrogen of **30** in the presence of the tertiary amine, or salts thereof, were unsuccessful, however, we were pleased to find that exhaustively methylated species **31** underwent direct conversion to *O*-methyl tolterodine when subjected to dissolving metal reduction. The net deamination procedure proceeds in an overall 82% yield for the two steps. And finally, deprotection of the phenol ether was effected by BBr_3 in good yield to afford (*R*)-tolterodine. Reverse phase chiral HPLC analysis proved that the integrity of the stereocenter set in the initial conjugate addition reaction had been preserved, within

experimental error, through the 4-step sequence affording enantioenriched **14** in 64% overall yield from anisidine **28**. Salt formation and recrystallization from methanol/acetone according to published procedure afforded tolterodine hydrogen tartrate (Detrol^{TM}) of >99% ee.

Conclusion

This report describes a novel method for the cleavage of dialkylamines from arenes using inexpensive reagents. The method does not require any other specific functionality on the aromatic amine substrates and is compatible with a range of oxygen, nitrogen, and carbon substituents. We believe this new transformation may serve to broaden the scope and selectivity of electrophilc aromatic substitution reactions. Furthermore, we have demonstrated the utility this transformation in concert with asymmetric organocatalytic Friedel-Crafts alkylation of activated benzenes by the asymmetric total synthesis of the pharmaceutical agent (*R*)-tolterodine.

Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Armarego and Perrin.[11] For detailed preparation of **1**, **6-8, 10**, see experimental section from Chapter 3. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Merck 230-400 mesh silica gel grade 9385 according to the method of Still.[12] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or potassium permanganate stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 spectrometers (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the University of California at Irvine Mass Spectral facility. High-performance liquid chromatography (HPLC) was performed on Hewlett-Packard

[11] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals;* 4th ed., Butterworth-Heinemann: Oxford, 1996.

[12] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

1100 Series chromatographs and columns as described below. Optical rotations were taken using a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C).

3-(4-Dimethylamino-2-methoxy-phenyl)-3-phenyl-propanol-*tert*-butyl-dimethylsilyl ether (9). 3-(4-Dimethylamino-2-methoxy-phenyl)-3-phenyl-propanol (0.250 g, 0.877 mmol, 1.0 equiv) was dissolved in dichloromethane (3.0 mL) and treated sequentially with triethylamine (0.148 mL, 1.05 mmol, 1.20 equiv) and *tert*-butyldimethylsilyl chloride (0.159 g, 1.05 mmol, 1.20 equiv). The reaction was stirred overnight and then loaded directly on a column of silica gel for purification. Gradient elution with 10–20% EtOAc in hexanes afforded the product as a pale yellow oil in 75% yield (244 mg, 0.659 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 4H, ArH), 7.20-7.13 (m, 2H, ArH), 6.35 (dd, *J* = 2.7, 8.8 Hz, 1H, ArH), 6.29 (d, J = 2.4 1H, ArH), 4.48 (t, *J* = 8.2 Hz. 1H, ArCH), 3.81 (s, 3H, OCH_3), 3.63 (t, *J* = 7.1 Hz, 2H, CH_2O), 2.97 (s, 6H, $N(CH_3)_2$), 2.33-2.24 (m, 2H, CHC**H$_2$**), 0.95 (s, 9H, $C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 150.5, 145.8, 128.3, 128.2, 125.7, 122.0, 105.1, 97.0, 62.1, 55.7, 41.2, 39.4, 38.5, 26.4, 18.8, -4.8. $[\alpha]_D$ = – 15.4 (c = 0.82, $CHCl_3$).

1-Methoxy-2-(3-*tert*-butyldimethylsiloxy-1-phenyl-propyl)-benzene (11). In a 25-mL pear-shaped flask equipped with a magnetic stir bar, **4a** (244 mg, 0.659 mmol, 1.00 equiv) was dissolved in iodomethane (0.41 ml, 6.6 mmol, 10 equiv). The neat reaction mixture was stirred at ambient temperature for 8 h at which time TLC analysis showed the starting material to be completely consumed. The iodomethane was removed *in vacuo* to furnish the quaternary ammonium iodide quantitatively (335 mg, 0.659 mmol) without need for further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.52 (d,

J = 2.7 Hz, 1H, ArH), 7.34 (d, *J* = 8.8, 1H, ArH), 7.28-7.12 (m, 6H, ArH), 4.57 (t, *J* = 7.7 Hz, 1H, ArCH), 4.05 (s, 3H, OCH_3), 3.99 (s, 9H, $N(CH_3)_3$), 3.55-3.49 (m, 2H, CH_2O), 2.20 (q, *J* = 7.7 Hz, 2H, CHC**H₂**), 0.95 (s, 9H, $C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 146.4, 143.0, 137.0, 128.9, 128.6, 128.3, 126.6, 110.0, 103.8, 61.2, 58.5, 58.0, 39.7, 37.6, 26.2, 18.6, -5.0. A portion of the quaternary ammonium salt (100 mg, 0.195 mmol, 1.00 equiv) was dissolved/suspended in tetrahydrofuran (3.0 mL) and added to a rapidly stirring solution of sodium (18.0 mg, 0.782 mmol, 4.0 equiv) in liquid ammonia (approx. 25 mL) at –78 °C. After 5 min, the cold reaction mixture was treated with benzylmethyl ether (0.2 mL) and the deep blue color was supplanted almost immediately by a bright orange. The mixture was then treated with isopropanol (2 mL) and stirred at –78 °C for another 5 minutes by which time all color had dissipated from the reaction. Diethyl ether (20 mL) and saturated aqueous ammonium chloride (10 mL) were added carefully and the reaction vessel was allowed to warm to room temperature. The organic phase was then dried over Na_2SO_4, concentrated and the residue purified by silica gel chromatography. Gradient elution with 2–10% EtOAc in hexanes provided the deaminated product in 96% yield (61.2 mg, 0.187 mmol). IR (film) 3027, 2954, 2929, 2856, 1601, 1492, 1462, 1438, 1244, 1100, 1051, 945.9, 834.8, 11\\775.2, 751.9, 698.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.12 (m, 7H, ArH), 6.93 (dt, *J* = 1.1, 7.7 Hz, 1H, ArH), 6.84 (d, *J* = 8.7 Hz, 1H, ArH), 4.58 (t, *J* = 7.7 Hz, 1H, ArCH), 3.78 (s, 3H, OCH_3), 3.58 (t, *J* = 7.1 Hz, 1H, C**H₂**O), 2.27 (dq, *J* = 0.9, 6.6 Hz, 2H, CHC**H₂**), 0.90 (s, 9H, $C(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 144.9, 142.0, 133.3, 128.7, 128.5, 128.4, 128.3, 127.9,

127.3, 16.1, 126.0, 61.8, 55.7,39.8, 38.3, 38.2, 26.3, 18.7, –4.9. $[\alpha]_D$ = – 15.7 (c = 0.977, $CHCl_3$).

4-Methyl-3-(1-pyrrolidino)-anisole (28). A solution of *n*-BuLi (2.5 M in hexanes, 30.0 mL, 75.0 mmol, 1.50 equiv) was added dropwise to a stirring solution of pyrrolidine (6.30 mL, 100 mmol, 2.00 equiv) in THF (75 mL) under argon at 0 °C. Thirty minutes after addition was begun, the ice-water bath was removed and the reaction allowed to warm to ambient temperature. One hour after the bath was removed, 2-bromo-4-methyl-anisole (10.0 g, 49.7 mmol, 1.00 equiv) was added very carefully. (Warning: rapid addition of aryl bromide can result in a violent exotherm after an induction period of 1-3 minutes!) The reaction mixture was stirred at ambient temperature for 24 h and then acidified slowly with conc. aq. HCl. The mixture was diluted with Et_2O and extracted twice with water. The aqueous layers were combined and treated with 4N aq. NaOH until pH of the solution exceeded 10. The resulting mixture was then extracted with three portions of CH_2Cl_2. This organic solution was dried over sodium sulfate, concentrated, and purified by silica gel chromatography. Gradient elution in 1–10% EtOAc in hexanes afforded the product as a pale yellow oil in 37% yield (3.56 g, 18.6 mmol).

(*R*)-3-(2-methoxy-5-methyl-4-(1-pyrrolidino)-phenyl)-dihydrocinnamaldehyde (29). A dry 2-dram vial equipped with a magnetic stir bar was charged (2*R*,5R*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one • hydrochloride (113 mg, 0.400 mmol, 0.200 equiv) and THF (2.0 mL). Cinnamaldehyde (0.756 mL, 6.00 mmol, 3.00 equiv) was added *via* syringe and the reaction vessel was cooled to 0 °C in an ice-water bath. Then, 4-methyl-3-(1-pyrrolidino)-anisole (0.324 mL, 2.00 mmol,

1.00 equiv) was added slowly *via* syringe so as not to raise the internal temperature of the reaction. The reaction was allowed to warm to +4 °C over the course of 8 h and then stirred for an additional 32 h. At that time, the reaction mixture was diluted with 50 mL of Et_2O and extracted twice with 50 mL 1N aq. HCl. The combined aqueous layers were washed with 2 x 50 mL Et_2O. The aqueous layer was then neutralized with 2N aq. NaOH (50 mL) and extracted with 2 x 150 CH_2Cl_2. These organic extracts were combined, dried over Na_2SO_4 and concentrated in vacuo to give a red-orange oil. Purification of the crude residue by silica gel chromatography (gradient elution: 5-20% EtOAc in hexanes) afforded the product as a colorless oil in 88% yield (571 mg, 1.77 mmol); 83% ee. IR (film) 2959, 2860, 2817, 1723, 1611, 1569, 1505, 1445, 1403, 1320, 1222, 1114, 1022, 700.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.2 Hz, 1H, CHO), 7.28-7.32 (m, 4H, ArH), 7.16-7.24 (m, 1H, ArH), 6.80 (s, 1H, ArH), 6.44 (s, 1H, ArH), 4.94 (t, *J* = 8.0 Hz, 1H, Ar_2CH), 3.80 (s, 3H, OCH_3), 3.19-3.23 (m, 4H, $N(CH_2)_2$), 3.09 (dd, *J* = 2.2, 8.2 Hz, 2H, C**H₂**CHO), 2.23 (s, 3H, $ArCH_3$), 1.90-2.00 (m, 2H, CH_2**(CH₂)₂**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 155.3, 149.0, 143.8, 1314, 128.6, 128.2, 126.4, 122.7, 120.2, 99.8, 55.8, 51.3, 49.0, 38.3, 25.4, 20.5; requires *m/z* 323.1885 for $[M]^+$, found *m/z* 323.1896. $[\alpha]_D$ = + 20.9 (c = 0.95, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiralpak AD column (0.46 x 25 cm) and AD guard (0.46 x 5 cm) (5.0% isopropanol/hexanes, 1 mL/min); *S* isomer t_r = 13.6 min, *R* isomer t_r = 16.1 min.

(*R*)-Diisopropyl-[3-(2-methoxy-5-methyl-4-pyrrolidin-1-yl-phenyl)-3-phenyl]-amine (30). In a dry 10 mL round-bottom flask equipped with a magnetic stirbar, a solution of **29** (571 mg, 1.77 mmol, 1.00 equiv) in THF (4.0 mL) was treated with

diisopropylamine (0.722 mL, 3.54 mmol, 2.00 equiv) and sodium triacetoxyborohydride (0.746 g, 3.54 mmol, 2.00 equiv). The reaction mixture was stirred for 6 h at ambient temperature and then diluted with 50 mL of Et_2O. The suspension was then treated with 25 mL aq. 2N NaOH. The layers were separated and the aqueous phase was extracted with 2x 20 mL Et_2O. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the product as a colorless oil in 97% yield (702 mg, 1.71 mmol) without further purification. IR (film) 2964, 2871, 2806, 1611, 1502, 1458, 1440, 1354, 1317, 1220, 1114, 699.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.32 (m, 4H, ArH), 7.12 (tt, *J* = 2.2, 7.1 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 6.41 (s, 1H, ArH), 4.24 (t, *J* = 7.7 Hz, 1H, Ar_2CH), 3.74 (s, 3H, OCH_3), 3.10-3.22 (m, 4H, $N(CH_2)_2$), 2.98 (dt, *J* = 6.6, 6.6 Hz, 2H, $C\mathbf{H_2}N(i\text{-}Pr)_2$), 2.26-2.38 (m, 2H, $N(C\mathbf{H})_\mathbf{2}$), 2.24 (s, 3H, $ArCH_3$), 1.90-2.00 (m, 2H, $CH_2\mathbf{(CH_2)_2}CH_2$), 0.94 (d, *J* = 6.5 Hz, 12H, $N(CH(C\mathbf{H_3})_\mathbf{2})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 148.1, 145.9, 130.8, 128.3, 128.2, 125.6, 125.3, 120.3, 100.1, 56.0, 51.3, 49.3, 44.8, 41.3, 37.6, 25.3, 21.0, 20.9, 20.3; requires *m/z* 408.3141 for $[M]^+$, found *m/z* 408.3148. $[\alpha]_D$ = + 1.20 (c = 0.48, $CHCl_3$).

(*R*)-Diisopropyl-[3-(2-methoxy-5-methyl-phenyl)-3-phenyl]-amine (31). In a dry 10 mL round-bottom flask equipped with a magnetic stirbar, methyl trifluoromethanesulfonate (0.60 mL, 5.3 mmol, 3.00 equiv) was added to a stirring solution of **30** (702 mg, 1.71 mmol, 1.00 equiv) in CH_2Cl_2 (8.8 mL). The resulting mixture was stirred at ambient temperature for 20 h. The volatiles were then evaporated to afford 1.34 g of ammonium salt **4,** which was used without further purification. ^1H NMR (300 MHz, CD_3OD) δ 7.43 (s, 1H, ArH), 7.19-7.39 (m, 5H, ArH), 7.17 (s, 1H, ArH), 4.46-4.55 (m, 2H, $ArN(C\mathbf{H}H)_\mathbf{2}$), 4.32 (dd, *J* = 6.0, 9.3 Hz, 1H, Ar_2CH), 3.87-4.06

(m, 4H, ArN(CH**H**)$_{\mathbf{2}}$, CHCH$_2$C**H**$_{\mathbf{2}}$), 3.91 (s, 3H, ArNCH$_3$), 3.41 (s, 3H, OCH$_3$), 3.23-3.35 (m, 1H, CHC**H**$_2$), 3.02-3.14 (m, 1H, CHC**H**$_2$), 2.86 (s, 3H, NC**H**$_{\mathbf{3}}$(iPr)$_2$), 2.63 (s, 3H, ArCH$_3$), 2.49-2.65 (m, 2H, N(C**H**)$_{\mathbf{2}}$), 2.31-2.38 (m, 4H, NCH$_2$**(CH$_2$)$_2$**), 1.21-1.39 (m, 12H, N(CH(C**H**$_{\mathbf{3}}$)$_{\mathbf{2}}$)$_{\mathbf{2}}$). A solution of sodium (393 mg, 17.1 mmol, 10.0 equiv) in freshly condensed liquid ammonia (100 mL) was prepared in a 3-neck round-bottomed flask equipped with a cold finger and a mechanical stirrer. The flask was maintained at –78 °C using a dry ice/acetone bath. To this stirring blue mixture, a homogeneous solution of salt **31** (1.71 mmol, 1.00 equiv) in THF (12 mL) and DMF (0.6 mL) was added in one portion. After 10 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate. The mixture was diluted with diethyl ether and stirred at ambient temperature until most of the ammonia had evaporated. The resulting ether suspension was diluted with water and the phases were separated. The aqueous layer was extracted with ether (x2) and the combined organics were washed with brine (x2) and dried over sodium sulfate. Concentration and subsequent purification via silica gel chromatography (25% EtOAc / 1% triethylamine / 74% hexanes) afforded **5** in 82% yield (478.1 mg, 1.41 mmol). IR (film) 2963, 2867, 2834, 1494, 1456, 1381, 1360, 1241, 1162, 1115, 1036, 804.0, 735.8, 698.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.32 (m, 4H, ArH), 7.14 (tt, *J* = 1.8, 6.9 Hz, 1H, ArH), 7.08 (d, *J* = 2.3 Hz, 1H, ArH), 6.95 (dd, *J* = 1.5, 8.5 Hz, 1H, ArH), 6.72 (d, *J* = 8.1 Hz, 1H, ArH), 4.36 (t, *J* = 7.7 Hz, 1H, Ar$_2$CH), 3.75 (s, 3H, OCH$_3$), 2.98 (dt, *J* = 6.6, 6.6 Hz, 2H, C**H**$_2$N(*i*-Pr)$_2$), 2.23-2.38 (m, 2H, N(C**H**)$_{\mathbf{2}}$), 2.27 (s, 3H, ArCH$_3$), 2.12-2.2.17 (m, 2H, CH$_2$**(CH$_2$)$_2$**CH$_2$), 0.94 (d, *J* = 6.5 Hz, 12H, N(CH(C**H**$_{\mathbf{3}}$)$_{\mathbf{2}}$)$_{\mathbf{2}}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 145.4, 133.7, 129.8, 128.6, 128.4,

128.3, 127.4, 125.9, 110.9, 55.8, 49.0, 44.4, 41.5, 37.3, 21.0, 20.8; requires *m/z* 339.2562 for $[M]^+$, found *m/z* 339.2564. $[\alpha]_D$ = - 6.14 (c = 0.95, $CHCl_3$).

Tolterodine: **(*R*)-Diisopropyl-[3-(2-hydroxy-5-methyl-phenyl)-3-phenyl]-amine (14).** In a dry 10 mL round-bottom flask equipped with a magnetic stirbar, a solution of **5** (478 mg, 1.41 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was cooled to –78 °C. A solution of boron tribromide (1.00 M in CH_2Cl_2, 2.71 mL, 2.71 mmol, 1.91 equiv) was added dropwise over the course of 30 min. The resulting solution was stirred for an additional 30 min before the reaction vessel was transferred to an ice-water bath. The reaction was maintained at 0 °C for 1 h and, cooled back down to –78 °C, and quenched with methanol. The mixture was then allowed to warm to ambient temperature and neutralized with saturated aqueous $NaHCO_3$. It was then diluted with 50 mL of CH_2Cl_2 and treated with 75 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with 3 x 50 mL CH_2Cl_2.. The organics were combined, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (25-50% *i*-PrOH/CH_2Cl_2) to afford tolterodine in 91% yield (418 mg) as a colorless oil which solidified on standing; 81% ee. This material was spectroscopically identical to the literature compound in all respects.[8,10] The enantiomeric ratio of the product was determined by HPLC ChromTech Chiral-AGP (0.2 x 10 cm) (isopropanol/0.01M potassium phosphate buffer 0.22 mL/min); *S* isomer t_r = 13.6 min, *R* isomer t_r = 16.1 min. The tartrate salt (**7**) was prepared and recrystallized to optical purity as previously described.[10]