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Development and Applications of N-Sulfinyl Organocatalysts

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Development and Applications of *N*-Sulfinyl Organocatalysts

By

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University of California, Berkeley

Committee in charge:

Professor Jonathan A. Ellman, Chair
Professor Richmond Sarpong
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Abstract

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The development of new catalysts for asymmetric organic transformations is a broad and important research goal in modern synthetic organic chemistry. The use of chiral ligands as a source of asymmetric induction in metal-catalyzed reactions has been a traditional focus of this field. One class of chiral ligands is those which incorporate enantiomerically pure sulfinamides. Chapter 1 provides an overview of this area of research. Also included are examples of sulfinamide-based ligands for reactions involving stoichiometric metals, as well as a few examples of sulfinamide-based organocatalysts that have been reported in the literature. The literature reviewed serves as an important foundation for the research described in Chapters 2 and 3.

Asymmetric organocatalysis, the use of chiral small molecules as metal-free catalysts, has developed into an area of intense research in the past decade. One mode of substrate activation by organocatalysts is hydrogen bonding. The urea/thiourea scaffold is one of the most effective and well developed types of hydrogen bonding organocatalysts. The acidity (and corresponding strength of the hydrogen bonding interaction) of the hydrogen bond donor is an important consideration for the development of efficient catalysts. Chapter 2 details the development of organocatalysts that incorporate an *N*-sulfinyl urea as a hydrogen bond donor. In these catalysts, the sulfinyl substituent serves both to acidify the urea N-H bond and to act as a source of asymmetric induction by virtue of the sulfur-based chirality that is presented proximal to the hydrogen bond donor. The application of these catalysts to two different nucleophilic addition reactions is described.

Organocatalysts that incorporate a nucleophilic amine have also been developed extensively in recent years. One of the earliest reported examples of this type of catalysis was the use of proline as a catalyst for the enantioselective intermolecular aldol reaction via a nucleophilic enamine intermediate. While the amine may be considered the primary catalytic site, the carboxylic acid has also been implicated in the catalytic cycle, and is proposed to provide a key hydrogen bonding interaction in the enantiodetermining step of the reaction. Chapter 3 describes the development of an *N*-sulfinyl proline amide as a novel and superior catalyst for the aldol reaction, again demonstrating the utility a sulfinyl N-H as a chiral hydrogen bond donor.

Chapter 1. A Survey of Sulfinamide Based Ligands and Catalysts.

Examples of ligands and catalysts that incorporate sulfinamides are reviewed. This material is adapted with permission from a larger review (Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of *tert*-Butanesulfinamide. *Chem Rev.* **2010**, ASAP *DOI: 10.1021/cr90038t*).

Introduction

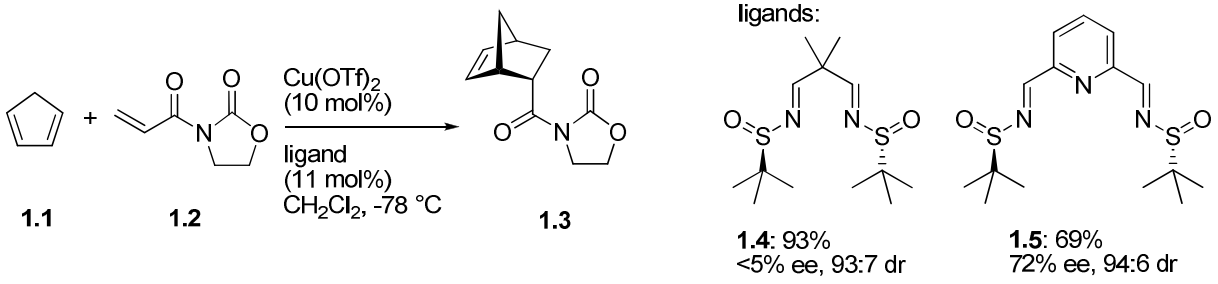
The development of new catalysts for asymmetric transformations has been a longstanding goal in synthetic organic chemistry research. Chiral ligands for metal-catalyzed transformations have been designed that incorporate a wide variety of types of chirality, including traditional carbon-based chiral centers, axial chirality, and more recently, heteroatomic chiral centers, including phosphorus[1] and sulfur.[2,3]

The ease of synthesis, stability, resident chirality, and potential for metal coordination of the S, N and O atoms of *N*-sulfinyl imines and amines has provided excellent opportunities for the development of *N*-sulfinyl-based ligands for asymmetric catalysis. In the past decade, several research groups have reported the development of such ligands. This review will provide a comprehensive overview of this area of research, including both catalytic and stoichiometric metal-ligand complexes, catalytic ligands used with stoichiometric metal reagents, and sulfinamide-based organocatalysts.

Catalytic Metal-Ligand Complexes

In 2001, Ellman and coworkers published the first study on the use of *N*-sulfinyl imine ligands for asymmetric Lewis acid catalysis of the Diels-Alder reaction.[4] This work was expanded upon in a subsequent full paper.[5] Initially, ligands such as **1.4** and **1.5** (Scheme 1.1) were designed by analogy to the highly successful bisoxazoline ligands.[6]The synthesis of these *C*2-symmetric *N*-*tert*-butanesulfinyl imine ligands was carried out by condensing the appropriate bis-aldehyde precursors with enantiomerically pure *tert*-butanesulfinamide, utilizing $Ti(OEt)_4$ or $CuSO_4$ as a Lewis acid and water scavenger. Metal complexes of these ligands (along with several others) were tested in the Diels-Alder reaction of cyclopentadiene with *N*-acryloyl oxazolidinone **1.2**. This transformation was chosen because it has served as a benchmark reaction for the evaluation of asymmetric Lewis acid catalysts.[7] While the $Cu(OTf)_2$ complex of ligand **1.4** provided high conversion, low enantioselectivity was obtained. The corresponding complex of ligand **1.5** was less active, but provided the desired product with moderate enantioselectivity.

Scheme 1.1 Initial Ligand Screening for the Diels-Alder Reaction



Extensive ligand optimization led to the design of bis(sulfinyl)imidoamidine ligand **1.9**. The synthesis of this ligand was carried out in three straightforward steps (Scheme 1.2). As the $Cu(SbF_6)_2$ complex, this ligand was found to efficiently catalyze the Diels-Alder reaction with very high stereoselectivity. The substrate scope of this reaction, outlined in Table 1.1, includes the reaction of cyclopentadiene (entries 1-4) or cyclohexadiene (entry 5) with several dienophiles with varying electronic properties, giving products with high selectivity. Modulation of

temperature and extended reaction times were successful in providing acceptable yields for less active substrates.

Scheme 1.2. Preparation of Bis(sulfinyl)imidoamidine Ligand **1.9**

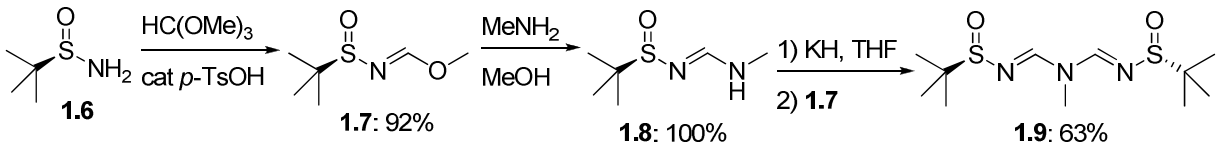
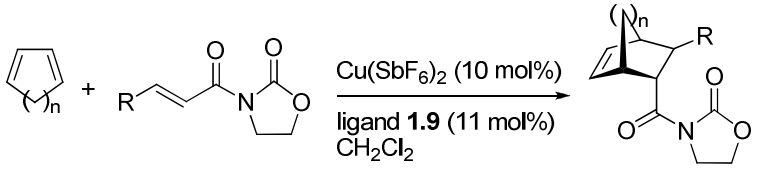


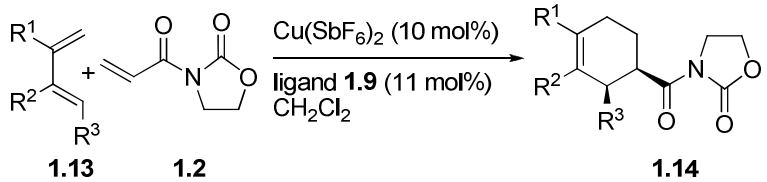
Table 1.1 Cu-catalyzed Diels-Alder Reaction with Ligand **1.9**

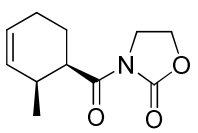


entry	n	R	time(h)	temp (°C)	yield (%)	ee (%)	dr (%)
1	1	H	0.1	-78	96	98	99:1
2	1	Me	8	-40	76	97	98:2
3	1	Ph	16	0	58	94	95:5
4	1	CO_2Et	2	-78	85	96	97:3
5	2	H	16	0	50	90	98:2

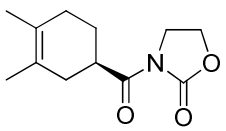
The scope of the reaction, particularly for acyclic dienes, was further investigated (Scheme 1.3). Although terminal diene substitution resulted in poor yields and selectivities, internal substitutions were well tolerated. However, internal substitution with increased steric bulk resulted in diminished enantioselectivity.

Scheme 1.3 Diels-Alder with Acyclic Dienes

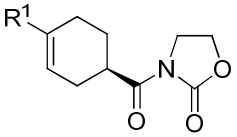




1.14a: 18%,
41% ee, 2:1:0.4 dr



1.14b:
96%, 92% ee



1.14c: R^1 = Me; 83%, 93% ee
1.14d: R^1 = Ph; 87%, 45% ee
1.14e: R^1 = $CH_2OTBDPS$;
33%, 62% ee

The crystal structure of a $CuCl_2$-ligand **1.9** complex was obtained, revealing a M_2L_4-helicate structure in which each ligand is coordinated to a copper center via the oxygen of the sulfinyl group (Figure 1.1). Additionally, IR data suggests that in both the solid state and in freshly prepared solutions of the $Cu(SbF_6)_2$-**1.9** complex, the primary species is oxygen bound. Nonlinearity was also observed with respect to the enantiomeric purity of the ligand, [8] suggesting that the active catalytic species is not a simple monomer.

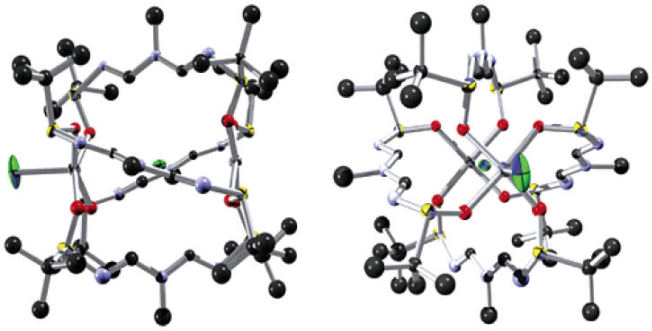
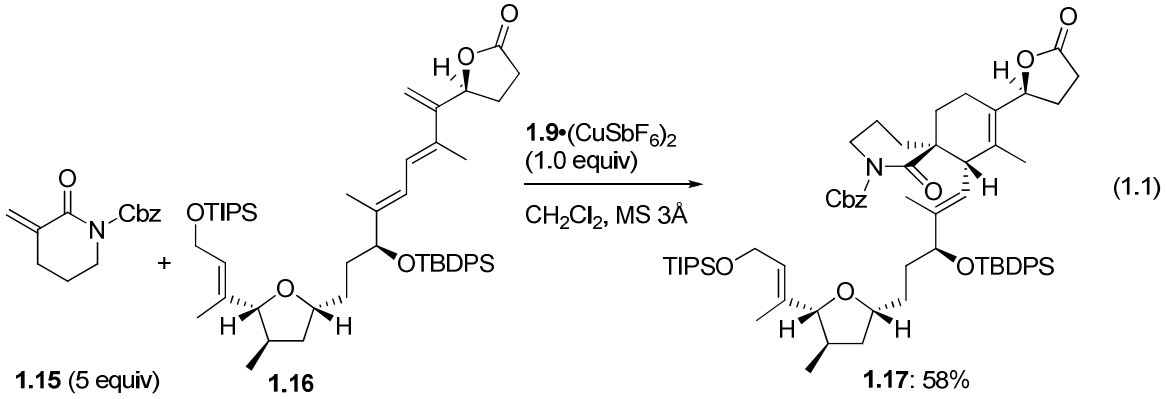


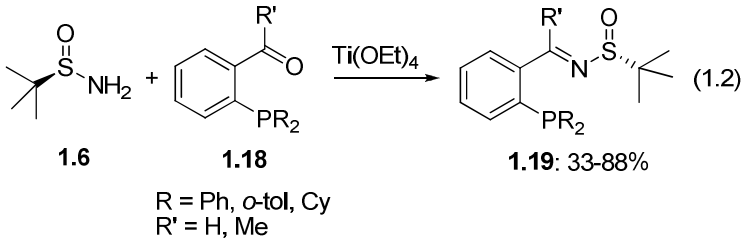
Figure 1.1 Crystal structure of the $CuCl_2$ – **1.9** complex. The $Cu_2Cl_6^-$ counterion was omitted for clarity.[5]

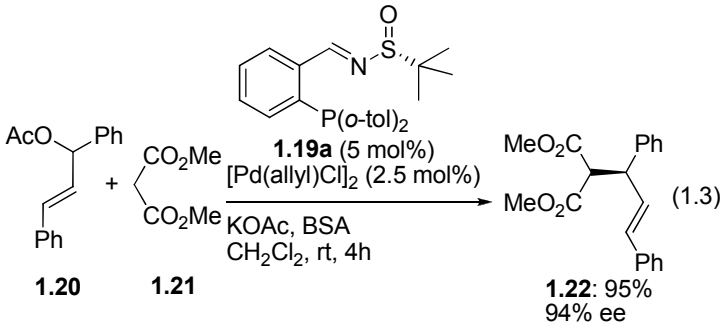
The utility of this catalyst in complex molecule synthesis was demonstrated by Murai and coworkers, who applied **1.9** to the synthesis of **1.17**, the spirocyclic core of gymnodimine. In this transformation a single diastereomer of the Diels-Alder product was observed (eq 1.1).[9]



(1.1)

A variety of ligands incorporating both phosphorus and *tert*-butanesulfinamide as binding elements have been developed.[10] The first report in this area was the development of *P*,*N*-sulfinyl imine ligands for Pd-catalyzed allylic alkylation.[11] In this study, the *N*-*tert*-butanesulfinyl imines were prepared via $Ti(OEt)_4$-mediated condensation of phosphine-containing aldehydes to give ligands of type **1.19** (eq 1.2). A crystal structure was obtained of a Pd-π-allyl complex of **1.19** (R = Ph), verifying the bidentate binding mode of this ligand via the phosphorus and the imine nitrogen.[11] Optimization of catalyst structure and reaction conditions revealed that imine ligand **1.19a** was capable of providing allylic alkylation product **1.22** (eq 1.3) in high yield and with excellent enantioselectivity.

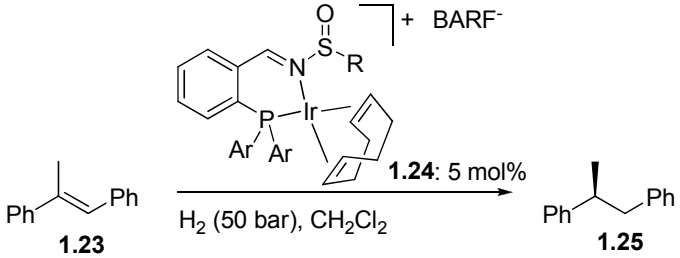




Having established the ability of *P*,*N*-sulfinyl imine ligands to induce enantioselectivity in transition metal-catalyzed reactions, Ellman and coworkers turned their attention to the application of this ligand class to Ir-catalyzed asymmetric hydrogenation.[12] Although only the *tert*-butanesulfinyl and *p*-toluenesulfinyl substituents had been explored in the allylic alkylation study (*vide supra*), a wide variety of *N*-sulfinyl substituents were investigated for the hydrogenation reaction to determine the steric and electronic influence of the sulfinyl group in this modular ligand scaffold. The imine ligands were prepared by condensation of the corresponding aldehyde and sulfinamide mediated by $Ti(OEt)_4$ (75-95% yield). The Ir complexes **124a-g** were then prepared in a high-yielding, two step, one-pot procedure involving ligand complexation with $[Ir(cod)Cl]_2$ followed by replacement of the chloride with the noncoordinating $BARF^-$ ($[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$) counterion (90-95% yield).

These complexes were then tested in the catalytic hydrogenation of an unfunctionalized olefin, α-methylstilbene **1.23** (Table 1.2). Under the optimized reaction conditions, complex **1.24a**, derived from ligand **1.19a** that was previously reported for Pd-catalyzed allylic alkylation, provided quantitative conversion to product **1.25** with very high enantioselectivity (entry 1). Although it was expected that increasing the steric bulk of the *N*-sulfinyl substituent would further improve the enantioselectivity observed for this transformation, unfortunately, neither the adamantanesulfinyl nor 3-ethylpentanesulfinyl substituents were effective towards this goal and resulted in both attenuated reactivity and selectivity (entries 2 and 3). The catalyst bearing the *p*-toluenesulfinyl substituent did provide quantitative conversion, but the product was obtained as a nearly racemic mixture (entry 4). The mesitylenesulfinyl substituent had the same detrimental effect on enantioselectivity and also resulted in much lower conversion (entry 5). Examination of the effects of substitution on the phosphorus aryl groups confirmed that the *o*-tolyl substituent was required for high conversion and selectivity (entries 1, 6, and 7), consistent with previous studies with oxazoline-based *P,N* ligands.[13]

Table 1.2 Hydrogenation of α-Methylstilbene

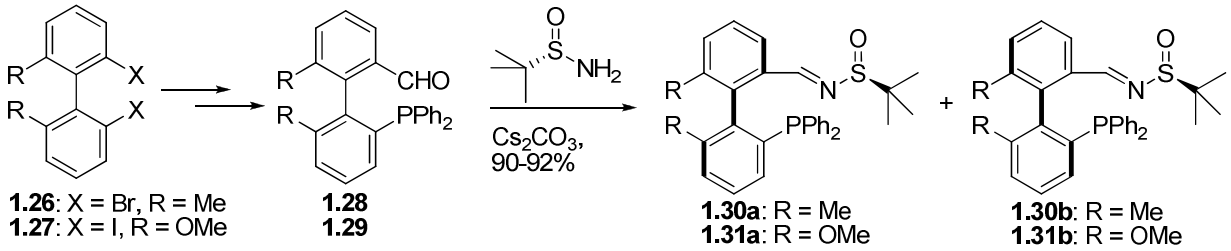


entry	catalyst	R	Ar	conv (%)	ee (%)
1	**1.24a**	(*R*)-*t*Bu	*o*-tol	>99	94
2	**1.24b**	(*S*)-1-adamantyl	*o*-tol	58	84
3	**1.24c**	(*S*)-3-ethylpentane	*o*-tol	75	84
4	**1.24d**	(*S*)-*p*-tolyl	*o*-tol	>99	5
5	**1.24e**	(*S*)-mesitylene	*o*-tol	52	7
6	**1.24f**	(*R*)-*t*Bu	3,5-Me_2Ph	53	57
7	**1.24g**	(*R*)-*t*Bu	Ph	20	55

Recently, Qin and coworkers have reported the development of biphenyl *P*,*N*-sulfinyl imine ligands, and their application in Pd-catalyzed addition of arylboronic acids to *N*-benzyl isatin.[14] While previously explored *N*-sulfinyl imine ligands relied solely on the chirality at sulfur for asymmetric induction, these novel structures (**1.30** and **1.31**, Scheme 1.4) incorporate the chiral sulfinyl group in conjunction with an axially chiral biaryl component. The multi-step synthesis of these ligands, beginning with *C*2-symmetric biaryl compounds **1.26** and **1.27**, proceeded via Cs_2CO_3-mediated condensation of enantiomerically pure *tert*-butanesulfinamide with biaryl aldehydes **1.28** and **1.29**, followed by chromatographic separation of the imine diastereomers.

Reaction of ligand **1.30a** with $[Pd(allyl)Cl]_2$ followed by counterion replacement of the Cl^- with SbF_6^- yielded a Pd-π-allyl complex that was analyzed by X-ray crystallography, allowing assignment of the stereochemistry of the ligand as well as confirming the expected *P*,*N*-chelate binding mode.

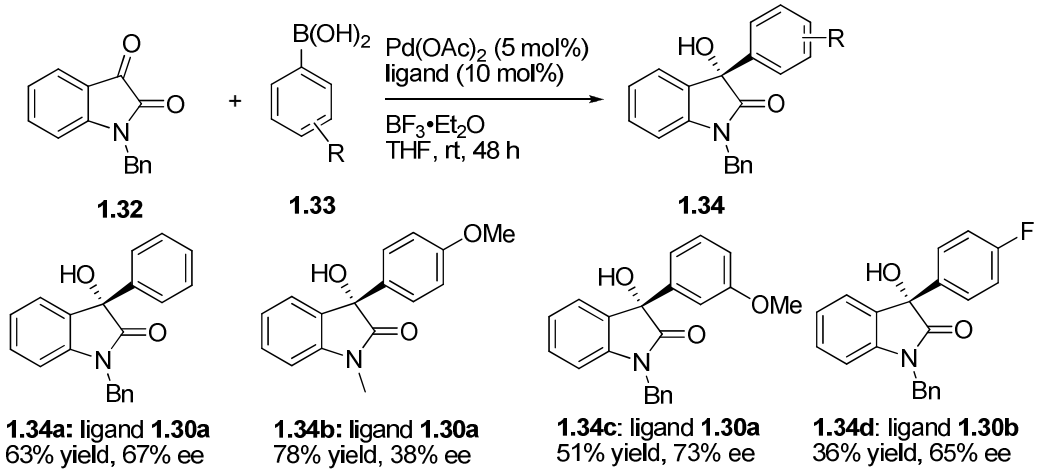
Scheme 1.4 Synthesis of Biaryl *P*,*N* Ligands



Biaryl ligands **1.30** and **1.31** were screened in the transition-metal catalyzed addition of phenylboronic acid to *N*-benzyl isatin **1.32** (Scheme 1.5). After optimization of reaction conditions, ligand **1.30a** was identified as the most active for this transformation. Comparison of the performance of ligand diastereomers **1.30a** and **1.30b** revealed that product stereochemistry was predominantly controlled by the ligands' axial chirality, rather than the sulfinyl stereocenter.

A brief survey of arylboronic acid coupling partners demonstrated the synthesis of **1.34a-d** in variable yields and with moderate selectivities.

Scheme 1.5 Arylboronic Acid Addition to Isatins



Adolfsson and coworkers investigated the use of amino-acid derived sulfinamide ligands of general structure **1.35** (Figure 1.2) in the enantioselective transfer hydrogenation of ketones.[15] Ligand **1.35a**, bearing the *N-tert*-butanesulfinyl group, proved to be inferior to the analogous *p*-toluenesulfinyl ligand **1.35b** in the Rh-catalyzed transfer hydrogenation of acetophenone (Scheme 1.6), providing the product alcohol **1.37** with inferior conversion (18% vs 87%) and enantioselectivity (34% vs. 43%). Further optimization of the reaction conditions, including additives, transition metal precatalyst, and diamine ligand structure, provided a set of reaction conditions (with *p*-toluenesulfinyl amine ligand **1.35c**) that allowed this transformation to take place with high enantioselectivity. The scope of the reaction was explored under the optimized conditions, providing products **1.37a-e** from a variety of substituted acetophenones (Scheme 1.7).

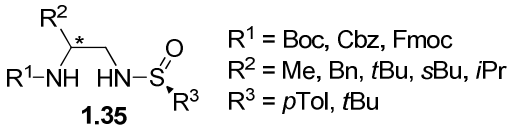
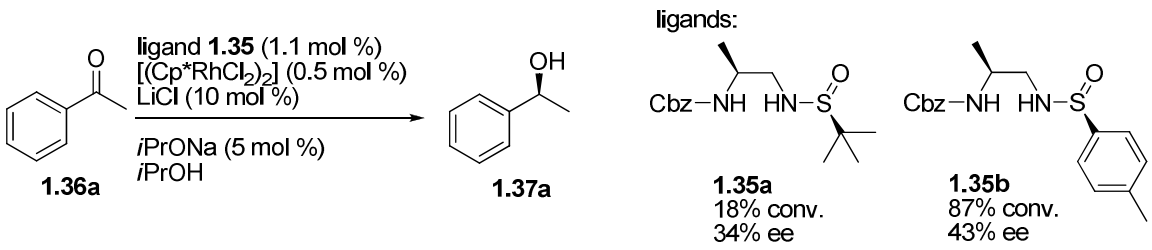
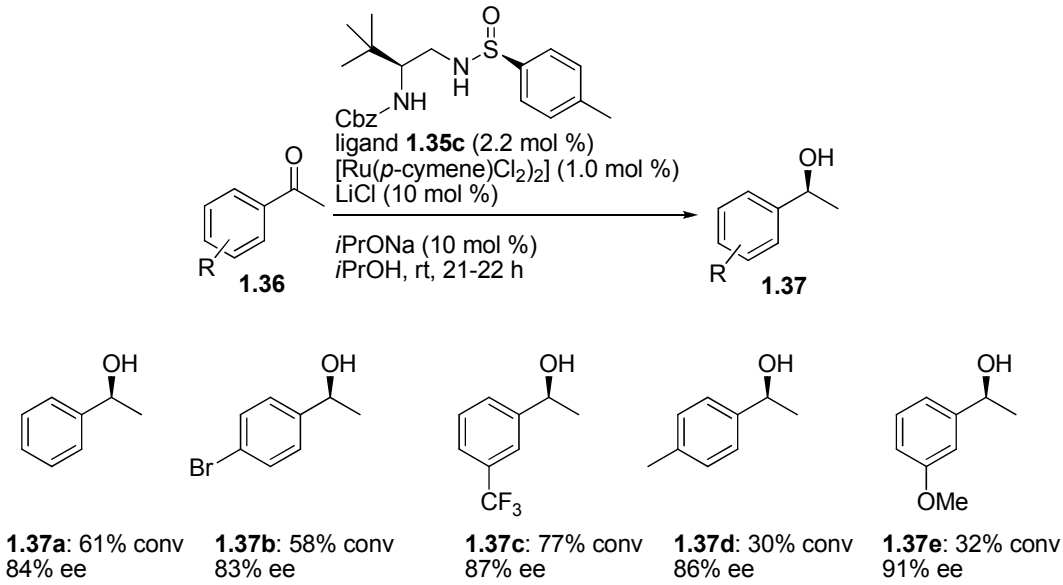


Figure 1.2 Amino-Acid Derived Sulfinyl Ligands

Scheme 1.6 Initial Ligand Screening in Transfer Hydrogenation of Acetophenone



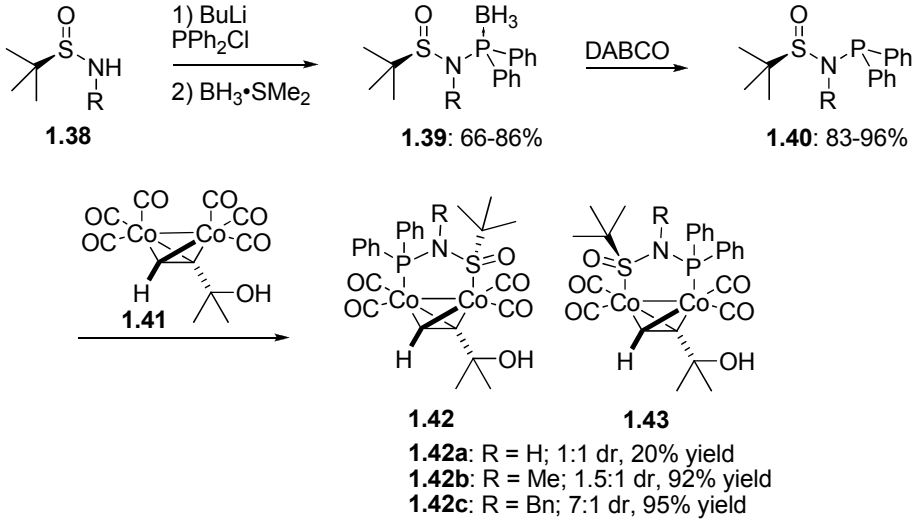
Scheme 1.7. Transfer Hydrogenation of Substituted Acetophenones



Metal-Ligand Complexes as Stoichiometric Reagents

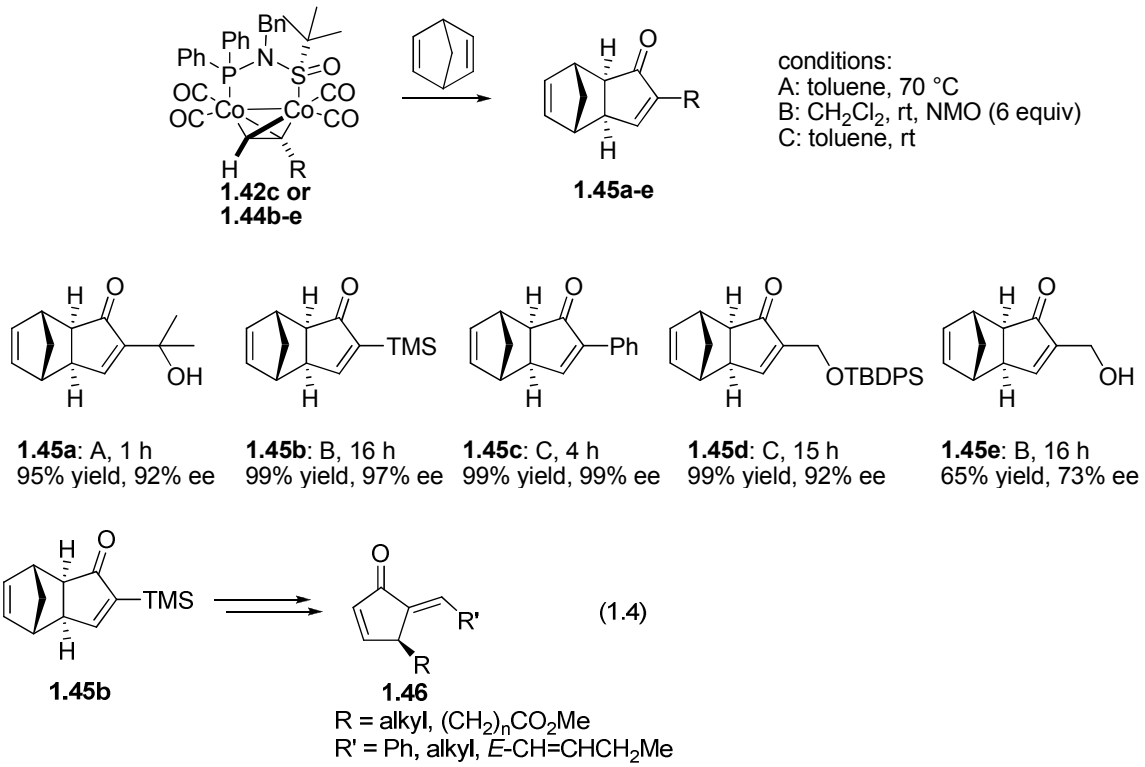
Riera, Verdaguer, and coworkers have developed a novel class of *N*-phosphino-*tert*-butanesulfinamide (PNSO) ligands **1.40** (Scheme 1.8).[16] The synthesis of these ligands was complicated by the potential for oxygen migration from sulfur to phosphorus. To prevent this, the ligands were isolated as their borane adducts **1.39**, then deprotected and isolated as free ligands. The reaction of these ligands with dicobalt hexacarbonyl alkyne **1.41** yielded mixtures of diastereomeric cobalt complexes **1.42** and **1.43**. The *N*-benzyl derivative **1.42c** was obtained with higher diastereoselectivity than the N-H or *N*-methyl derivatives **1.42a** or **1.42b**.

Scheme 1.8 Synthesis of Dicobalt-PNSO Complexes



A series of complexes **1.44**, all bearing *N*-benzyl substitution, were then prepared analogously for subsequent use in the Pauson-Khand reaction (Scheme 1.9), and the major diastereomers were isolated in stereochemically pure form by crystallization (**1.44e**, R = CH_2OH was isolated as a >20:1 mixture of diastereomers, complete separation was not possible). The Pauson-Khand reaction with norbornadiene gave chiral cyclopentenones **1.45** in high yields and with moderate to high enantiomeric purities (73-99% ee) (Scheme 1.9). In contrast, when similar ligands that incorporated the *p*-toluenesulfinyl group were tested in the Pauson-Khand reaction, lower enantioselectivities (28-94%) were observed.[17] This difference was attributed to the stronger S-Co bond observed in the *p*-toluenesulfinyl complexes, diminishing the required hemi-labile character of the ligands. The utility of the Pauson-Khand reaction products was demonstrated in the synthesis of cross-conjugated cyclopentenone derivatives such as **1.46** (eq 1.4), which were evaluated as ligands for the activation of the transcription factor peroxisome proliferator activated receptor-γ (PPAR-γ).[18]

Scheme 1.9 Pauson-Khand Reaction



Non-Catalyst Ligand-Metal Complexes

In 1991, Roesky and coworkers reported the synthesis and characterization of a series of 8-membered-ring organometallic complexes **1.47**, in which racemic *tert*-butanesulfinamides were used as bidentate ligands via simultaneous N and O coordination to aluminum, indium, or gallium (Figure 1.3). [19]

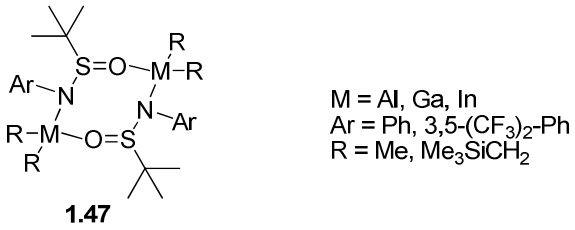
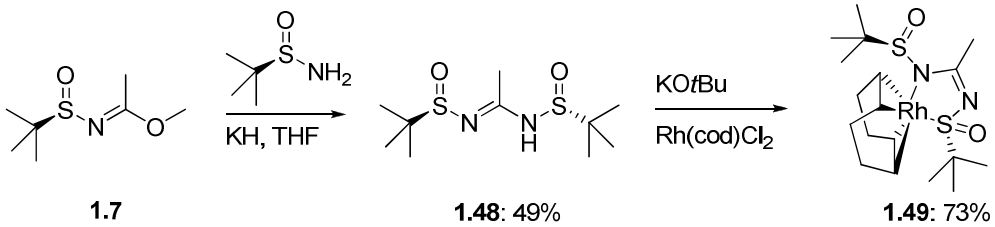


Figure 1.3 NSO Heterocyclic Complexes

An early publication by the Ellman group on sulfinamide-containing chiral ligands detailed the synthesis and crystal structure of an *N*,*S*-bonded *N*,*N*'-bis(*tert*-butanesulfinyl)amidinate Rh(I) complex (Scheme 1.10).[20] Acid-catalyzed condensation of *tert*-butanesulfinamide with trimethyl orthoacetate yielded imidate **1.7**, which was then reacted with the potassium salt of a second equivalent of *tert*-butanesulfinamide to provide *pseudo*-*C*2 symmetric *N*,*N*'-bis(sulfinyl)amidine ligand **1.48**. Treatment of this ligand with base in the presence of $[Rh(cod)Cl]_2$ provided the air-stable Rh(I) complex **1.49**, which was characterized by X-ray structural analysis. Interestingly, this amidinate complex displays asymmetric metal binding via the nitrogen and the sulfur of the two sulfinyl groups.

Scheme 1.10 Synthesis of Complex **1.49**



Riera, Verdaguer, and coworkers examined the ability of the PNSO ligands (*vide supra*) to form a variety of cationic Rh(I) complexes (Figure 1.4).[21] While these ligands act as *P,S*-ligands in their interaction with dimeric cobalt species (Scheme 1.8), they were found to bind either as *P,S* or *P,O* ligands to rhodium, depending on the coordination environment. In addition to examining the structures of these complexes, ligand displacement studies were performed to establish the hemi-labile nature of these ligands, allowing coordination sites for incoming phosphines. In particular, treatment of complex **1.50a** with either two equivalents of PPh_3 or one equivalent of the bidentate diphenylphosphinoethane (dppe) allowed displacement of the cyclooctadiene (COD) ligand. However, treatment of **1.50b** or **1.50c** with four equivalents of PPh_3 had no effect, demonstrating that the PNSO ligands are more competent ligands than monophosphines. Treatment of **1.50b** with two equivalents of dppe caused complete ligand displacement, while the cyclohexyl analogue **1.50c** was unreactive toward dppe.

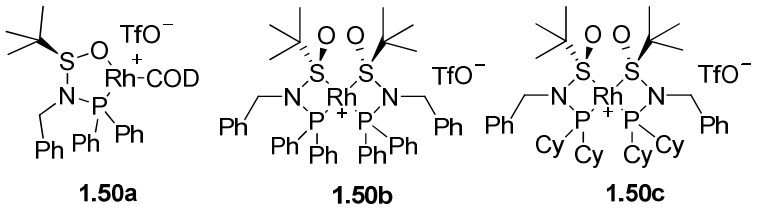
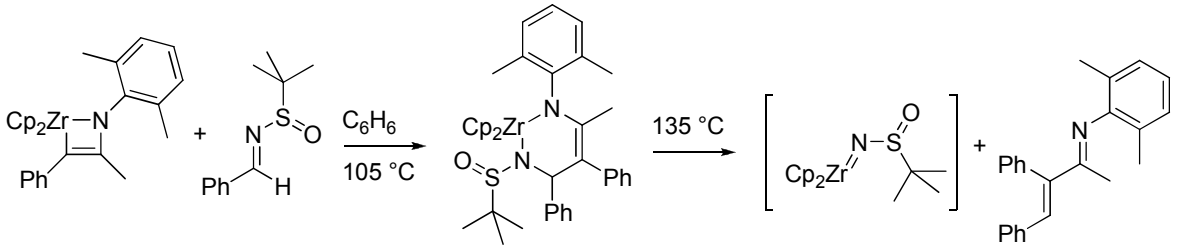


Figure 1.4 PNSO Rhodium Complexes

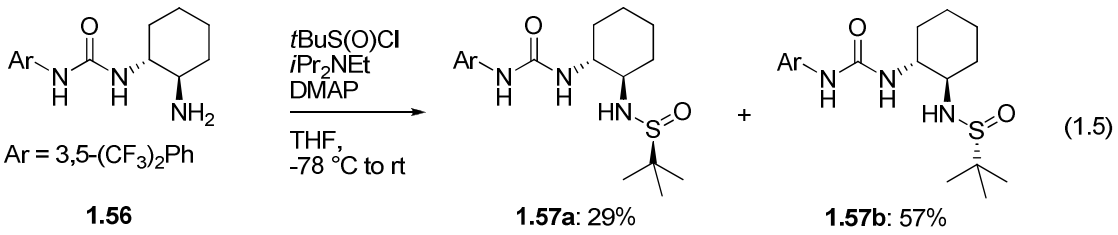
Bergman and Ruck explored the insertion of *N-tert*-butanesulfinyl imine **1.52** into the zirconium-carbon bond of an azazirconacyclobutene **1.51** providing six-membered metallocycle **1.53** (Scheme 1.11).[22] Formation of the metallocycle occurred at 105 °C, and upon further heating to 135 °C it underwent a retro-[4+2] cycloaddition to afford α,β-unsaturated imine **1.55**. However, the novel *N-tert*-butanesulfinyl imidozirconocene **1.54** was not observed by ^{1}H NMR or as a precipitate from the reaction mixture. Due to the instability of imine **1.52** above 115 °C the authors hypothesize that the sulfinyl group did not survive the elevated temperatures required for the retro-[4+2] cycloaddition.

Scheme 1.11 Reaction of *N-tert*-Butanesulfinyl Imine **1.52** with Azazirconacyclobutene **1.51**



Catalytic Ligands with Stoichiometric Metal Reagents

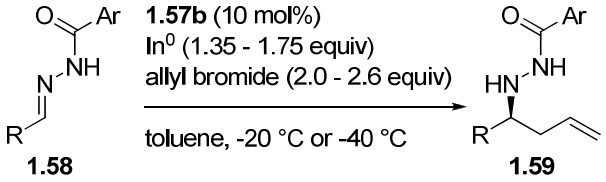
Catalyst **1.57b** (eq 1.5), which combines a hydrogen-bonding urea for electrophile activation along with the Lewis basic *tert*-butanesulfinamide group for nucleophile activation, was reported by the Jacobsen group for the indium-mediated allylation of acyl hydrazones (Table 1.3).[23] Diastereomers **1.57a** and **1.57b** were prepared by treating amine **1.56** with *tert*-butanesulfinyl chloride and were separated by silica gel chromatography (eq 1.5). It is proposed based on the X-ray crystal structure of **1.57b** that an internal hydrogen bond between the sulfinyl N-H and the urea oxygen may help to rigidify the catalyst structure and increase the urea acidity. The stereochemistry of the sulfinyl group was found to be critical in the catalytic allylation reaction, as demonstrated by the observation that **1.57a** provided allylation product with 26% ee, compared to **1.57b**, which provided the desired product with 91% ee under otherwise identical conditions.



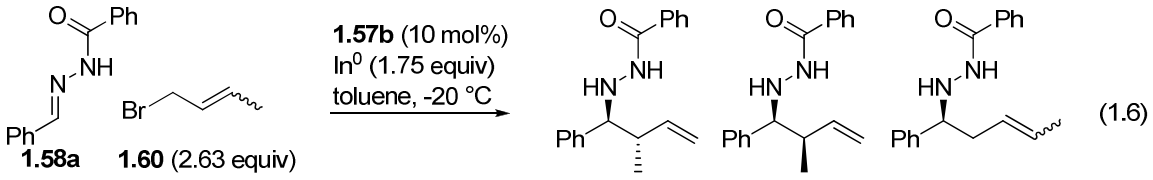
In contrast to hydrazones **1.58** derived from aryl and heteroaryl aldehydes, which underwent allylation with high selectivity (entries 1-9, Table 1.3), those derived from alkyl aldehydes exhibited poor selectivity in the allylation reaction (generally <50% ee). This limitation was partially overcome by increasing the electron-withdrawing character of the hydrazone *N*-acyl protecting group, as demonstrated by entry 10. The use of substituted allyl bromides **1.60** was also investigated (eq 1.6). While high enantioselectivity was achieved (≥85% ee for each product), poor diastereo- and regiocontrol were observed. The similar distribution of

products arising from *E* vs. *Z* crotyl bromide suggests that the allyl indium species may not be configurationally stable under the reaction conditions.

Table 1.3. Allylation of Acyl Hydrazones



entry	R	Ar	yield (%)	ee (%)
1	Ph	Ph	87	92
2	*p* -Cl-Ph	Ph	83	92
3	2-furyl	Ph	90	87
4	2-thienyl	Ph	82	93
5	*p* -(CO_2Me)-Ph	Ph	92	76
6	*o* -Br-Ph	Ph	78	93
7	*o* -Tol	Ph	89	95
8	1-naphthyl	Ph	89	95
9	*p*-MeO-Ph	Ph	79	93
10[a]	*i*Pr	3,5-(CF_3)$_2$-Ph	55	80



(1.6)

Qin and coworkers explored the use of *tert*-butanesulfinamide-based ligands **1.64-1.66** (Figure 1.5) as catalysts for the addition of diethylzinc to aldehydes.[24] Synthesis of optimal ligand **1.64a** was carried out by condensation of *tert*-butanesulfinamide with salicylaldehyde, followed by $NaBH_4$ reduction of the imine.

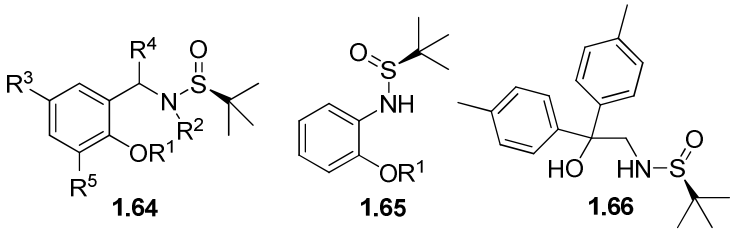
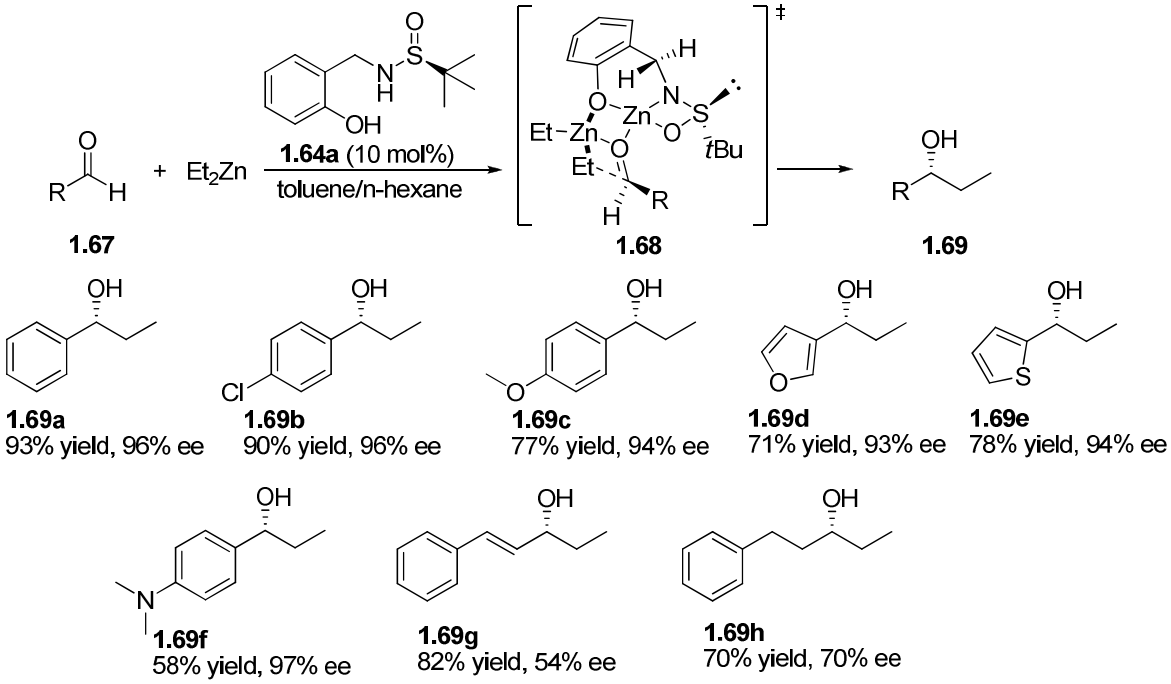


Figure 1.5 Potential Ligands for Diethylzinc Additions

The use of **1.64a** as a catalyst for addition of diethylzinc to aldehydes was highly enantioselective for aromatic and heteroaromatic aldehyde substrates, yielding alcohols **1.69a-f**,

while moderate selectivity was observed for the addition to alkenyl and alkyl aldehydes to yield alcohols **1.69g** and **h** (Scheme 1.12). Transition state **1.68** was proposed to explain the observed stereochemistry of the product. In this structure, coordination of the phenolic oxygen, the nitrogen, the sulfinyl oxygen, and the carbonyl oxygen to a single zinc ion is expected to provide a highly ordered structure. Delivery of the ethyl group from a second zinc species, which is coordinated to the phenolic oxygen and the carbonyl oxygen, is stereospecific, and the aldehyde facial selectivity is explained by placing the aldehyde R group in the position further away from the bulky *tert*-butanesulfinyl group.

Scheme 1.12 Addition of Diethylzinc to Aldehydes



Organocatalysts

The first sulfinamide organocatalyst was reported by Sun and coworkers in 2006 for the enantioselective reduction of *N*-aryl ketimines with trichlorosilane. [25] In initial studies, it was found that *tert*-butanesulfinamide was capable of catalyzing the desired transformation (eq 1.7) in 60% yield and with 21% ee. Structure optimization led to the design of catalysts **1.73** (Figure 1.6), which incorporate a proximally placed Brönsted acid in addition to the Lewis basic sulfinyl moiety. This hydroxyl group was found to be important for high enantioselectivity, and modulation of its acidity by changing the aryl substitution pattern further enhanced the performance of the catalyst, with the best performance obtained (92% yield, 92% ee) by catalyst **1.73c**.

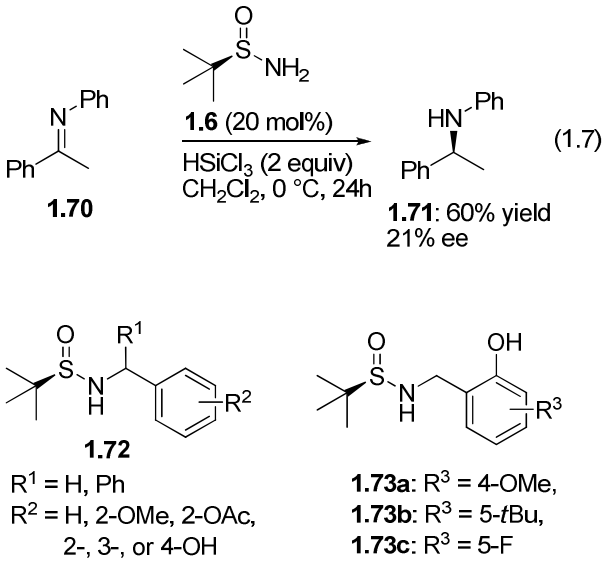


Figure 1.6 Catalyst Structure Optimization

After optimization of reaction conditions, the scope of the **1.73c**-catalyzed enantioselective reduction of imines was examined (Table 1.4, reaction conditions A). The imine *N*-substituent was limited to aryl derivatives, although varying electronic substitution (entries 10-13) was well tolerated, including the use of the *p*-methoxyphenyl (PMP) group (entries 12, 14-16). When the imine R^1 group was aromatic and R^2 was aliphatic, high levels of enantioselectivity were achieved for a variety of aryl groups (entries 1-7) and alkyl groups (entries 17-20). Significantly, high enantioselectivities were even achieved when R^1 and R^2 were branched alkyl groups and methyl, respectively, albeit with slightly lower selectivity (entries 8-9).

While a rationalization of the transition state leading to enantioselectivity for catalyst **1.73c** was not proposed in the initial report, a clear positive nonlinear effect with respect to enantioselectivity was observed, suggesting that more than one catalyst molecule is involved in the stereochemistry-determining step.[25] Subsequent work by the same group expanded further on this observation, with a dimeric binding mode proposed to explain these results (Figure 1.7).[26] This model also is consistent with the observed importance of the hydroxyl group, which could provide an organized non-covalent tether between the two catalyst molecules.

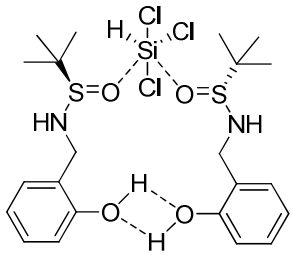
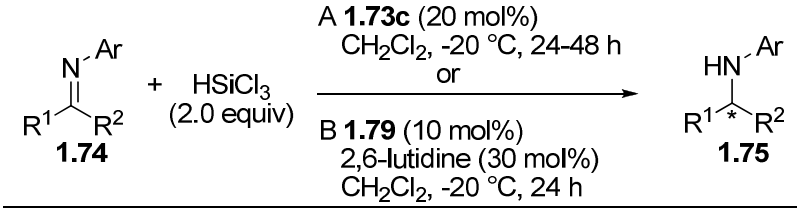


Figure 1.7 Proposed Binding Mode for Reduction

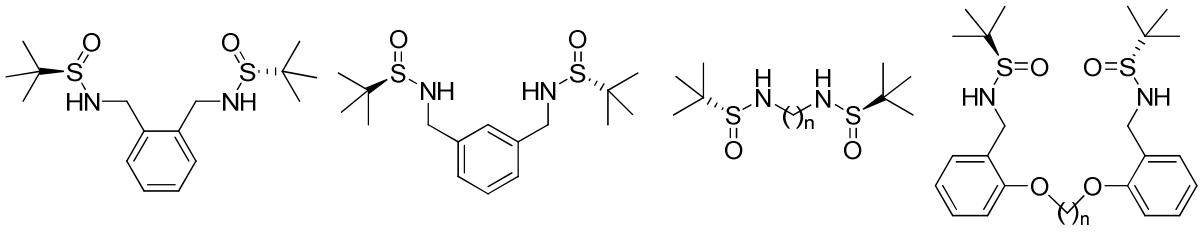
Table 1.4 Organocatalytic Reduction of *N*-Aryl Imines.



				A: catalyst **1.73c**		B: catalyst **1.79**	
entry	R^1	R^2	Ar	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	Me	Ph	92	92	91	96
2	4-CF_3-Ph	Me	Ph	93	92	95	95
3	4-NO_2-Ph	Me	Ph	94	90	90	93
4	4-Br-Ph	Me	Ph	92	92	92	95
5	4-OMe-Ph	Me	Ph	98	93	83	95
6	2-Np	Me	Ph	96	90	77	94
7	6-OMe-2-Np	Me	Ph	97	91	80	93
8	Cy	Me	Ph	78	74	84	75
9	*i*Pr	Me	Ph	78	79	87	82
10	Ph	Me	4-Cl-Ph	94	92	93	95
11	Ph	Me	4-Me-Ph	87	91	88	92
12	Ph	Me	4-OMe-Ph	97	91	92	92
13	Ph	Me	2-OMe-Ph	73	88	75	72
14	4-CF_3-Ph	Me	4-OMe-Ph	80	90	90	83
15	2-Np	Me	4-OMe-Ph	86	88	86	91
16	Ph	Et	4-OMe-Ph	84	92	84	92
17	Ph	Et	Ph	92	93	86	94
18	Ph	*n*Pr	Ph	87	91	87	91
19	Ph	*c*Pr	Ph	-	-	70	93
20	Ph	*n*Bu	Ph	94	93	89	91
21	Ph	*i*Bu	Ph	82	86	82	93

Based on this working hypothesis, bis-sulfinyl catalysts **1.76**-**1.80** (Figure 1.8) were designed to incorporate a variety of different tethers.[26] Catalyst **1.79** was identified from this set as an effective and highly enantioselective catalyst for the reduction of ketimines, in most cases providing superior results to those obtained with the original sulfinyl catalyst (Table 1.4, conditions B versus A). It was also found that addition of a sub-stoichiometric amount of 3,5-lutidine had a beneficial effect on the enantioselectivity of the reaction (96% ee with 0.3 equiv vs. 91% without), although stoichiometric amounts shut down the reaction. Importantly, the enantiomeric purity of bis-sulfinyl catalyst **1.79** was found to have a linear correlation with product enantioselectivity, consistent with the expectation that a single molecule of this bidentate catalyst is involved in the stereodetermining step.

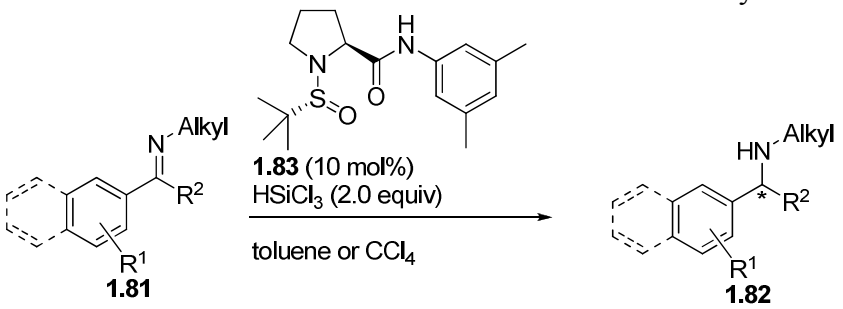
While catalysts **1.73c** and **1.79** were broadly applicable to the reduction of *N*-aryl ketimines, they were not successful for reactions with imines with aliphatic nitrogen substituents. For highly enantioselective reductions of this substrate class, Sun and coworkers recently reported sulfinamide catalyst **1.83** (Table 1.5).[27] The substrate scope for this reaction includes *N*-benzyl (entries 1-12, 24), *N*-allyl (entries 13-20), and saturated unbranched (entry 21) and β-branched *N*-alkyl substitution (entry 22) of aromatic ketimines.



1.76 **1.77** **1.78**: n = 2-6 **1.79**: n = 5 **1.80**: n = 2-6

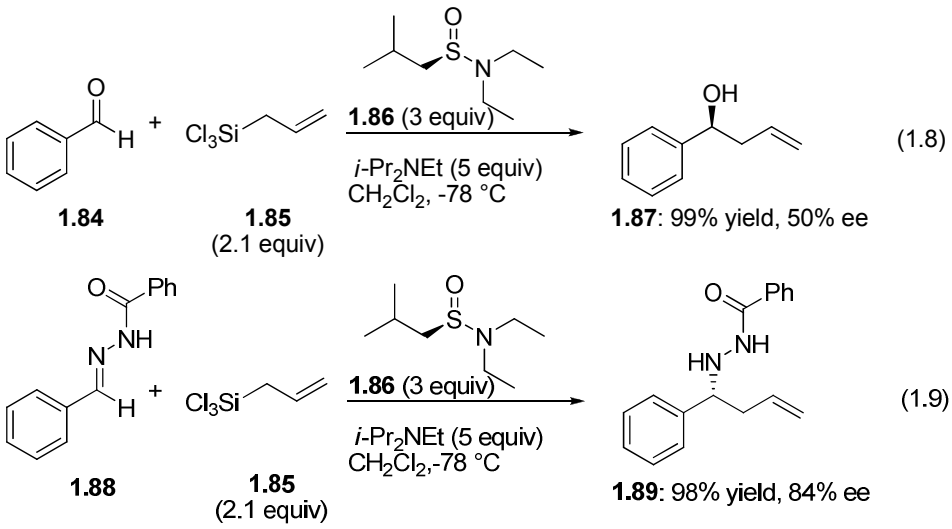
Figure 1.8. Bis-sulfinyl Catalysts for Reduction of Ketimines

Table 1.5 Enantioselective Reduction of Aromatic *N*-Alkyl Ketimines



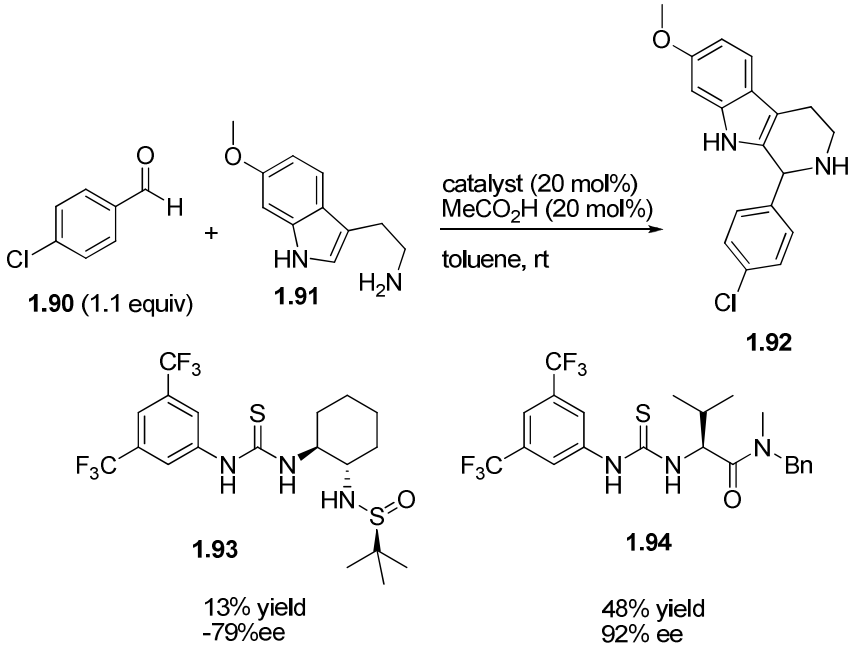
				toluene		CCl_4	
entry	R^1	R^2	Alkyl	yield (%)	ee (%)	yield (%)	ee (%)
1	H	Me	Bn	98	96	90	97
2	4-F	Me	Bn	80	96	82	97
3	4-Cl	Me	Bn	92	95	-	-
4	3-Cl	Me	Bn	98	97	-	-
5	4-Br	Me	Bn	80	96	-	-
6	3-Br	Me	Bn	93	97	-	-
7	4-CF_3	Me	Bn	94	98	93	96
8	4-NO_2	Me	Bn	80	>99	98	94
9	4-Me	Me	Bn	95	91	95	91
10	4-OMe	Me	Bn	54	78	90	92
11	2-Naphthyl	Me	Bn	96	96	83	98
12	6-OMe-2-Naphthyl	Me	Bn	70	82	89	95
13	H	Me	allyl	82	92	80	93
14	4-F	Me	allyl	88	90	83	96
15	4-Cl	Me	allyl	97	89	-	-
16	2-Cl	Me	allyl	75	97	-	-
17	4-Br	Me	allyl	83	93	-	-
18	4-CF_3	Me	allyl	65	97	-	-
19	4-NO_2	Me	allyl	97	96	-	-
20	4-Me	Me	allyl	88	83	80	85
21	H	Me	nPr	67	66	60	90
22	H	Me	iBu	56	70	80	87
23	H	Me	4-OMeBn	85	93	83	95
24	H	Et	Bn	80	89	-	-

Rowlands and coworkers recently reported the development of *N*-isobutylsulfinamide **1.86** as a Lewis basic promoter (3 equiv used) for the asymmetric allylation of benzaldehyde **1.84** (eq 1.8) or *N*-benzoyl hydrazone **1.88** (eq 1.9) with allyl silane **1.85**.[28] Extensive optimization of the sulfinamide structure was described for this system.



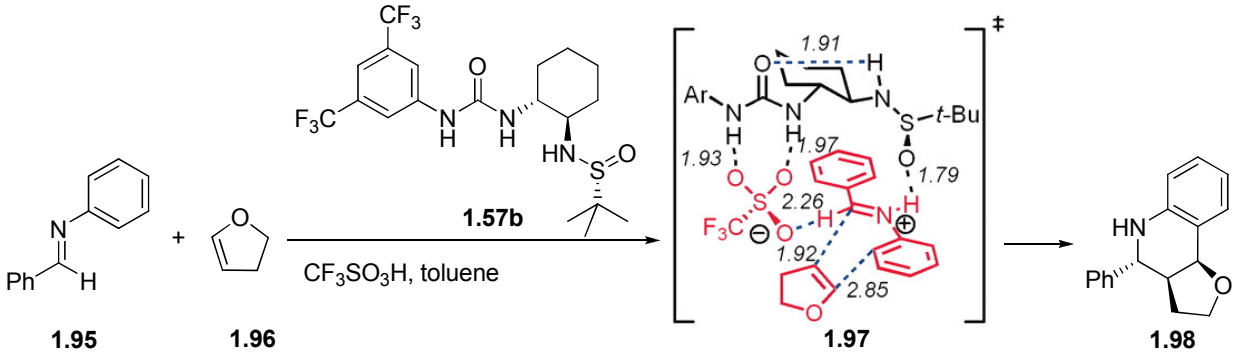
Catalyst **1.93**, the thiourea analogue of the urea catalyst **1.57b** developed by Jacobsen and coworkers for indium-mediated allylation of hydrazones (*vide supra*) was screened in the enantioselective one-pot Pictet-Spengler reaction (Scheme 1.13), providing the product with 79% ee.[29] However, catalyst **1.93** provided only 13% yield, while catalyst **1.94** provided the product in 48% yield. Further optimization was therefore carried out with catalyst **1.94**, which lacks the sulfinamide functionality.

Scheme 1.13 Catalyst Screening for the Pictet-Spengler Reaction



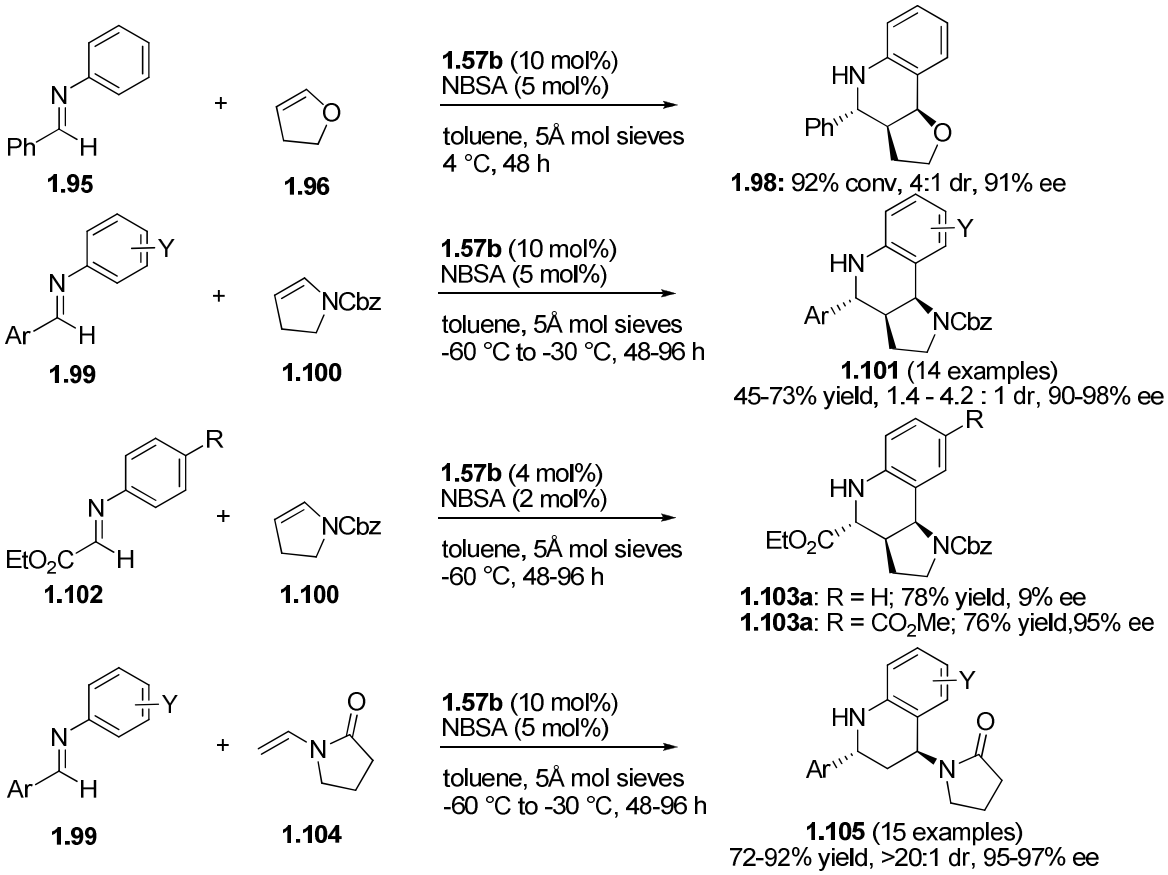
Catalyst **1.57b**, has recently been applied as a cocatalyst, along with a sulfonic acid, in the Povarov reaction (Schemes 1.14 and 1.15).[30] Experimental evidence in conjunction with molecular modeling studies allowed Jacobsen and coworkers to propose transition state **1.97** for this formal [4+2] cycloaddition between an *N*-aryl imine and an electron-rich olefin. In this transition state, the urea is hydrogen-bonded to the sulfonamide cocatalyst, which in turn interacts with the iminium C-H. The sulfinyl group acts as a hydrogen-bond acceptor for the iminium N-H. While the modeling and kinetics studies were performed with trifluoromethanesulfonic acid as a cocatalyst, screening revealed that superior results were obtained using 2-nitrobenzenesulfonic acid (NBSA). As shown in Scheme 1.15, a variety of imines and alkenes were suitable reaction partners under the optimized reaction conditions.

Scheme 1.14. Model Povarov Reaction and Computed Transition State



1.95 **1.96** **1.97** **1.98**

Scheme 1.15. Substrate Scope of Povarov Reactions



1.95 **1.96** **1.99** **1.100** **1.102** **1.100** **1.99** **1.104**

In contrast to all of the organocatalysts discussed above, which rely on the Lewis basic nature of the sulfinamide oxygen for activation of substrates, Ellman and coworkers have disclosed the development of *N*-sulfinyl urea catalysts such as **1.104-1.107** (Figure 27). In these catalysts, the sulfinyl group serves as both a chiral directing group and as an acidifying substituent on the urea, making it a stronger hydrogen-bonding organocatalyst. The design of these catalysts in the context of both the enantioselective aza-Henry reaction (eq 1.10)[31] and the addition of thioacetic acid to nitroalkenes (eq 1.11)[32] is described in Chapter 2 of this manuscript. Moreover, the use of *N*-prolyl *tert*-butanesulfinamides in the first examples of *N*-sulfinyl modified organocatalysts acting through enamine intermediates is described in Chapter 3.

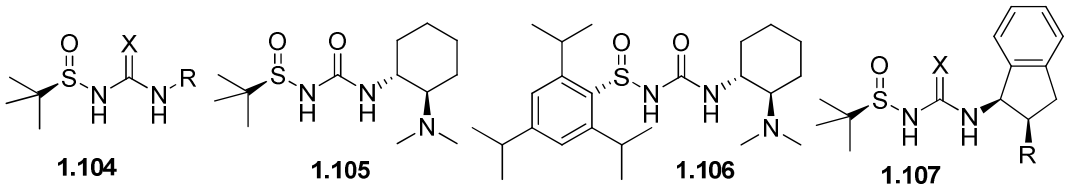
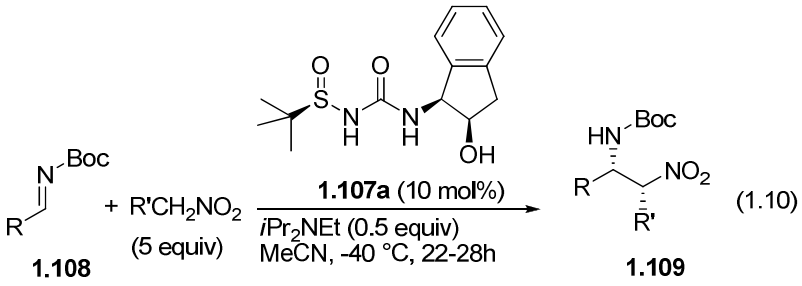
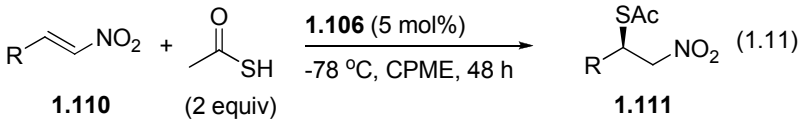


Figure 27 *N*-Sulfinyl Urea Catalysts





Conclusions

A wide variety of ligands have been reported which incorporate either an *N*-sulfinyl imine or an *N*-sulfinyl amine as a stereogenic center. Metal binding has been observed via the oxygen, nitrogen, or sulfur, depending on the structure of the ligand and the identity of the metal. The utility of these ligands in asymmetric synthesis has been explored. More recently, sulfinamide-containing organocatalysts have also been reported. Most of these organocatalysts rely on the Lewis basicity of the sulfinyl oxygen for activation of the substrates, either by coordination to silane reagents or by acting as a hydrogen bond acceptor toward a cationic substrate. In contrast, recent work that is the subject of the remainder of this dissertation has explored the use of the sulfinyl group as a chiral, acidifying substituent when incorporated into a hydrogen-bonding organocatalyst.

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Chapter 2. Development and Applications of *N*-Sulfinyl Ureas as Hydrogen-Bonding Organocatalysts.

A new class of organocatalysts has been developed, incorporating an N-sulfinyl group as a urea substituent. The sulfinyl group serves to simultaneously acidify the urea and provide effective asymmetric induction in hydrogen-bond catalyzed reactions. pK measurements of N-sulfinyl ureas in DMSO demonstrate that the sulfinyl substituent is 2-3 pK units more acidifying than the frequently reported 3,5-bis-CF_3-aryl substituent. The utility of this new catalyst structure is demonstrated by the high selectivity provided in the aza-Henry reaction for both aromatic and aliphatic N-Boc imine substrates. The majority of this work was published as a communication and is reproduced with permission (Robak, M. T.; Trincado, M.; Ellman, J. A. Enantioselective Aza-Henry Reaction with an *N*-Sulfinyl Urea Organocatalyst. *J. Am. Chem. Soc.* **2007**, *129*, 15110) Copyright 2005 American Chemical Society.

The highly enantioselective addition of thioacetic acid to nitroalkenes using a new N-sulfinyl urea organocatalyst is also described. The addition of thioacetic acid proceeds in high yields and enantioselectivities for a variety of aromatic and aliphatic nitroalkene substrates. This new method is useful for preparing chiral 1,2-aminothiol derivatives, as demonstrated by the first enantioselective synthesis of the clinically used antifungal drug sulconazole. The majority of this work was published as a communication and is reproduced with permission (Kimmel, K. L.; Robak, M. T.; Ellman, J. A. Enantioselective Addition of Thioacetic Acid to Nitroalkenes via *N*-Sulfinyl Urea Organocatalysis. *J. Am. Chem. Soc.* **2009**, *131*, 8754) Copyright 2009 American Chemical Society.

Authorship

This work was conducted in collaboration with Dr. Monica Trincado and Kyle Kimmel. I synthesized the majority of the *N*-sulfinyl urea catalysts and performed the pK measurements described. Monica developed the initial synthesis of catalysts **2.24** and **2.25**. I further optimized the synthesis of these catalysts and performed all of the studies described for the aza-Henry reaction. I also identified the thioacetic acid addition to nitroalkenes as a potential application of *N*-sulfinyl urea catalysts and performed the initial exploratory work on this reaction. Kyle optimized the thioacetic acid addition reaction conditions, synthesized the additional catalysts for this study, and developed the enantioselective synthesis of (*R*)-sulconazole.

Introduction

Hydrogen-bonding organocatalysts have been developed for a variety of reactions such as the Diels-Alder reaction and nucleophilic additions to carbonyl, imine, and nitroolefin functionalities.[1,2] Many of these reactions have traditionally been catalyzed by Lewis acids. Organocatalysts have several potential advantages over these metal-based catalysts, including air and moisture stability, functional group compatibility, and decreased product inhibition due to the relatively weak enthalpic forces between catalyst and product.[2-4] The most well-developed classes of hydrogen-bonding organocatalysts include ureas and thioureas, amidinium and guanidinium salts, diols, phosphoric acids, and cinchona alkaloid derivatives.[1,2] As described in Chapter 1, numerous studies have demonstrated the utility of sulfinamides as the chiral controlling element in both metal-based catalysts and organocatalysts. Herein, we report on the development of a new class of organocatalyst that incorporates an *N*-sulfinyl substituent on a hydrogen-bond donating urea. In this catalyst scaffold, the *N*-sulfinyl substituent is both acidifying and serves as a chiral controlling element.

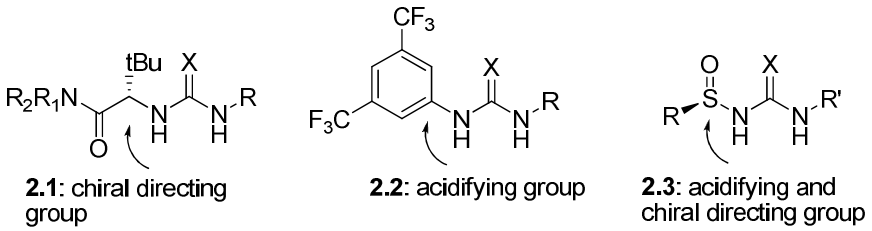


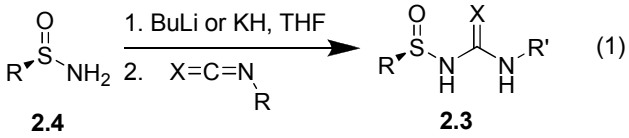
Figure 2.1: Urea (X = O) and thiourea (X = S) asymmetric organocatalysts

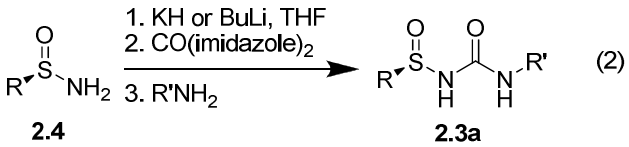
The development of new stereoselective hydrogen-bonding catalysts poses several challenges. One of the biggest challenges stems from the fact that neither the proton itself, nor the heteroatom to which it is attached (oxygen or nitrogen) can be part of a stereogenic center. In the urea scaffold, this is typically addressed by placing a chiral center adjacent the urea nitrogen. For example, catalysts with the general structure **2.1** (Figure 2.1), have been extensively developed by Jacobsen and coworkers.[1] A second consideration in the design of these catalysts is the acidity of the proton(s) of interest. A decrease in the pK_a of the hydrogen-bond donor moiety corresponds to an increase in the hydrogen-bond donating ability.[1,5] One approach to increase acidity is to use a thiourea rather than a urea.[6] Another frequently used strategy to increase the acidity is to attach an electron-poor aryl ring to the heteroatom hydrogen-bond donor. In particular, the bis-CF_3 aryl group is the most frequently reported acidifying substituent (**2.2**, Figure 2.1). However, this precludes the incorporation of a chiral center at that site. We

anticipated that an *N*-sulfinyl substituent on the urea or thiourea would simultaneously address both of these challenges (**2.3**, Figure 2.1). In this way, the close proximity of the chiral center traditionally obtained by using sp^3 carbon centers attached to the nitrogen would be maintained, while the acidity often achieved by the use of electron-poor aryl subtituents would also be obtained.

Catalyst Synthesis and Properties

A variety of *N*-sulfinyl ureas and thioureas were synthesized in one step by condensing an enantiomerically pure sulfinamide (**2.4**) with the appropriate isocyanate or isothiocyanate, respectively (eq 1). Many simple isocyanates and isothiocyanates are commercially available, so the modular nature and straightforward synthesis of this scaffold therefore enabled facile catalyst optimization. Alternatively, sequential treatment of a sulfinamide with a base, followed by 1,1'-carbonyldiimidazole, and then finally an amine provided the desired *N*-sulfinyl ureas **2.3a** in one pot (eq 2). This synthetic sequence was particularly valuable for the installation of R' groups for which the corresponding isocyanates are neither commercially available nor readily synthesized.





The acidifying nature of the sulfinyl substituent was demonstrated by measuring the pK in DMSO of *N*-sulfinyl urea **2.5** and thiourea **2.7**, using the overlapping indicator method established by Bordwell and coworkers (Figure 2.2).[7] For comparison, the pK's of electron-poor aryl urea **2.6** and thiourea **2.8** were also measured. These measurements clearly establish that the sulfinyl group is 2-3 pK units more acidifying than the frequently used 3,5-bis-CF_3-aryl group.

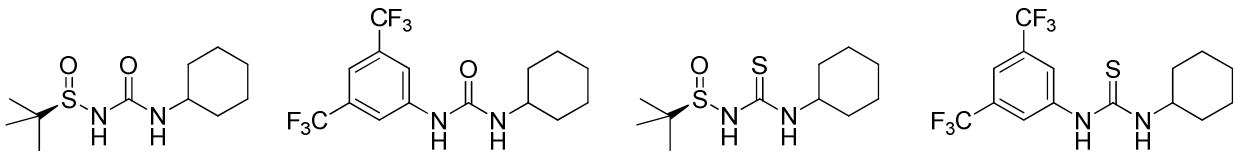


Figure 2.2: The pK's of ureas and thioureas in DMSO

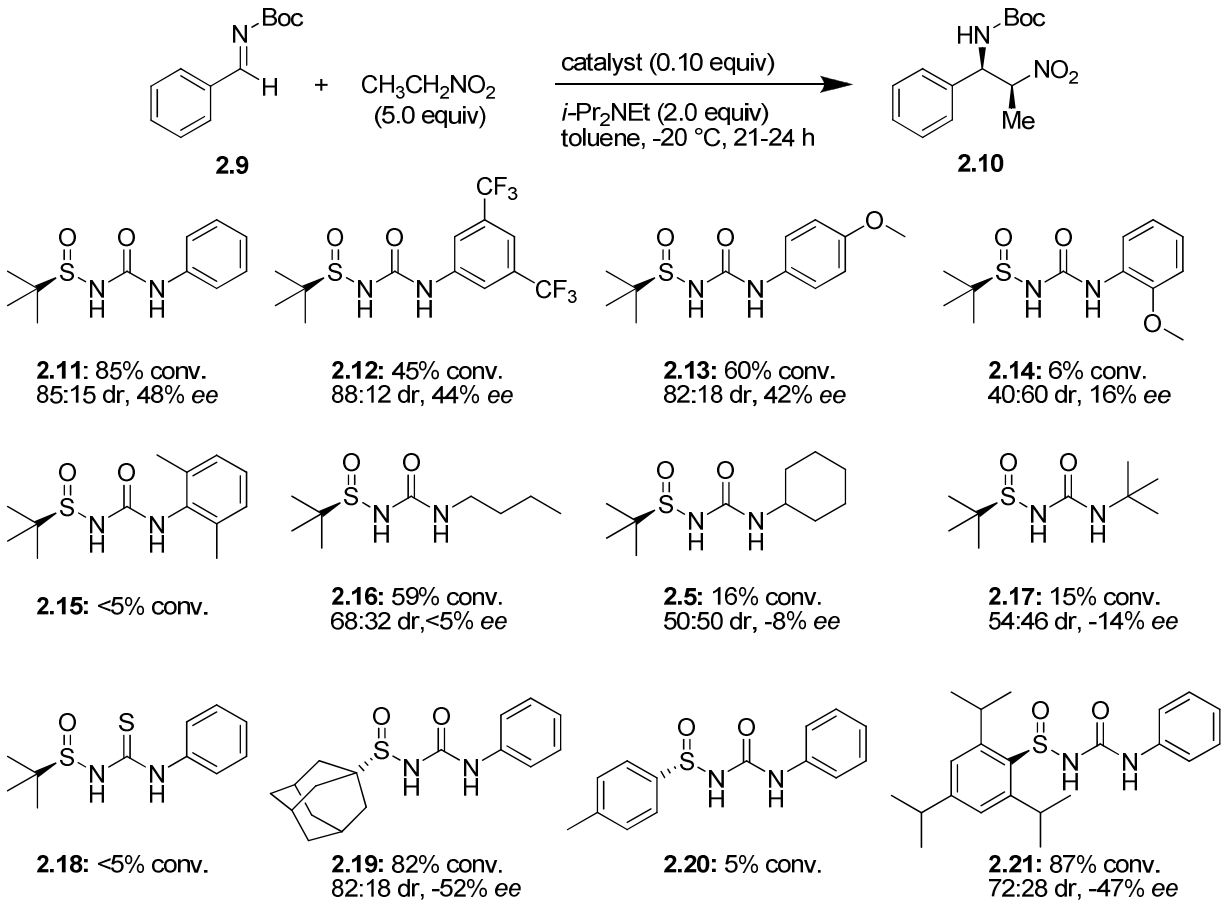
The Aza-Henry Reaction

In order to evaluate the potential of the sulfinyl urea scaffold as an asymmetric hydrogen-bonding organocatalyst, we decided to focus on the aza-Henry (or nitro-Mannich) reaction. A number of organocatalysts, including thioureas, have been previously reported for this reaction, in which a nitroalkane is added to an imine.[8-12] Therefore, this reaction serves as a good benchmark for the evaluation of our new *N*-sulfinyl ureas. Following a brief optimization of

reaction conditions (not shown), a number of *N*-sulfinyl ureas and thioureas were screened as catalysts in the aza-Henry reaction of *N*-Boc imine **2.9** with nitroethane to afford product **2.10** (Scheme 2.1). Promising initial results were obtained using *N*-*tert*-butanesulfinyl urea **2.11**, bearing a phenyl substituent. Variation of the electronic properties of the aromatic group did not result in improvements in selectivity (**2.12** and **2.13**), while substitution at the 2-position of aromatic substituents was detrimental, resulting in low yields (**2.14** and **2.15**). Catalysts with aliphatic substitution provided the product with dramatically lower selectivity and conversion (**2.5, 2.16,** and **2.17**). Thiourea **2.18** was found to be unstable under the reaction conditions, and was therefore inactive as a catalyst.

Several alternative sulfinyl groups were also explored. Adamantyl sulfinamide derivative **2.19** offered no significant advantage over the corresponding *tert*-butanesulfinamide derivative. While the *N*-toluenesulfinyl urea **2.20** exhibited poor solubility under the reaction conditions and therefore provided low conversion in the aza-Henry reaction, *N*-trisylsulfinyl urea **2.21** was a more competent catalyst, providing the product with a comparable level of selectivity to that achieved by the *tert*-butanesulfinyl analogue. Notably, the opposite enantiomer of product **2.10** was formed when this catalyst was used.

Scheme 2.1. Aza-Henry Reaction with Monofunctional *N*-Sulfinyl Urea Catalysts

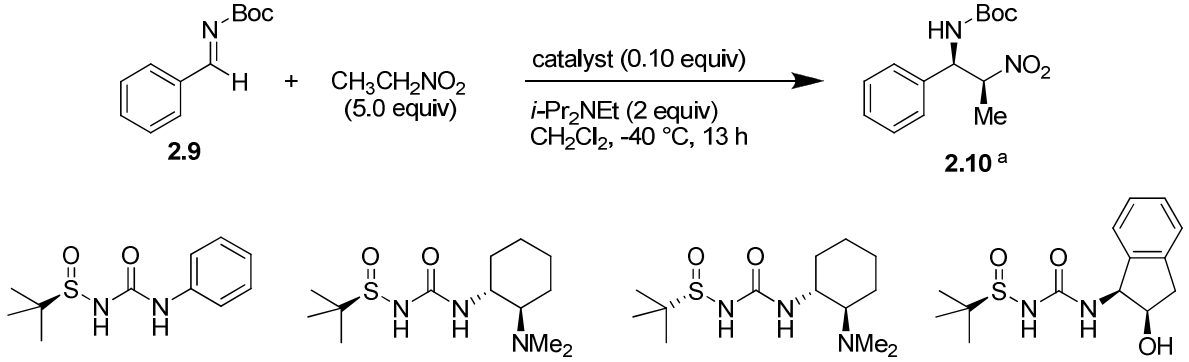


[a] Conversion to product was determined by ^{1}H NMR analysis of crude product relative to hexamethylbenzene as an internal standard. Diastereomeric ratio (*syn*:*anti*) and enantiomeric excess were determined by chiral HPLC analysis. In the absence of catalyst, no product was observed.

Many successful organocatalysts are bifunctional, incorporating either additional hydrogen bond donors or tethered bases in addition to the primary hydrogen-bond donating site. The flexibility of the urea scaffold allowed exploration of more complex substituents in combination with the sulfinyl substituent. However, while toluene was the optimal solvent for the aza-Henry reaction with simple sulfinyl urea catalyst **2.11**, poor solubility was observed for some more highly functionalized catalyst structures. For this reason, the activities of select catalysts were also evaluated in dichloromethane (Scheme 2). In contrast to the reaction in toluene, significant background reaction was observed in dichloromethane, favoring the *anti* diastereomer in the absence of catalyst.

Two different sulfinyl urea catalysts were identified which provided the aza-Henry reaction product in high yields and with high stereoselectivity. Catalyst **2.22**, which incorporates a tertiary amine base into the catalyst scaffold, was found to be highly effective both in the presence and absence of the amine base additive which was otherwise required, while its diastereomer **2.23** was found to be inferior. Alternatively, aminoindanol derivative **2.24**, which includes a hydroxyl group as a hydrogen bond donor, was found to be a highly efficient catalyst, providing a high yield of the desired product with 80:20 dr and 90% ee.

Scheme 2.2. Identification of Bifunctional *N*-Sulfinyl Urea Catalysts for Aza-Henry Reaction



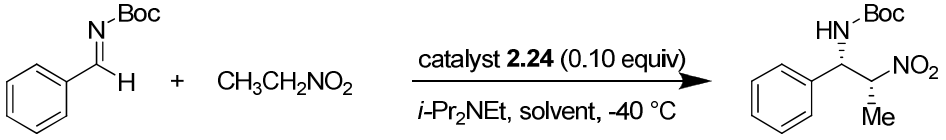
[a] Conversion to product was determined by ^{1}H NMR analysis of crude product relative to hexamethylbenzene as an internal standard. Diastereomeric ratio (*syn*:*anti*) and enantiomeric excess were determined by chiral HPLC analysis. In the absence of catalyst, 23% conversion to product is observed with 25:75 dr favoring the *anti* diastereomer. [b] No *i*-Pr_2NEt added.

With an efficient and selective catalyst identified, further optimization of the reaction conditions was undertaken (Table 2.1). As expected, THF was a poor solvent, presumably due to its ability to act as a hydrogen bond acceptor, thereby competing with the substrate for catalyst binding. Very low conversion was observed in toluene due to the lack of solubility of catalyst **2.24** in this solvent (entry 3). Slightly higher selectivity was observed in acetonitrile than in CH_2Cl_2. While variation of the stoichiometry of $EtNO_2$ with respect to imine had no effect on the selectivity of the reaction (data not shown), lowering the amount of added base, which should theoretically only be needed in catalytic amounts, gave slight improvements in selectivity at the expense of reaction rate (entries 5-8).

Under optimized reaction conditions, several variants of catalyst **2.24** were tested to determine the relationship between the structure of the catalyst and its activity (Scheme 2.3). The influence of the chirality of the sulfinyl group is demonstrated by comparison to diastereomer

2.25, and also to derivatives **2.27-2.29** that bear other acidifying but achiral functionality at this site. Thiourea derivative **2.26** was found to be less effective as a catalyst than **2.24**. It is possible that the thiourea is acidic enough to be partially deactivated by proton transfer to the amine base additive. The hydroxyl group of **2.24** is essential for the high enantioselectivity observed, as demonstrated by the inferior performances of derivatives **2.30**, which lacks the alcohol functionality, and **2.31**, which has a silyl protecting group. For both of these catalysts, the results obtained were similar to the background reaction in the absence of catalyst.

Table 2.1. Aza-Henry Reaction Optimization.

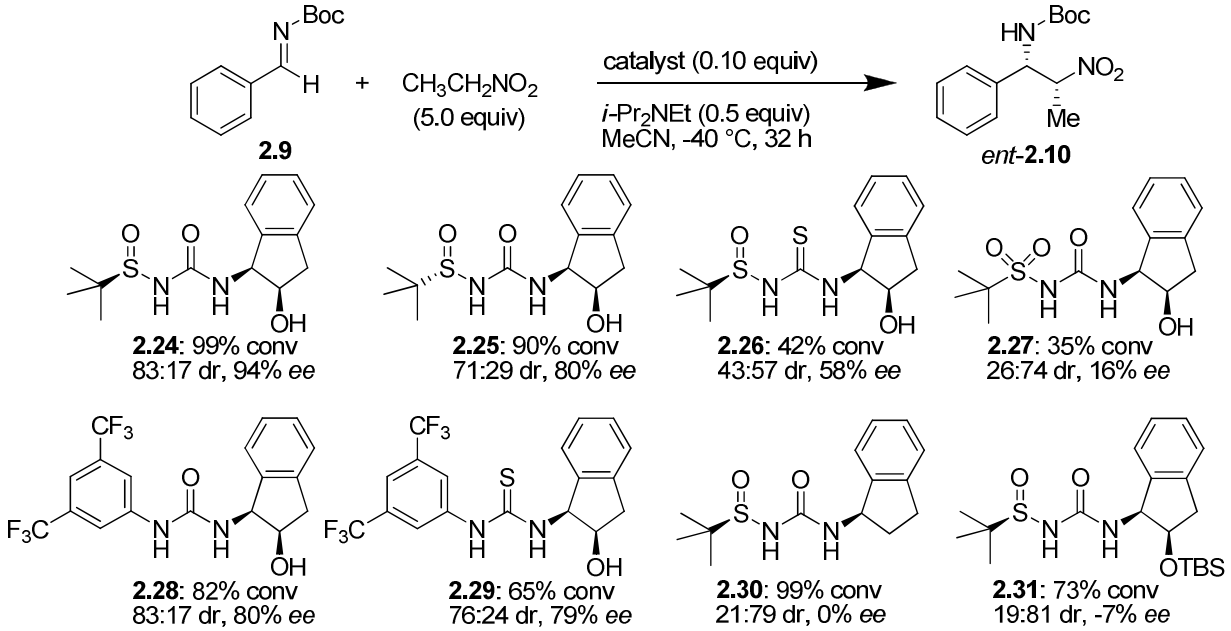


2.9 *ent*-**2.10**

entry	solvent	equiv $EtNO_2$	equiv *i*-Pr_2NEt	time	conv [a]	d.r. [b]	*ee* (%)[b]
1	CH_2Cl_2	5.0	2.0	13 h	82	80:20	90
2	THF	5.0	2.0	13 h	<5	-	28
3	PhMe	5.0	2.0	13 h	5	87:13	79
4	PhCl	5.0	2.0	13 h	23	84:16	84
5	MeCN	5.0	2.0	13 h	100	82:18	92
6	MeCN	2.0	1.0	25 h	92	86:14	94
7	MeCN	2.0	0.5	25 h	88	88:12	95
8	MeCN	2.0	0.1	25 h	31	91:9	96

[a] Conversion to product was determined by ^1H NMR analysis of crude product relative to hexamethylbenzene as an internal standard. [b] Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC analysis.

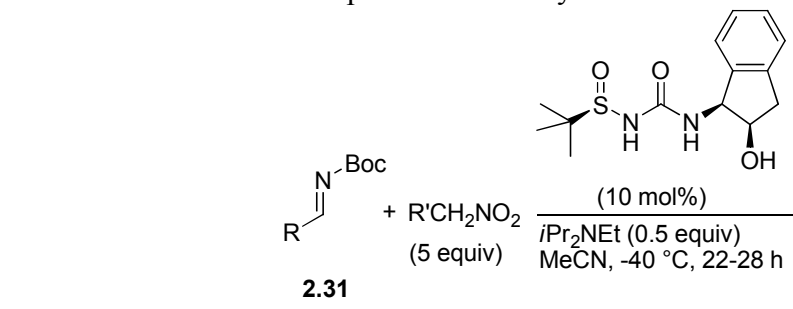
Scheme 2.3. Structure-Activity Relationship of Catalyst **2.24** under Optimized Conditions



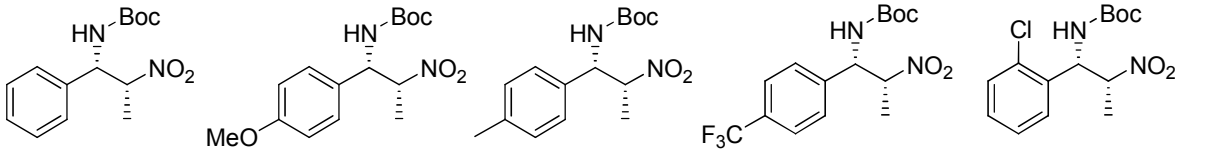
[a] Conversion to product was determined by ^1H NMR analysis of crude product relative to hexamethylbenzene as an internal standard. Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC analysis. In the absence of catalyst, quantitative conversion to product is observed with 16:84 dr favoring the *anti* diastereomer.

The scope of the reaction with respect to both the imine and the nitroalkane was explored under the optimized reaction conditions (Scheme 2.4). Excellent enantioselectivity was observed with imines bearing both electron rich and electron poor aromatic substituents. In addition, aliphatic *N*-Boc imines were found to be effective substrates, yielding adducts **2.32g** and **2.32h** with high diastereoselectivity and excellent enantioselectivity. Because these products were previously unreported, the absolute configuration of product **2.32h** was confirmed by chemical correlation and NOE studies (see experimental section for details). Finally, the formation of **2.32i** and **2.32j** with excellent selectivity reveals that the reaction is not limited to nitroethane as a substrate.

Scheme 2.4. Substrate Scope for Aza-Henry Reaction



2.31 **2.32**



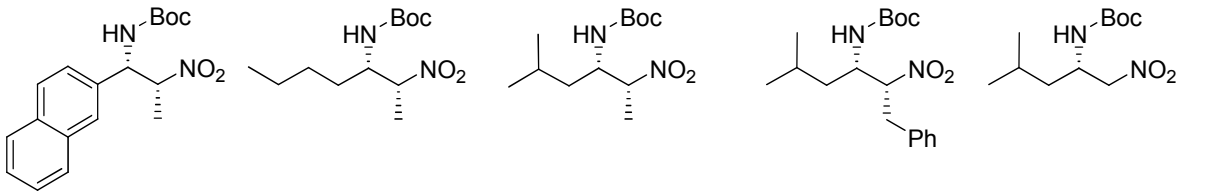
2.32a: 84% yield, 85:15 dr, 95% *ee*

2.32b: 64% yield, 90:10 dr, 95% *ee*

2.32c: 68% yield, 79:21 dr, 95% *ee*

2.32d: 92% yield, 77:23 dr, 92% *ee*

2.32e: 88% yield, 80:20 dr, 94% *ee*



2.32f: 80% yield, 84:16 dr, 93% *ee*

2.32g: 80% yield, 92:8 dr, 96% *ee*

2.32h: 76% yield, 93:7 dr, 96% *ee*

2.32i: 62% yield, 88:12 dr, 96% *ee*

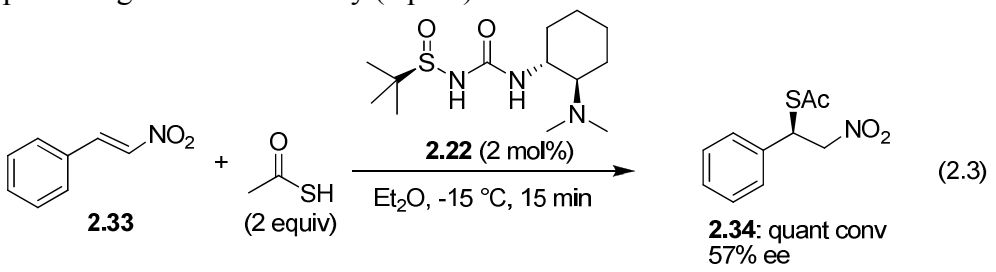
2.32j: 64% yield, 95% *ee*

[a] Isolated yields are reported. Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC analysis.

The Addition of Thioacetic Acid to Nitroalkenes

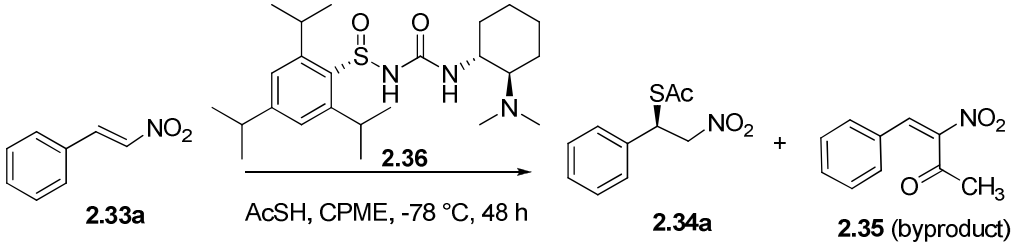
Having demonstrated the utility of the sulfinyl urea catalyst scaffold in the aza-Henry reaction, we sought the opportunity to apply this type of catalyst to a reaction that had significant room for improvement over previously published catalysts. With this in mind, we chose to explore thioacetic acid additions to nitroalkenes, where the only previous report[13] gave enantioselectivities ranging from 20 to 70% using thiourea organocatalyst **2.40** (see Scheme 2.5). Initial catalyst screening under unoptimized reaction conditions revealed that *N*-*tert*-butanesulfinyl catalyst **2.22**, which was previously identified as a competent catalyst for the aza-

Henry reaction (*vide supra*), provided the desired addition product **2.34** cleanly and with promising enantioselectivity (eq 2.3).



Further catalyst optimization revealed that *N*-trisylsulfinyl urea **2.36** in cyclopentyl methyl ether (CPME) at −78 °C (Table 2.2, entry 1) provided superior results, promoting the addition of thioacetic acid to *trans*-β-nitrostyrene (**2.33**) with 87% ee. At this temperature no background reaction is observed; however, ~30% of byproduct **2.35** is produced. To minimize the production of **2.35**, which could arise via a Baylis−Hilman type mechanism, the catalyst loading, substrate concentration, and equivalents of thioacetic acid were optimized (Table 2.2). As expected, byproduct formation was inhibited by lower reaction concentrations (entry 2), smaller excess of thioacetic acid (entries 3 and 4), and increased catalyst loading (entry 5). Under optimized conditions, the desired product was formed in 82% yield with 90% ee and with only 6% of byproduct **2.35** being produced (entry 7).

Table 2.2. Optimization of Thioacetic Acid Addition.



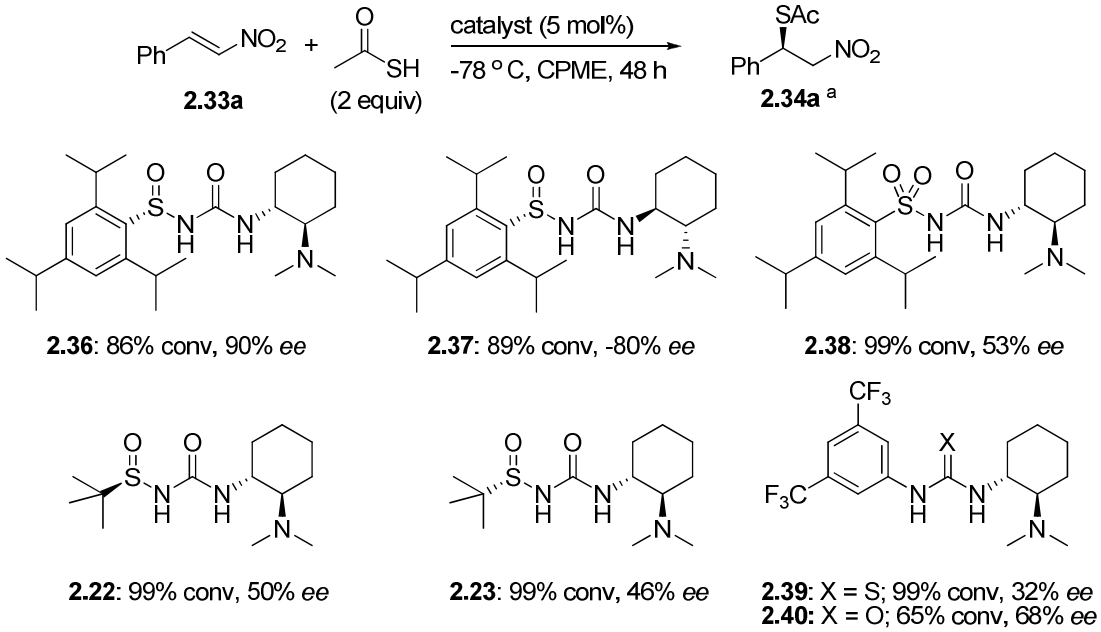
entry	mol% catalyst	conc. (M)	equiv thioacid	ratio[a] **2.34a:2.33a:2.35**	ee[b] (%)
1	2.0	0.4	2.0	71:0:29	87
2	2.0	0.1	2.0	86:4:10	90
3	2.0	0.4	1.0	42:55:3	88
4	2.0	0.4	5.0	32:0:68	82
5	5.0	0.4	2.0	85:0:15	87
6	0.5	0.4	2.0	42;25:33	80
7	5.0	0.1	2.0	82:12:6	90

[a] Product ratios were determined by ^{1}H NMR analysis. [b] Enantiomeric excess was determined by chiral HPLC analysis.

The thioacetic acid addition reaction was evaluated under the optimized reaction conditions with a range of urea catalysts (Scheme 2.5). The *N*-trisylsulfinyl urea diastereomer **2.37**, the *N*-trisylsulfonyl urea **2.38**, and both diastereomers **2.22** and **2.23** of the corresponding *N*-*tert*-butanesulfinyl urea resulted in lower selectivities. Sulfinyl urea **2.36** was then compared with catalysts containing the achiral *N*-3,5-bis(trifluoromethyl)phenyl group, which have proven to be very effective catalysts for a number of transformations.[10,14-16] Thiourea **2.39**, which was

previously reported as a catalyst for this reaction,[13] provided the product with a dramatically lower selectivity, while urea **2.40** provided only moderate enantioselectivity and poor conversion. Sulfinyl catalyst **2.36** appears to possess the ideal steric demand, acidity, and stereochemistry, whereas all other catalysts surveyed lack at least one of these essential characteristics.

Scheme 2.5. Catalyst Evaluation in Thioacetic Acid Addition to Nitroalkenes



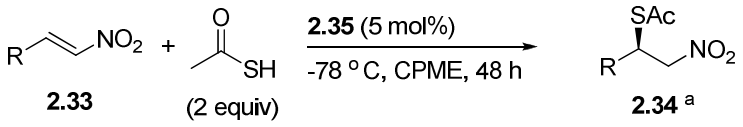
[a] Conversion was determined by ^{1}H NMR ratio of starting material to product. Enantiomeric excess was determined by chiral HPLC analysis.

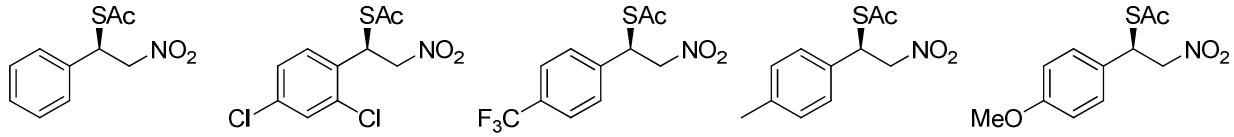
The scope of the reaction was then explored for both aromatic and aliphatic nitroalkenes (Scheme 2.6). Electronic variation via *para* substitution shows that more electron-deficient nitroalkenes provide a higher yield (**2.34b** and **2.34c**), while electron-rich derivatives provide higher enantioselectivities (**2.34d** and **2.34e**). *Ortho* substitution also results in an increase in enantioselectivity (**2.34f**). Significantly, *o*,*p*-dichloro-*trans*-β-nitrostyrene, which can be converted to sulconazole (*vide infra*), provides both high yield and enantioselectivity (**2.34b**). Aliphatic nitroalkenes also undergo the addition reaction in good yield for both linear (**2.34g** and **2.34h**) and branched (**2.34i**) substrates, although with somewhat reduced enantioselectivity relative to the aryl substrates. The role of the configuration of the *N*-sulfinyl stereocenter in the urea catalyst is clearly complex because *N*-sulfinyl catalyst **2.37** provided the cyclohexyl product **2.34i** with higher selectivity (84% ee) than *N*-sulfinyl catalyst **2.36** (70% ee), which was the preferred catalyst for all other substrates.

The utility of the method was next demonstrated by the first asymmetric synthesis of sulconazole from addition product **2.43b** in only four steps (Scheme 2.7). Reduction of the 1,2-nitrothiolate was unprecedented in the literature and is complicated by thiol poisoning of typical transition metal catalysts employed in nitro reduction. However, by using excess tin(II) chloride and anhydrous hydrochloric acid, reduction of **2.34** was achieved with concomitant acyl transfer to the amine, providing thiol amide **2.41** in 74% yield. Alkylation of the unmasked thiol with benzyl bromide **2.42** followed by quantitative amide hydrolysis gave free amine **2.43** in 71% overall yield. Final condensation of the amine with glyoxal and formaldehyde[17] afforded *R*-

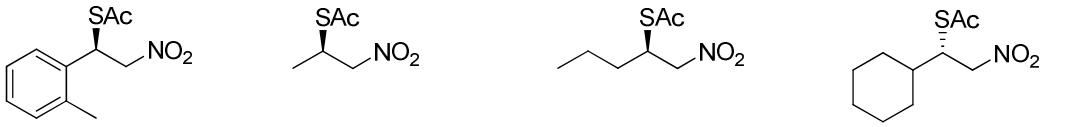
sulconazole in 74% yield. The drug was synthesized in 96% ee and 32% overall yield for the five steps from β-nitrostyrene **2.33b**.

Scheme 2.6. Substrate Scope for Thioacetic Acid Addition to Nitroalkenes





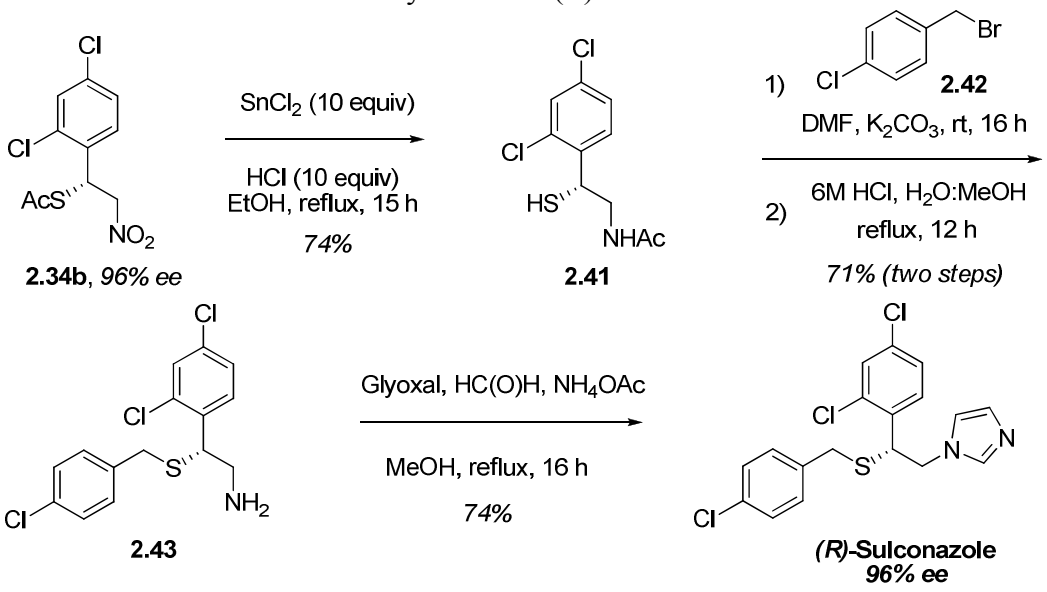
2.34a: 73% yield, 90% *ee*
2.34b: 84% yield, 96% *ee*
2.34c: 88% yield, 85% *ee*
2.34d: 65% yield, 91% *ee*
2.34e: 65% yield, 93% *ee*



2.34f: 63% yield, 94% *ee*
2.34g: 64% yield, 78% *ee*
2.34h: 82% yield, 80% *ee*
2.34i: 95% yield, 84% *ee* [b]

[a] Isolated yields are reported. Enantiomeric excess was determined by chiral HPLC analysis. [b] Catalyst **2.36** was used

Scheme 2.7. Enantioselective Synthesis of (*R*)-Sulconazole



Conclusions

We have established *N*-sulfinyl ureas as a new class of organocatalysts with the sulfinyl group serving both as an acidifying agent and as a chiral controlling element. These catalysts are straightforward to prepare from the corresponding sulfinamide in combination with either an isocyanate or 1,1'-carbonyl diimidazole and an amine. The effectiveness of this class of

organocatalysts was first demonstrated by catalysis of the aza-Henry reaction with high selectivity, including the first examples of enantioselective hydrogen-bonding catalyzed additions to aliphatic *N*-Boc imines. We have further demonstrated that an *N*-sulfinyl urea organocatalyst can promote the addition of thioacetic acid to aromatic and aliphatic nitroalkenes, with enantioselectivity that is far superior to that previously reported. Finally, we demonstrated that this enantioselective addition reaction can serve as a general method for preparing chiral 1,2-aminothiols in compounds of pharmaceutical interest, as exemplified by the expedient synthesis of *R*-sulconazole in 96% ee and good overall yield.

Experimental

General Methods. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Tetrahydrofuran (THF), toluene, and methylene chloride (CH_2Cl_2) were passed through columns of activated alumina under nitrogen pressure immediately prior to use. Acetonitrile (MeCN) and *N,N*-Diisopropylethylamine (*i*-Pr_2NEt) were distilled over calcium hydride under an atmosphere of nitrogen immediately prior to use. Nitroethane and nitromethane were fractionally distilled and stored under nitrogen. Flash column chromatography was carried out either with Merck 60 230-240 mesh silica gel, or using a Biotage SP Flash Purification System (Biotage No. SP1-B1A) with Flash+ cartridges (Biotage No. FPK0-1107-16046). ^1H and $^{13}C\{^1H\}$ NMR chemical shifts are reported in ppm relative to either the residual solvent peak (^1H, ^{13}C) or TMS (^1H) as an internal standard. IR spectra were recorded as thin films on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory or as KBr pellets on a Nicolet MAGNA-IR 850 spectrometer, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. Mass spectrometry (HRMS) was carried out by the University of California at Berkeley Mass Spectrometry Facility.

Di-*tert*-butyl tricarbonate and β-phenylnitroethane were prepared according to literature procedures.[18,19] Imines **2.31a-h** were prepared from α–amido sulfone precursors according to literature procedures.[20-22] **2.6**, **2.8**, **2.28**, and **2.29** are literature compounds.[15,23]

Preparation of *N*-Sulfinyl Ureas from Sulfinamides and Isocyanates:

General Procedure A. A stirred solution of (*R*)-*tert*-butanesulfinamide (121 mg, 1.0 mmol) in THF (10 mL) was cooled in a dry ice/acetone bath under a nitrogen atmosphere. Butyllithium in hexanes (1.1 mmol) was added dropwise, and the solution was stirred for 15 min, and then the cold bath was removed and the solution was stirred at rt for 15 min. The appropriate isocyanate (1.1 equiv) was added dropwise, and stirring was continued at rt for 3-5 h. The reaction was quenched by the addition of water (0.5 mL), and the resulting mixture was concentrated.

General Procedure B. A stirred solution of (*R*)-*tert*-butanesulfinamide (1.0 equiv) in THF (0.20 M) was cooled in a dry ice/acetone bath under nitrogen atmosphere. Butyllithium in hexanes (1.0 - 2.0 equiv) was added dropwise, and the solution was stirred for 20 min. The appropriate isocyanate (1.2-1.5 equiv) was added dropwise. The solution was stirred for 30 min, after which time the cold bath was removed and stirring was continued at rt for 1 - 18 h.

2.5. General procedure A was followed, using freshly distilled cyclohexyl isocyanate. The residue was diluted with CH_2Cl_2 (75 mL) and extracted with 0.1 M aqueous NaOH (50 mL, then an additional 25 mL). The combined aqueous layer was acidified to pH < 2 with saturated aqueous $NaHSO_4$ and then extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. Crystallization from CH_2Cl_2/EtOAc yielded 145 mg (59%) of white crystalline solid, mp 187-188 °C. IR (film): 3327, 3202, 2933, 2854, 1695, 1537, 1418, 1031, 1011 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H), 5.83 (d, *J* = 7.8 Hz, 1H), 3.66-3.54 (m, 1H), 1.98-1.85 (m, 2H), 1.77-1.65 (m, 2 H), 1.62-1.54 (m, 1H), 1.41-1.29 (m, 2H), 1.28 (s, 9H), 1.27-1.15 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.2, 56.8, 49.5, 33.3, 33.3, 25.7, 25.0, 22.5. HRMS (FAB+) calcd for $C_{11}H_{23}N_2O_2S$ $[MH]^+$ 247.1480; found 247.1478.

Cyclohexyl isothiocyanate: Cyclohexylamine (1.14 mL, 10.0 mmol) was added to a flask containing CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The mixture was stirred at 0 °C for 5 min, and then the stirring was stopped and thiophosgene (0.84 mL, 11 mmol) was added directly to the bottom (organic) layer via syringe. The reaction mixture was stirred for 30 min, and then the layers were separated. The organic layer was dried with Na_2SO_4 and concentrated. Silica gel chromatography, eluting with hexanes, afforded 0.408 g (29%) of cyclohexyl isothiocyanate as a pale yellow oil. The ^1H and ^{13}C NMR spectra are consistent with literature values. [24]

2.7. General procedure A was followed. The crude residue was diluted with 0.1 M aqueous NaOH (50 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The aqueous layer was acidified to pH <2 with saturated aqueous $NaHSO_4$, and then extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude material was recrystallized from EtOAc and collected by vacuum filtration. The mother liquor was reduced in volume and a second crop of crystals was collected, to give a total of 100 mg (38%) of thiourea **2.7** as colorless prisms, m.p. 115-118 °C. IR (KBr): 3297, 3158, 2930, 1547, 1497, 1038 cm^{-1}. ^1H NMR (400 MHz, DMSO-d6): δ 8.86 (s, 1H), 8.27 (d, *J* = 7.7 Hz, 1H), 4.05-3.95 (m, 1H), 1.95-1.82 (m, 2H), 1.70-1.60 (m, 2H), 1.58-1.50 (m, 1H), 1.38-1.15 (m, 5 H), 1.18 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6): δ 181.8, 56.0, 53.1, 31.9, 25.5, 24.6, 22.8. HRMS (FAB+) calcd for $C_{11}H_{23}N_2OS_2$ $[MH]^+$ 263.1252; found 263.1248.

2.11. General procedure B was followed with (*R*)-*tert*-butanesulfinamide (303 mg, 2.50 mmol), *n*-butyllithium (3.8 mL, 5.0 mmol), and phenyl isocyanate (0.41 mL, 3.8 mmol). After 16 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and extracted with water (60 mL). The aqueous layer was rinsed with CH_2Cl_2 (4 x 15 mL) and then acidified to pH < 2 with saturated aqueous $NaHSO_4$. The aqueous layer was extracted with CH_2Cl_2 (6 x 20 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was crystallized from CH_2Cl_2/EtOAc and isolated by filtration and rinsing on the filter paper with an additional 2 mL of EtOAc to yield 410 mg (68%) of urea **2.11** as a white crystalline solid, mp 171-172 °C. IR (film): 3271, 1686, 1443, 1185, 1032, 891, 759, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.69 (s, 1 H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.24 (apparent t, *J* = 8 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.1, 137.7, 129.1, 124.1, 120.0, 56.9, 22.5. HRMS (FAB+) calcd for $C_{11}H_{17}N_2O_2S$ $[MH]^+$ 241.1011; found 241.1004.

2.12. General procedure A was followed. The crude residue was diluted with water (50 mL), acidified to pH < 2 with aqueous $NaHSO_4$, and product was extracted into CH_2Cl_2 (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. Flash column chromatography on a Biotage Flash+ cartridge with a gradient of 1% to 10% of MeOH in CH_2Cl_2 afforded 191 mg (50%) of a white solid, mp 74-83 °C. IR (film): 3281, 1716, 1575, 1474, 1382, 1276, 1170, 1127, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.15 (s, 1H), 7.83 (s, 2H), 7.49 (s, 1H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD): δ 154.8, 141.79, 133.3 (q, J_{CF} = 33 Hz), 124.6 (q, J_{CF} = 272 Hz), 119.9, 117.2, 57.2, 22.6. HRMS (FAB+) calcd for $C_{13}H_{15}F_6N_2O_2S$ $[MH]^+$ 377.0758; found 377.0761.

2.13. General procedure B was followed with (*R*)-*tert*-butanesulfinamide (121 mg, 1.00 mmol), butyllithium (0.80 mL, 2.0 mmol), and 4-methoxyphenyl isocyanate (0.19 mL, 1.5 mmol). After 5 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with 0.2 M NaOH (3 x 20 mL). The aqueous layer was acidified to pH < 2 with saturated aqueous $NaHSO_4$, then extracted with CH_2Cl_2 (2 x 20 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography on silica gel, eluting with 1:1 hexanes:EtOAc to 1:9 hexanes:EtOAc, yielded 79 mg of a white solid, mp 45-53 °C. IR: 3302, 1511, 1421, 1241, 1170, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.78 (br s, 1H), 7.20 (d, *J* = 9 Hz, 2H), 6.73 (d, *J* = 9 Hz, 2H), 3.70 (s, 3H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.5, 153.4, 130.5, 122.2, 114.3, 56.8, 55.5, 22.6. MS (FAB+) calcd for $C_{12}H_{18}N_2O_3S$ $[M+Li]^+$ 277; found 277.

2.14. General procedure B was followed with (*R*)-*tert*-butanesulfinamide (121 mg, 1.00 mmol), butyllithium (0.55 mL, 1.2 mmol), and 2-methoxyphenyl isocyanate (0.16 mL, 1.2 mmol). After 5 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and extracted with aqueous sodium hydroxide (0.2 M, 60 mL). The aqueous layer was rinsed with CH_2Cl_2 (2 x 10 mL) and then acidified to pH < 2 with saturated aqueous $NaHSO_4$. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography on a Biotage Flash+ cartridge with a gradient of 12% to 100% of EtOAc in hexanes afforded 150 mg (56%) of a white solid, mp 172-173 °C. IR: 3279, 1708, 1540, 1458, 1438, 1417, 1172, 1040 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09-8.03 (m, 2H), 7.45 (br s, 1H), 6.99 (t , *J* = 7.3 Hz, 1H), 6.90 (t , *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.7, 148.4, 127.8, 123.3, 120.9, 119.3, 110.2, 57.2, 56.1, 22.5. HRMS (FAB+) calcd for $C_{12}H_{19}N_2O_3S$ $[MH]^+$ 271.1116; found 271.1123.

2.15. General procedure B was followed with (*R*)-*tert*-butanesulfinamide (121 mg, 1.00 mmol), butyllithium (1.5 mL, 2.0 mmol), and 2,6-dimethylphenyl isocyanate (0.21 mL, 1.5 mmol). After 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and extracted with water (25 mL). The aqueous layer was rinsed with CH_2Cl_2 (10 mL) and then acidified to pH < 2 with saturated aqueous $NaHSO_4$. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated. The crude white solid was triturated with 5 mL of EtOAc and isolated by filtration to yield 240 mg (88%) of a white solid, mp 191-194 °C. IR: 3293, 1715, 1537, 1470, 1411, 1183, 1028 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 7.15-7.05 (m, 3H), 2.22 (s, 6H), 1.31 (s, 9H). HRMS (FAB+) calcd for $C_{13}H_{21}N_2O_2S$ $[MH]^+$ 269.1324; found 269.1329.

2.16. General procedure B was followed with (*R*)-*tert*-butanesulfinamide (121 mg, 1.00 mmol), THF (6 mL), butyllithium (0.50 mL, 1.2 mmol), and *n*-butyl isocyanate (0.13 mL, 1.2 mmol). After 6 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and extracted with 0.2 M NaOH (25 mL). The aqueous layer was rinsed with CH_2Cl_2 (3 x 10 mL) and then acidified to pH < 2 with saturated aqueous $NaHSO_4$. The aqueous layer was extracted with CH_2Cl_2 (25 mL), and the extract was dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography on a Biotage Flash+ cartridge with a gradient of 12% to 100% of EtOAc in hexanes afforded 76 mg (34%) of the product as a clear oil. IR (film): 3340, 2959, 2872, 1655, 1542, 1042 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (br s, 1H), 5.65 (br s, 1H), 3.27-3.20 (m, 2H), 1.56-1.47 (m, 2H), 1.41-1.30 (m, 2H), 1.28 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 56.8, 40.5, 32.0, 22.5, 20.2, 14.0. HRMS (FAB+) calcd for $C_9H_{21}N_2O_2S$ $[MH]^+$ 221.1324; found 221.1321.

2.17. General procedure B was followed with (*R*)-*tert*-butanesulfinamide (121 mg, 1.00 mmol), THF (6 mL), butyllithium (0.50 mL, 1.3 mmol), and *tert*-butyl isocyanate (0.14 mL, 1.3 mmol). After 3 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with 0.2 M NaOH (3 x 20 mL). The aqueous layer was acidified to pH < 2 with saturated aqueous $NaHSO_4$ and then extracted with CH_2Cl_2 (2 x 20 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated. The crude solid was triturated with EtOAc (3 mL) and isolated by filtration and rinsing on the filter with EtOAc (2 x 2 mL) to yield 129 mg (59%) of the urea as a white powdery solid, mp 195-196 °C. IR (film): 3335, 3231, 2963, 1708, 1552, 1412, 1364, 1259, 1030, 1011 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (br s, 1H), 5.70 (br s, 1H), 1.36 (s, 9H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.8, 56.6, 51.3, 29.1, 22.5. HRMS (FAB+) calcd for $C_9H_{21}N_2O_2S$ $[MH]^+$ 221.1324; found 221.1327.

2.18. General procedure A was followed, using freshly distilled phenyl isothiocyanate. The crude residue was diluted with 0.1 M aqueous NaOH (50 mL) and washed with CH_2Cl_2 (2 x 25 mL). The aqueous layer was then acidified to pH < 2 with aqueous $NaHSO_4$, and the product was extracted into CH_2Cl_2 (2 x 25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude solid was triturated with EtOAc (2 x 2 mL) and isolated by vacuum filtration to yield 133 mg (52%) of the thiourea as a white flaky solid, mp 92.5-93.0 °C. IR (film): 3239, 1483, 1442, 1312, 1169, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (br s, 1H), 8.50 (br s, 1H), 7.49-7.38 (m, 2H), 7.38-7.28 (m, 2H), 7.26-7.17 (m, 1H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 181.8, 137.6, 129.4, 127.2, 125.0, 57.9, 22.9. HRMS (FAB+) calcd for $C_{11}H_{17}N_2OS_2$ $[MH]^+$ 257.0782; found 257.0775.

2.19. General procedure B was followed with (*S*)-1-adamantylsulfinamide (150 mg, 0.750 mmol), butyllithium (0.36 mL, 0.90 mmol), and phenyl isocyanate (0.10 mL, 0.90 mmol). After 7 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and extracted with 0.2 M NaOH (2 x 10 mL). The combined aqueous layers were acidified to pH < 2 with saturated aqueous $NaHSO_4$ and then extracted with CH_2Cl_2 (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Crystallization of the crude material from CH_2Cl_2/EtOAc yielded 167 mg (70%) of an off-white crystalline solid, mp 203-204 °C. IR: 3296, 2909, 1713, 1548, 1448, 1018 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (br s, 1H), 7.95 (br s, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7,21 (apparent t, *J* = 8 Hz, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 2.22-2.14 (m, 3H), 1.95-1.87 (m,

6H), 1.83-1.66 (m, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.0, 137.9, 129.1, 123.9, 119.9, 58.7, 36.4, 34.7, 28.6. HRMS (FAB+) calcd for $C_{17}H_{23}N_2O_2S$ $[MH]^+$ 319.1480; found 319.1482.

2.20. General procedure B was followed with (*S*)-*p*-toluenesulfinamide (116 mg, 0.750 mmol) THF (5 mL), butyllithium (0.36 mL, 0.90 mmol), and phenyl isocyanate (0.10 mL, 0.90 mmol). A suspension of white precipitate formed in the reaction mixture. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and MeOH (1 mL) and extracted with 0.2 M NaOH (20 mL). The aqueous layer was acidified to pH < 2 with saturated aqueous $NaHSO_4$, and then extracted with CH_2Cl_2 (3 x 25 mL). MeOH (1 mL) was added to the combined extracts (to aid in solubility), which were then dried over Na_2SO_4, filtered, and concentrated. Trituration with 3 mL of EtOAc followed by filtration yielded 48 mg (23%) of a white powdery solid, mp 124-126 °C (dec.). IR: 3297, 3248, 1638, 1549, 1453, 1414, 1098, 1074 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.49 (s, 1H), 8.71 (s, 1H), 7.66 (d, J = 8.2, 2H), 7.47-7.40 (m, 4H), 7.30 (apparent t, J = 8.5 Hz, 2H), 7.03 (t, J = 7.3, 1H), 2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ 152.8, 141.7, 141.1, 138.5, 129.8, 129.0, 124.9, 123.0, 118.8, 20.9. MS (FAB+) calcd for $C_{14}H_{14}N_2O_2S$ $[M]^+$ 275; found 275.

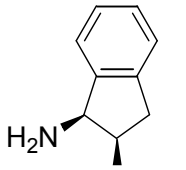
2.21. General procedure B was followed with (*R*)-2,4,6-triisopropylbenzenesulfinamide (267 mg, 1.00 mmol), butyllithium (0.55 mL, 1.2 mmol), and phenyl isocyanate (0.13 mL, 1.2 mmol). After 6 h, the reaction mixture was quenched with saturated aqueous $NaHSO_4$ (1 mL) and diluted with water (9 mL). The mixture was extracted with CH_2Cl_2 (40 mL). The organic layer was washed with brine (10 mL) dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography on a Biotage Flash+ cartridge with a gradient of 1% to 10% of MeOH in CH_2Cl_2 afforded 115 mg (30%) of a white solid, mp 144.5-145.5 °C (dec.). IR: 3314, 3054, 2963, 1679, 1601, 1549, 1445, 1383, 1052 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.31 (m, 4H), 7.18-7.12 (m, H), 7.11 (s, 2H), 6.93 (br s, 1H), 4.00-3.90 (m, 2H), 2.89 (septet., J = 6.9 Hz, 1H), 1.30-1.22 (m, 18H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.8, 153.3, 149.1, 137.2, 135.7, 129.6, 125.3, 123.6, 121.7, 34.6, 28.9, 24.8, 24.2, 23.9. HRMS (FAB+) calcd for $C_{22}H_{31}N_2O_2S$ $[MH]^+$ 387.2106; found 387.2099.

2.22 (1*R*,2*R*)-*N*,*N*-Dimethylcyclohexanediamine (0.537 g, 3.78 mmol) was dissolved in CH_2Cl_2 (20 mL) and added dropwise over 5 min to a solution of di-tert-butyltricarbonate (1.05 g, 4.0 mmol) in CH_2Cl_2 with stirring. After stirring at rt for 30 min, 0.10 mL of pyridine was added, and the solution was concentrated to yield the crude isocyanate.

(*R*)-*tert*-Butanesulfinamide (484 mg, 4.00 mmol) was dissolved in 40 mL of THF and cooled to -78 °C. Butyllithium (1.8 mL of a 2.2 M solution in hexanes, 4.0 mmol) was added dropwise, and then the reaction mixture was warmed to rt and stirred for 15 min. The crude isocyanate was dissolved in 3 mL of THF, and the resulting solution was added dropwise, with rinsing with an additional 2 mL of THF. The solution was stirred for an additional 2 h at rt. The reaction was quenched by dropwise addition of water (1.0 mL), and the resulting mixture was then concentrated. The residue was diluted with 10 mL of brine and extracted with ethyl acetate (6 x 25 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography on silica gel (1%MeOH, 0.1% NH_4OH in CH_2Cl_2 to 10% MeOH, 1% NH_4OH in CH_2Cl_2) gave 357 mg (33%) of the urea as a white solid, mp 53-60 °C. IR (KBr): 3337, 2932, 1701, 1655, 1541, 1049 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (br s, 1H), 5.76 (br s, 1H), 3.45-3.30 (m, 1H), 2.48-2.38 (m, 1H), 2.32-2.16 (m, 1H), 2.25 (s, 6H), 1.88-1.72 (m, 2 H), 1.70-

1.60 (m, 1H), 1.37-1.02 (m, 4H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.3, 66.4, 56.5, 51.8, 39.8, 32.7, 25.1, 24.5, 22.1, 21.4. HRMS (FAB+) calcd for $C_{13}H_{28}N_3O_2S$ $[MH]^+$ 290.1902; found 290.1897.

2.23 The crude isocyanate was prepared from (1*R*,2*R*)-*N*,*N*-dimethylcyclohexanediamine (0.553 g, 3.89 mmol) as described above. (*R*)-*tert*-Butanesulfinamide (509 mg, 4.20 mmol) was dissolved in 40 mL of THF and cooled to -78 °C. Butyllithium (1.9 mL of a 2.2 M solution in hexanes, 4.2 mmol) was added dropwise, and then the reaction mixture was warmed to rt and stirred for 15 min. The crude isocyanate was dissolved in 6 mL of THF, and the resulting solution was added dropwise, with rinsing with an additional 3 mL of THF. The solution was stirred for an additional 3 h at rt. The reaction was quenched by dropwise addition of acetic acid (3 drops), and the resulting mixture was then concentrated. The residue was diluted with 4 mL of brine and extracted with EtOAc (5 x 5 mL). The organic layers were discarded, and the aqueous layer was made basic by the addition of 0.5 mL of concentrated NH_4OH. This mixture was then extracted with EtOAc (6 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield a crude oil which crystallized upon standing overnight. The crystals were triturated with EtOAc, collected by vacuum filtration, and rinsed on the filter with EtOAc and hexanes. The filtrate was then concentrated and the procedure was repeated twice, yielding 3 crops of the urea (total 336 mg, 30%) as a white solid, mp 150-153 °C. IR (KBr): 3558, 3312, 3248, 2931, 1647, 1533, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 (br s, 1H), 6.17 (br s, 1H), 3.48-3.34 (m, 1H), 2.45-2.16 (m, 2H), 2.24 (s, 6H), 1.88-1.72 (m, 2 H), 1.70-1.60 (m, 1H), 1.37-1.05 (m, 4H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.3, 66.4, 56.3, 52.0, 40.0, 32.9, 25.0, 24.6, 22.2, 22.0. HRMS (FAB+) calcd for $C_{13}H_{28}N_3O_2S$ $[MH]^+$ 290.1902; found 290.1908.

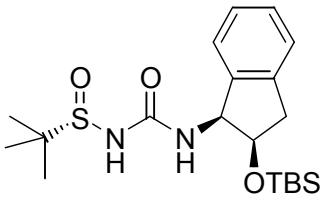


S1

A solution of *tert*-butylchlorodimethylsilane (8.1 g, 54 mmol) in CH_2Cl_2 was added to a stirred solution of (1*S*,2*R*)-cis-1-aminoindan-2-ol (4.00 g, 26.8 mmol), 4-dimethylaminopyridine (0.66 g, 5.4 mmol), and triethylamine (7.4 mL, 53 mmol) in CH_2Cl_2 (40 mL). After stirring 18 h, the reaction mixture was extracted with water (50 mL) followed by brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. Flash column chromatography on silica gel eluting with 2% to 50% EtOAc in hexanes afforded 7.1 g (100%) of the product as a light brown oil. IR (film): 2954, 2856, 1472, 1254, 1111, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-36 (m, 1H), 7.25-7.16 (m, 3H), 4.44 (apparent q, 1H), 4.12 (d, J = 5.3 Hz, 1H), 3.01 (dd, J = 5.9 Hz, 15.8 Hz, 1H), 2.88 (dd, J = 4.8 Hz, 15.8 Hz, 1H), 1.48 (br s, 2H), 0.90 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 144.4, 140.1, 127.6, 126.7, 124.8, 124.6, 75.3, 59.5, 39.2, 25.8, 18.2, -4.6, -4.8. HRMS (FAB+) calcd for $C_{15}H_{26}NOSi$ $[MH]^+$ 264.1784; found 264.1791.

2.31 Amine **S1** (2.46 g, 9.35 mmol) was dissolved in CH_2Cl_2 (100 mL). Saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was stirred for 15 min in an ice bath. The stirring was stopped, and a solution of triphosgene (0.925 g, 3.12 mmol) in CH_2Cl_2 (5 mL) was added directly to the CH_2Cl_2 layer via syringe. Stirring was resumed (1 min at slow speed,

followed by 1 min at high speed), and then the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated to yield crude isocyanate as a brown oil.
(*R*)-*tert*-Butanesulfinamide (1.13 g, 9.35 mmol) was dissolved in 75 mL of THF and cooled to -78 °C. Butyllithium (4.25 mL of a 2.2 M solution in hexanes, 9.35 mmol) was added dropwise, and then the reaction mixture was warmed to -40 °C and stirred for 15 min. The crude isocyanate was added dropwise, with rinsing with an additional 5 mL of THF. The cold bath was allowed to melt gradually, and the solution was stirred for an additional 16 h at rt. The reaction was quenched by dropwise addition of water (5 mL), and then the resulting mixture was concentrated. The residue was diluted with EtOAc (250 mL) and water (300 mL), and acidified to pH <2 with saturated aqueous $NaHSO_4$. The layers were separated, and the organic layer was washed with brine (50 mL) then dried over Na_2SO_4 and concentrated. Flash column chromatography on a Biotage Flash+ cartridge with a gradient of 12% to 60% of EtOAc in hexanes, followed by trituration with 5% EtOAc in hexanes afforded 3.30 g (86%) of the urea as a colorless powder, mp 177-179 °C (phase change at 100°C). IR (KBr): 3356, 2955, 1705, 1653, 1539 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.22-7.08 (m, 3H), 6.19 (d, *J* = 8.6 Hz, 1H), 5.26 (dd, *J* = 5.2 Hz, 8.4 Hz, 1H), 4.64-4.58 (m, 1H), 3.07 (dd, *J* = 4.9 Hz, 16.2 Hz, 1H), 2.88 (d, *J* = 16.2 Hz, 1H), 1.26 (s, 9H), 0.85 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 141.2, 139.7, 127.7, 127.0, 124.7, 124.5, 74.0, 58.1, 56.8, 40.4, 25.8, 22.1, 18.1, -4.8, -4.9. HRMS (FAB+) calcd for $C_{20}H_{35}N_2O_3SSi$ $[MH]^+$ 411.2138; found 411.2137.



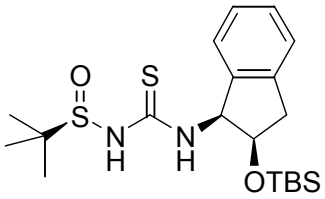
S2

Crude isocyanate was prepared as described above from amine **S1** (1.75 g, 6.65 mmol). (*S*)-*tert*-Butanesulfinamide (812 mg, 6.7 mmol) was dissolved in 30 mL of THF and cooled to -78 °C. Butyllithium (3.05 mL of a 2.2 M solution in hexanes, 6.7 mmol) was added dropwise, and then the reaction mixture was warmed to rt and stirred for 15 min. The crude isocyanate dissolved in 3 mL of THF was added dropwise, and then the solution was stirred for 16 h at rt. The reaction was quenched by dropwise addition of water (1 mL), and then the resulting mixture was concentrated. The residue was diluted with EtOAc (75 mL) and water (100 mL), and acidified to pH <2 with saturated aqueous $NaHSO_4$. The layers were separated, and the organic layer was washed with brine (100 mL) and then dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (0% to 5% MeOH in CH_2Cl_2) yielded 2.38 g (87%) of urea **S2** as an off-white foamy solid, mp 74-77 °C. IR (KBr): 3352, 2955, 2928, 2856, 1654, 1526, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (br s, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.25-7.14 (m, 3H), 6.16 (d, *J* = 8.2 Hz, 1H), 5.22 (dd, *J* = 5.4 Hz, 8.0 Hz, 1H), 4.65-4.58 (m, 1H), 3.07 (dd, *J* = 5.1 Hz, 16.2 Hz, 1H), 2.89 (dd, *J* = 1.9 Hz, 16.2 Hz, 1H), 1.28 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.4, 141.1, 139.6, 127.9, 126.9, 124.8, 124.7, 73.9, 58.1, 57.1, 40.3, 25.9, 22.2, 18.1, -4.7, -4.8. HRMS (FAB+) calcd for $C_{20}H_{35}N_2O_3SSi$ $[MH]^+$ 411.2138; found 411.2133.

2.24 Urea **2.31** (398 mg, 0.969 mmol) was dissolved in 3 mL of THF. To this solution was added 3 mL of a 1.0 M solution of tetrabutylammonium fluoride in THF. After 16 h, the reaction mixture was diluted to 25 mL with EtOAc, and washed with water (15 mL) followed by brine (15 mL). The aqueous layers were combined and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (50% EtOAc in hexanes to 100% EtOAc) followed by recrystallization from EtOAc yielded 246 mg (86%) of urea **2.24** as a white solid, mp 172-173 °C. IR (KBr): 3512, 3324, 2946, 1635, 1541, 1066 cm^{-1}. ^1H NMR (400 MHz, CD_3CN): δ 7.34 (br s, 1H), 7.28-7.15 (m, 4H), 6.22 (d, *J* = 8.2 Hz, 1H), 5.14 (dd, *J* = 8.4 Hz, 4.9 Hz, 1H), 4.50-4.42 (m, 1H), 3.41 (br s, 1H), 3.10 (dd, *J* = 16.4 Hz, 4.8 Hz, 1H), 2.83 (d, *J* = 16.5 Hz, 1H), 1.22 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN): δ 156.6, 142.9, 141.6, 128.7, 127.8, 126.2, 125.1, 73.8, 59.3, 56.3, 40.5, 22.7. HRMS (FAB+) calcd for $C_{14}H_{21}N_2O_3S$ $[MH]^+$ 297.1273; found 297.1271.

2.24 Alternate Procedure: (*R*)-*tert*-Butanesulfinamide (121 mg, 1.00 mmol) was dissolved in 10 mL of THF in a flame-dried flask under N_2. The solution was cooled in an ice bath. Butyllithium (0.26 mL of a 1.6 M solution in hexanes, 1.0 mmol) was added dropwise, and the resulting mixture was stirred for 10 min at 0 °C. In a separate flame-dried flask, 1,1'-carbonyldiimidazole (162 mg, 1.00 mmol) was dissolved in 5 mL of THF. This flask was cooled in an ice bath with stirring. The sulfinamide reaction mixture was transferred dropwise to this flask, resulting in the formation of a white precipitate. The resulting reaction mixture was stirred at 0 °C for 20 min, then the ice bath was removed and stirring continued at rt for an additional 30 min. A solution of (1*S*,2*R*)-cis-1-aminoindan-2-ol (164 mg, 1.10 mmol) in THF (10 mL) was added to the reaction mixture, and the resulting mixture was stirred for 30 min. The reaction was then quenched by the addition of sat. aq. $NaHSO_4$, then diluted with brine (20 mL). The reaction mixture was extracted with EtOAc (25 mL), and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The product was purified by reverse phase chromatography (C18 column, 5% to 95% MeCN in H_2O, 0.1% TFA) and lyophilized, then dried under vacuum over P_2O_5 to yield 271 mg (91%) of a fluffy white solid. The ^1H and ^{13}C NMR are the same as above.

2.25. Urea **S2** (1.64 g, 4.00 mmol) was dissolved in 12 mL of THF. To this solution was added 12 mL of a 1.0 M solution of tetrabutylammonium fluoride in THF. After 16 h, the reaction mixture was concentrated, and then the residue was diluted with 40 mL of water. This mixture was extracted with CH_2Cl_2 (50 mL followed by 2 x 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (0% to 5% MeOH in CH_2Cl_2) to yield 891 mg (75%) of the urea as a white solid, mp 116-119 °C. IR (KBr): 3336, 2961, 1654, 1541, 1226, 1052 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 7.28-7.11 (m, 4H), 6.76 (d, *J* = 8.8 Hz, 1H), 5.32-5.25 (m, 1H), 5.18 (d, *J* = 4.0 Hz, 1H), 4.63-4.57 (m, 1H), 3.12 (dd, *J* = 5.0 Hz, 16.4 Hz, 1H), 2.98 (d, *J* = 16.3 Hz, 1H), 1.29 (s, 9H) . $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ.156.4, 140.9, 140.3, 127.8, 126.7, 125.1, 124.2, 72.8, 58.6, 56.4, 39.5, 22.5 .HRMS (FAB+) calcd for $C_{14}H_{21}N_2O_3S$ $[MH]^+$ 297.1273; found 297.1271.

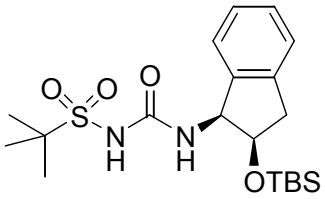


S3

Amine **S1** (3.50 g, 13.3 mmol) was dissolved in CH_2Cl_2 (150 mL). Aqueous K_2CO_3 (0.5 M, 150 mL) was added and the mixture was stirred for 15 min at rt. The stirring was stopped, and thiophosgene (2.04 mL, 26.6 mmol) was added directly to the CH_2Cl_2 layer via syringe. The biphasic mixture was stirred for 1.5 h, and then the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated to yield crude isothiocyanate as a brown oil.

(*R*)-*tert*-Butanesulfinamide (812 mg, 6.7 mmol) was dissolved in 30 mL of THF and cooled to -78 °C. Butyllithium (3.05 mL of a 2.2 M solution in hexanes, 6.7 mmol) was added dropwise, and then the reaction mixture was warmed to rt and stirred for 15 min. Half of the crude isothiocyanate (6.65 mmol) dissolved in 3 mL of THF was added dropwise, and then the solution was stirred for 45 h at rt. The reaction was quenched by dropwise addition of water (1 mL), and then the resulting mixture was concentrated. The residue was diluted with EtOAc (125 mL) and water (150 mL), and acidified to pH <2 with saturated aqueous $NaHSO_4$. The layers were separated, and the organic layer was washed with water (100 mL) followed by brine (100 mL) and then dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography on silica gel (0% to 5% MeOH in CH_2Cl_2), followed by trituration with EtOAc/hexanes. The mixed fractions were collected separately and subjected to a second purification under the same conditions to yield a total of 1.41 g (50%) of thiourea **S3** as a pale brown solid, mp 122-124 °C. IR (KBr):3273, 2955, 2928, 1491, 1254, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 6.3 Hz, 1H), 7.29-7.19 (m, 3H), 6.03 (dd, *J* = 5.0, 8.5 Hz, 1H) 4.74 (apparent t, 1H), 3.14 (dd, *J* = 4.7 Hz, 16.4 Hz, 1H), 2.92 (d, *J* = 16.4 Hz, 1H), 1.29 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 182.4, 140.2, 139.7, 128.0, 127.3, 124.9, 124.5, 73.8, 63.1, 58.1, 40.7, 25.8, 22.2, 18.1, -4.8, -4.8. HRMS (FAB+) calcd for $C_{20}H_{35}N_2O_3S_2Si$ $[MH]^+$ 427.1909; found 427.1916.

2.26 Thiourea **S3** (300 mg, 0.71 mmol) was dissolved in 10 mL of THF. To this solution was added 2.13 mL of a 1.0 M solution of tetrabutylammonium fluoride in THF. The solution was stirred for 16 h at rt, and then diluted with saturated aqueous ammonium chloride. The resulting mixture was extracted twice with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified by reverse phase chromatography on a Biotage C18 column using a gradient of 5% to 95% MeCN in H_2O (with 0.1% TFA) to yield the product (209 mg, 94%) as a white solid, mp 65-67 °C. IR (KBr): 3403, 3284, 2937, 1502, 1048 cm^{-1}. ^1H NMR (400 MHz, DMSO-d6): δ 9.49 (br s, 1H), 8.75 (d, J = 8.3 Hz, 1H), 7.32-7.14 (m, 4H), 5.73 (dd, *J* = 8.1 Hz, 5.0 Hz, 1H), 5.49 (d, *J* = 4.2, 1H), 4.56-4.48 (m, 1H), 3.12 (dd, *J* = 16.4 Hz, 4.6 Hz, 1H), 2.83 (d, *J* = 16.3 Hz, 1H), 1.22 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN): δ 185.0, 141.8, 141.7, 129.0, 127.7, 126.3, 125.4, 73.6, 63.8, 57.4, 40.7, 22.9. HRMS (FAB+) calcd for $C_{14}H_{21}N_2O_2S_2$ $[MH]^+$ 313.1044; found 313.1044.



S4

$RuCl_3$ (1 mg) and $NaIO_4$ (321 mg, 1.5 mmol) were added in one portion to a stirred solution of urea **2.31** (411 mg, 1.00 mmol) in MeCN (3 mL), CH_2Cl_2 (3 mL), and water (4.5 mL) at 0 °C. After 5 min, the ice bath was removed and stirring was continued for 20 min at rt. The reaction mixture was then diluted with EtOAc (25 mL) and washed with water (10 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was redissolved in EtOAc, filtered through a plug of silica, and concentrated to give 405 mg (95%) of product **S4** as a colorless powder, mp 216-219 °C. IR (KBr): 3350, 2933, 1680, 1523, 1332, 1127 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.02 (br s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.30 (d, , *J* = 7.2 Hz, 1H), 7.25-7.15 (m, 3H), 5.25-5.20 (m, 1H), 4.66-4.61 (m, 1H), 3.07 (dd, *J* = 5.3 Hz, 16.1 Hz, 1H), 2.91 (dd, *J* = 3.1 Hz, 16.1 Hz, 1H), 1.46 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.4, 140.8, 139.9, 128.0, 126.8, 124.9, 73.7, 61.9, 58.0, 40.3, 25.8, 24.1, 18.1, -4.7, -5.0. HRMS (FAB+) calcd for $C_{20}H_{35}N_2O_4SSi$ $[MH]^+$ 427.2087; found 427.2091.

2.27 Tetrabutylammonium fluoride (0.75 mL of a 1.0 M solution in THF) was added to a flask containing compound **S4** (107 mg, 0.250 mmol) and the solution was stirred for 20 h. An additional 1 mL of THF was added and the solution was stirred for 2 days. The mixture was diluted with EtOAc (30 mL) and washed with water (15 mL) followed by brine (15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Crystallization from EtOAc yielded 38.3 mg (49%) of product **8f** as a white solid, mp 170-173 °C. IR (KBr): 3347, 2989, 2823, 1683, 1529, 1328, 1125 cm^{-1}. ^1H NMR (400 MHz, DMSO-d6): δ 10.20 (br s, 1H), 7.25-7.13 (m, 5 H), 5.37 (d, *J* = 4.6 Hz, 1H), 5.04 (dd, J = 8.1 Hz, 5.1 Hz, 1H), 4.42 (apparent q, 1H), 3.06 (dd, J = 16.3 Hz, 4.8 Hz, 1H), 2.77 (d, J = 16.2, 1H), 1.37 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN): δ□153.6, 143.0, 141.0, 129.2, 128.1, 126.6, 125.5, 73.9, 63.1, 59.4, 41.0, 24.8. HRMS (FAB+) calcd for $C_{14}H_{20}LiN_2O_4S$ $[MLi]^+$ 319.1304; found 319.1300.

2.30. CH_2Cl_2 (12 mL) and saturated aqueous $NaHCO_3$ (12 mL) were added to a flask containing (*R*)-1-aminoindane hydrochloride salt (209 mg, 1.23 mmol), and the mixture was stirred for 15 min in an ice bath. The stirring was stopped, and a solution of triphosgene (0.122 g, 0.411 mmol) in CH_2Cl_2 (1.2 mL) was added directly to the CH_2Cl_2 layer via syringe. Stirring was resumed (3 min at slow speed, followed by 2 min at high speed), and then the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated to yield crude isocyanate as a brown oil.

(*R*)-*tert*-Butanesulfinamide (149 mg, 1.23 mmol) was dissolved in 12 mL of THF, and the resulting solution was cooled to -78 °C. Butyllithium (0.60 mL of a 2.2M solution in hexanes, 1.3 mmol) was added dropwise, and then the reaction mixture was warmed to rt and stirred for 15 min. The crude isocyanate dissolved in 1 mL of THF was added dropwise, with rinsing with an additional 1 mL of THF. The solution was stirred for an additional 5 h at rt. The reaction was quenched by dropwise addition of water (0.5 mL), and then the resulting mixture was concentrated. The residue was diluted with 0.01 M aqueous NaOH (50 mL), and the resulting solution washed with CH_2Cl_2 (3 x 25 mL). The aqueous layer was then acidified to pH

<2 with saturated aqueous $NaHSO_4$ and then extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was redissolved in EtOAc and then concentrated to give a brown oil which crystallized upon standing. The crystals were collected by vacuum filtration and rinsed with EtOAc (2x3 mL) on the filter to yield 83 mg (28%) of product as colorless needles, mp 178-180 °C (dec). IR (KBr): 3326, 3221, 2965, 1702, 1536, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (br s, 1H), 7.38-7.32 (m, 1H), 7.24-7.16 (m, 3H), 6.04 (d, J = 7.8 Hz, 1H), 5.31 (apparent q, 1H), 3.00-2.90 (m, 1H), 2.88-2.77 (m, 1H), 2.60-2.50 (m, 1H), 1.88-1.73 (m, 1H), 1.24 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ154.8, 143.2, 142.8, 128.0, 127.0, 124.7, 124.1, 56.9, 55.9, 34.2, 30.1, 22.2. HRMS (FAB+) calcd for $C_{14}H_{20}LiN_2O_2S$ $[MLi]^+$ 287.1406; found 287.1408.

Representative procedure for the enantioselective aza-Henry reaction (catalyst screening conditions, Scheme 2.2)

A dry vial containing 0.025 mmol of a potential catalyst under nitrogen was charged with 1.0 mL of a freshly prepared stock solution of imine (0.25 M) and hexamethylbenzene (0.013 M) in CH_2Cl_2. After stirring for 10 min, the vial was cooled to -40 °C, and *i*-Pr_2NEt (87 μL, 0.50 mmol) and $EtNO_2$ (90 μL, 1.25 mmol) were added sequentially. The solution was stirred at -40 °C for 13 h. The vial was removed from the cold bath, the reaction was quenched with 1 M aqueous HCl (3 mL), and the resulting mixture was extracted with CH_2Cl_2 (2 x 4 mL). The extract was dried over Na_2SO_4 and decanted. A 4 mL aliquot of the extract was concentrated for ^1H NMR analysis, while a 0.2 mL aliquot of the extract was filtered through a plug of silica gel, eluting with CH_2Cl_2 followed by concentration for HPLC analysis. The conversion to product **2.10** was determined by integration relative to the hexamethylbenzene internal standard. The dr and ee were determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/iPrOH 90/10, 1 mL min^{-1}): t_R (1*R*,2*S*) = 9.9 min, t_R (1*S*,2*R*) = 11.2 min, t_R (*anti*) = 12.5 min, 14.9 min. Stereochemical assignments are based on literature determinations.[10]

General Procedures for the Enantioselective Aza-Henry Reaction (Scheme 2.4).

To obtain reproducible results, the catalyst was dried under vacuum over P_2O_5 overnight prior to use.

Procedure C. An oven dried vial containing 0.05 mmol of catalyst **2.24** and 0.50 mmol of imine **2.9** under nitrogen was charged with MeCN (2.0 mL). The mixture was stirred at rt for 15 min, then cooled in a -78 °C bath. Nitroalkane (2.5 mmol) and *i*-Pr_2NEt (44 μL, 0.25 mmol) were added, and then the vial was transferred to a bath at -40 °C and the solution was stirred for 28 h. The reaction vial was removed from the cold bath and the reaction was quenched with 1 M aqueous HCl (4 mL). The resulting mixture was extracted with EtOAc (12 mL, then 2 x 4 mL). The organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by chromatography.

Procedure D. An oven dried flask containing 0.05 mmol of catalyst **2.24** and 0.50 mmol of imine **2.9** under nitrogen was charged with MeCN (2.0 mL) followed by *i*-Pr_2NEt (44 μL, 0.25 mmol). The solution was stirred at -40 °C for 10 min, and then $EtNO_2$ (180 μL, 2.5 mmol) was

added. After stirring for 27 h, the reaction was quenched with 1 M aqueous HCl (4 mL), and the resulting mixture was extracted with CH_2Cl_2 (12 mL, then 2 x 4 mL). The organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography, eluting with EtOAc/hexanes.

2.32a. General procedure D was followed, affording 117 mg (84%) of an 85:15 mixture of diastereomers as a white solid after chromatography. The ^{1}H NMR spectrum is consistent with values previously reported in the literature.[10,12] The ee of the major diastereomer was determined to be 95% by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90/10, 1 mL min^{-1}): t_R (major) = 10.4 min, t_R (minor) = 11.8 min. The ee of the minor diastereomer was determined to be 53% ee under the same analysis conditions: t_R (minor) = 13.6 min, t_R (major) = 16.4 min.

2.32b. General procedure C was followed, affording 99 mg (64%) of a 90:10 mixture of diastereomers as a white solid after chromatography. The ^{1}H NMR spectrum is consistent with values previously reported in the literature.[8] The ee of the major diastereomer was determined to be 95% by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90/10, 1 mL min^{-1}): t_R (major) = 15.5 min, t_R (minor) = 16.3 min. The ee of the minor diastereomer was determined to be 23% ee under the same analysis conditions: t_R (minor) = 18.4 min, t_R (major) = 23.0 min.

2.32c. General procedure D was followed, affording 102 mg (68%) of an 79:21 mixture of diastereomers as a white solid after chromatography. The ^{1}H NMR spectrum is consistent with values previously reported in the literature.[8] The ee the major diastereomer was determined to be 95% by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90/10, 1 mL min^{-1}): t_R (major) = 9.6 min, t_R (minor) = 10.7 min. The ee of the minor diastereomer was determined to be 60% ee under the same analysis conditions: t_R (minor) = 11.4 min, t_R (major) = 13.1 min.

2.32d. General procedure C was followed, affording 161 mg (92%) of a 77:23 mixture of diastereomers as a white solid after chromatography. The ^{1}H NMR spectrum is consistent with values previously reported in the literature.[12] The ee of the major diastereomer was determined to be 92% by chiral HPLC analysis (Chiralpak AD-H, hexanes/EtOH 95/05, 1 mL min^{-1}): t_R (major) = 11.4 min, t_R (minor) = 14.2 min. The ee of the minor diastereomer was determined to be 23% ee under the same analysis conditions: t_R (minor) = 16.4 min, t_R (major) = 27.6 min.

2.32e. General procedure C was followed, affording 139 mg (88%) of an 80:20 mixture of diastereomers as a white solid after chromatography. The ^{1}H NMR spectrum is consistent with values previously reported in the literature.[8] The ee of the major diastereomer was determined to be 94% by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90/10, 1 mL min^{-1}): t_R (minor) = 11.0 min, t_R (major) = 13.0 min. The ee of the minor diastereomer was determined to be 87% ee under the same analysis conditions: t_R (minor) = 9.6 min, t_R (major) = 17.3 min.

2.32f. General procedure D was followed, affording 132 mg (80%) of an 84:16 mixture of diastereomers as a white solid after chromatography. The ^{1}H NMR spectrum is consistent with values previously reported in the literature.[8] The ee of the major diastereomer was determined to be 93% by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90/10, 1 mL min^{-1}): t_R (major) = 13.8 min, t_R (minor) = 15.4 min. The ee of the minor diastereomer was determined to be 22% ee under the same analysis conditions: t_R (minor) = 17.7 min, t_R (major) = 20.2 min.

2.32g. General procedure C was followed on 0.25 mmol scale, affording 52 mg (80%) of a 92:8 mixture of diastereomers as a white solid after chromatography. The ee of the major diastereomer was determined to be 96% by chiral HPLC analysis (Chiralpak AS, hexanes/EtOH 99/1, 1 mL min^{-1}): t_R (minor) = 9.7 min, t_R (major) = 11.1 min. The ee of the minor diastereomer was determined to be 70% under the same analysis conditions. t_R (major) = 6.7 min, t_R (minor) = 7.4 min. The diastereomers were separated by silica gel chromatography for NMR analysis.

(*syn*, major): ^{1}H NMR (400 MHz, $CDCl_3$, 80:20 mixture of rotamers): 4.75-4.60 (m, 1.6H), 4.55-4.38 (m, 0.4H), 4.11-4.00 (m, 0.2H), 4.00-3.90 (m, 0.8H), 1.53 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H), 1.61-1.20 (m, 6H), 0.95-0.83 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.4, 85.6, 80.1, 53.5, 29.2, 28.3, 28.1, 22.2, 15.1, 13.9.

(*anti*, minor): ^{1}H NMR (400 MHz, $CDCl_3$, 90:10 mixture of rotamers): δ 4.98-4.85 (m, 0.9H), 4.78-4.70 (m, 0.9H), 4.68-4.53 (m, 0.2H), 3.96-3.78 (m, 1H), 1.57 (d, J = 6.8 Hz, 3H), 1.42 (s, 9H), 1.61-1.20 (m, 6H), 0.95-0.82 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.8, 85.6, 79.9, 52.7, 31.9, 28.3, 28.1, 22.3, 16.4, 13.9. HRMS (FAB+) calcd for $C_{12}H_{25}N_2O_4$ $[MH]^+$ 261.1814; found 261.1809.

2.32h. General procedure C was followed on 0.25 mmol scale, affording 49 mg (75%) of a 93:7 mixture of diastereomers as a white solid after chromatography. The ee of the major diastereomer was determined to be 96% by chiral HPLC analysis (Chiralpak AS, hexanes/EtOH 99/1, 1 mL min^{-1}): t_R (minor) = 7.7 min, t_R (major) = 9.6 min. The ee of the minor diastereomer was not determined. The diastereomers were separated for NMR analysis by silica gel chromatography.

(*syn*, major): ^{1}H NMR (400 MHz, $CDCl_3$, 82:18 mixture of rotamers): δ 4.85-4.75 (m, 0.18 H), 4.75-4.62 (m, 1.64H), 4.50-4.40 (m, 0.18H), 4.22-4.12 (m, 0.18H), 4.08-3.96 (m, 0.82H), 1.78-1.60 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H), 1.45 (s, 9H), 1.27 (apparent t, 2H), 0.98-0.88 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.2, 85.8, 80.0, 51.8, 38.4, 28.2, 24.7, 23.4, 21.3, 15.1. HRMS (FAB+) calcd for $C_{12}H_{25}N_2O_4$ $[MH]^+$ 261.1814; found 261.1821.

(*anti*, minor) ^{1}H NMR (400 MHz, $CDCl_3$, 85:15 mixture of rotamers): δ 4.97-4.82 (m, 0.85 H), 4.76-4.65 (m, 1H), 4.65-4.55 (m, 0.15H), 4.08-3.88 (m, 1H), 1.78-1.62 (m, 1H), 1.57 (d, J = 6.3 Hz, 3H), 1.45 (s, 9H), 1.42-1.16 (m, 2H), 1.02-0.85 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.6, 86.0, 79.8, 50.8, 41.0, 28.2, 24.7, 23.0, 21.8, 16.3.

2.32i. General procedure C was followed, affording 104 mg (62%) of an 88:12 mixture of diastereomers as a white solid after reverse phase chromatography (Biotage C18 25+M cartridge, 30% to 100% MeCN in H_2O with 0.1% TFA). The ee of the major diastereomer was determined to be 96% by chiral HPLC analysis (Chiralpak AD-H, hexanes/EtOH 97/3, 1 mL min^{-1}): t_R (major) = 8.6 min, t_R (minor) = 16.2 min. The ee of the minor diastereomer was not determined. The diastereomers were separated for analysis by silica gel chromatography.

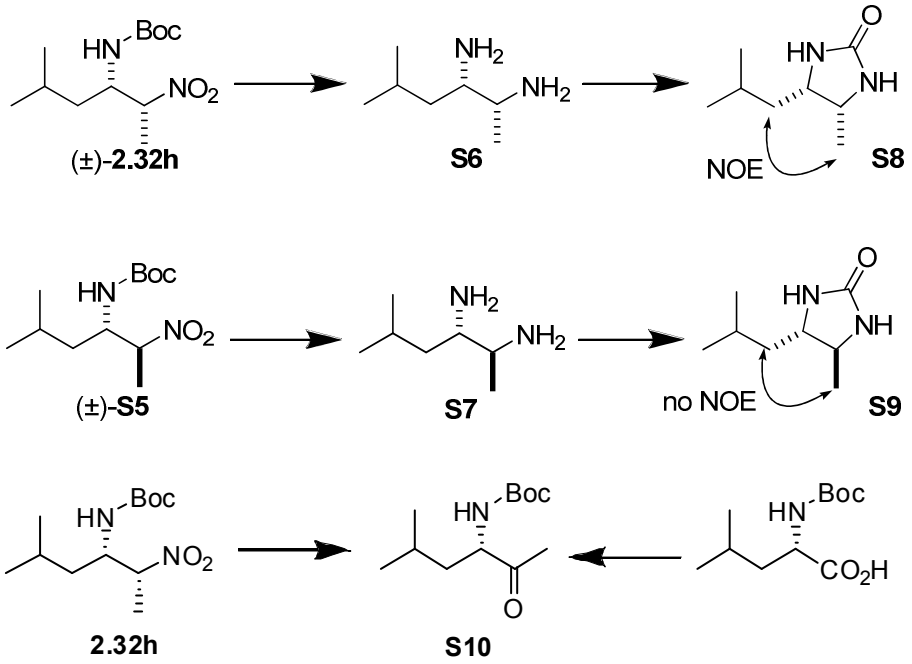
(*syn*, major): ^{1}H NMR (400 MHz, $CDCl_3$, 77:23 mixture of rotamers): δ 7.31-7.18 (m, 3H), 7.18-7.11 (d, J = 7.1 Hz, 2H), 5.40 (d, J = 8.9 Hz, 0.23H), 4.92-4.83 (m, 0.77H), 4.73-4.60 (m, 1H), 4.19-4.08 (m, 1H), 3.33 (dd, J = 10.7 Hz, 14.6 Hz, 1H), 3.15-3.00 (m, 1H), 1.80-1.60 (m, 1H), 1.45 (s, 9H), 1.42-1.20 (m, 2H), 0.98-0.87 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, mixture of rotamers, major rotamer peaks reported): δ 155.2,135.5, 128.7, 128.7, 127.3, 92.6, 80.1, 51.3, 38.7, 36.0, 28.2, 24.6, 23.4, 21.1. mp 132-133 °C. HRMS (FAB+) calcd for

$C_{18}H_{28}N_2O_4Na$ $[MNa]^+$ 359.1947; found 359.1956. IR (NaCl): 3355, 2960, 2929, 1680, 1545, 1160 cm^{-1}.

(*anti*, minor): ^1H NMR (400 MHz, $CDCl_3$, 9:1 mixture of rotamers): δ δ 7.33-7.22 (m, 3H), 7.18-7.11 (m, 2 H), 5.00 (d, *J* = 10.2 Hz, 0.9H), 4.82-4.72 (m, 1.1H), 4.20-4.10 (m, 0.9 H) 4.00-3.90 (m, 0.1 H), 3.31 (dd, *J* = 9.9 Hz, 14.5 Hz, 1H), 3.15 (dd, J = 4.5 Hz, 14.5 Hz, 1H), 1.75-1.62 (m, 1H), 1.48 (s, 9H), 1.40-1.24 (m, 2H), 0.95-0.87 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.6,135.3, 128.9, 128.8, 127.5, 92.9, 80.0, 49.9, 41.5, 37.0, 28.3, 24.7, 22.8, 21.9.

2.32j. General procedure C was followed on 0.25 mmol scale, affording 39.5 mg (64%) of the product as a white solid, mp 67-69 °C, after silica gel chromatography (10% EtOAc in Hexanes). The ee was determined to be 95% by chiral HPLC analysis (Chiralpak AS, hexanes/*i*PrOH 98/2, 1 mL min^{-1}): t_R (major) = 10.1 min, t_R (minor) = 12.2 min. ^1H NMR (400 MHz, $CDCl_3$, 85:15 mixture of rotamers): δ 4.95-4.70 (m, 1H), 4.58-4.46 (m, 1.7H), 4.45-4.35 (m, 0.3H), 4.25-4.14 (m, 1H), 1.80-1.60 (m, 1H), 1.44 (s, 9H), 1.45-1.22 (m, 2H), 0.98-0.92 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.0, 80.0, 78.7, 47.4, 40.5, 28.2, 24.7, 22.7, 21.8. HRMS (FAB+) calcd for $C_{11}H_{23}N_2O_4$ $[MH]^+$ 247.1658; found 247.1655. IR (NaCl): 3340, 2963, 1684, 1557, 1167 cm^{-1}.

Determination of the Stereochemistry of Product 2.32h



Reduction of nitro group and removal of Boc group:

Racemic **2.31h** (260 mg, 1.00 mmol) was dissolved in MeOH (7.5 mL) and cooled to 0 °C. $NiCl_2$ (135 mg, 1.04 mmol) was added to the solution with stirring, followed by addition of $NaBH_4$ (188 mg, 5.1 mmol). After stirring for 15 min, the reaction was quenched with sat. aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were washed with brine (75 mL), dried over Na_2SO_4, and concentrated. The crude residue was filtered through a short plug of silica, eluting with 90:10:1 CH_2Cl_2:MeOH:NH_4OH,

and then was concentrated. The white solid obtained was redissolved in a mixture of MeOH (3.5 mL) and conc. HCl (1.5 mL) and was stirred at rt for 16 h. The mixture was diluted with 1N aqueous NaOH (40 mL), and extracted with CH_2Cl_2 (5 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield 101 mg (77% over two steps) of diamine **S6** in approximately 95% purity by ^{1}H NMR.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86-2.78 (m, 1H), 2.72-2.64 (m, 1H), 1.78-1.64 (m, 1H), 1.38 (br s, 4H), 1.20-1.12 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 53.9, 51.0, 42.5, 24.5, 23.6, 21.4, 17.4.

Racemic **S5** (260 mg, 1.00 mmol) was dissolved in MeOH (7.5 mL) and cooled to 0 °C. $NiCl_2$ (135 mg, 1.04 mmol) was added to the solution with stirring, followed by addition of $NaBH_4$ (188 mg, 5.1 mmol). After stirring for 15 min, the reaction was quenched with sat. aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were washed with brine (75 mL), dried over Na_2SO_4, and concentrated. The crude residue was filtered through a short plug of silica, eluting with 90:10:1 CH_2Cl_2:MeOH:NH_4OH, and then was concentrated. The clear oil obtained was redissolved in a mixture of MeOH (3.5 mL) and conc. HCl (1.5 mL) and was stirred at rt for 4 h. The mixture was diluted with 1N aqueous NaOH (40 mL), and extracted with CH_2Cl_2 (5 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield 120 mg (91% over two steps) of diamine **S7** in approximately 95% purity by ^{1}H NMR.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72-2.64 (m, 1H), 2.55-2.47 (m, 1H), 1.80-1.68 (m, 1H), 1.34 (br s, 4H), 1.30-1.12 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 54.4, 51.2, 43.6, 24.5, 23.6, 21.3, 20.6.

Cyclization:

Diamine **S6** (52 mg, 0.49 mmol) was dissolved in CH_2Cl_2 (5 mL). A solution of di-*tert* butyl tricarbonate (155 mg, 0.59 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min to the diamine solution with stirring. The mixture was stirred an additional 10 min, and then was concentrated. The crude residue was purified by silica gel chromatography (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to yield 45 mg (59%) of the cyclized product **S8** as a white solid. NMR (400 MHz, $CDCl_3$): δ 5.73 (br s, 1H), 5.62 (br s, 1H), 3.85-3.75 (m, 2H), 1.67-1.55 (m, 1H), 1.55-1.45 (m, 1H), 1.26-1.18 (m, 1H), 1.11 (d, *J* = 5.8 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.1, 53.7, 51.4, 38.3, 25.0, 23.5, 21.6, 15.7. HRMS (FAB+) calcd for $C_8H_{17}N_2O$ $[MH]^+$ 157.1341; found 157.1340.

Diamine **S7** (52 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (4 mL). A solution of di-*tert* butyl tricarbonate (125 mg, 0.48 mmol) in CH_2Cl_2 (4 mL) was added dropwise over 10 min to the diamine solution with stirring. The mixture was stirred an additional 10 min, and then was concentrated. The crude residue was purified by silica gel chromatography (100% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to yield 43 mg (69%) of the cyclized product **S9** as a white solid. NMR (400 MHz, $CDCl_3$): δ 5.78 (br s, 1H), 5.72 (br s, 1H), 3.45-3.35 (m, 1H), 3.35-3.27 (m, 1H), 1.75-1.60 (m, 1H), 1.52-1.43 (m, 1H), 1.36-1.27 (m, 1H), 1.22 (d, *J* = 6.1 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.5, 58.5, 54.6, 44.4, 24.8, 23.2, 21.9, 20.8. HRMS (FAB+) calcd for $C_8H_{17}N_2O$ $[MH]^+$ 157.1341; found 157.1338.

Synthesis of Ketone:

Compound **2.32h** (130 mg, 0.50 mmol) was dissolved in 1 mL of MeOH. A solution of NaOMe in MeOH (1.0 mmol in 1.0 mL, freshly prepared from Na and MeOH) was added,

followed by an additional 3 mL of MeOH. The mixture was cooled in a -78 °C bath, and ozone was bubbled through until a pale blue color persisted. The solution was stirred for 1 h, and then purged with dry N_2. Dimethylsulfide (0.5 mL) was added, and then the cold bath was removed and the mixture was stirred for 16 h at rt. The solution was concentrated, then diluted with 5 mL of water and extracted with 5 mL of CH_2Cl_2. The organic layer was washed with brine (2 x 5 mL), dried over Na_2SO_4, and concentrated. Flash column chromatography on a Biotage Flash+ cartridge with a gradient of 3% to 24% EtOAc in hexanes provided 61.3 mg (53%) of ketone **S10** as a thick oil which solidified upon standing. The ^{1}H NMR spectrum is consistent with literature data.[6] The product was determined to be 91% ee by chiral HPLC analysis (Chiralpak AS, hexanes/EtOH 99/1, 1 mL min^{-1}): t_R (major) = 7.0 min, t_R (minor) = 9.5 min. $[\alpha]^{26}_D$ = + 34.7° (*c* = 1, $CHCl_3$).

Ketone **S10** was also prepared from Boc-Leucine according to the literature procedure[25] in >99% ee. $[\alpha]^{26}_D$ = + 38.9° (*c* = 1, $CHCl_3$)

Addition of Thioacetic Acid to β-Nitrostyrene (eq 2.3):

β-Nitrostyrene **2.33** (29.8 mg, 0.200 mmol) and catalyst **2.22** (1.2 mg, 0.0040 mmol, 2 mol%) were dissolved in Et_2O (1 mL) and cooled to -15 °C with stirring. Thioacetic acid (29 μL, 0.40 mmol, 2.0 equiv) was added, and the reaction mixture was stirred for 15 min. Formation of product was observed as a white precipitate. The reaction mixture was diluted with 4 mL of Et_2O to dissolve the precipitate, removed from the cold bath, and extracted with sat aq $NaHCO_3$. The organic layer was filtered directly through a plug of silica to remove the catalyst, eluting with additional Et_2O. The solvent was removed by rotary evaporation, providing analytically pure product as determined by ^{1}H NMR (the spectrum is consistent with the literature report).[13] The ee of the product was determined to be 57% by chiral HPLC (Chiralpak AS, 95/5 Hexanes/iPrOH, 1 mL min^{-1}): t_R (minor) = 12.8 min, t_R (major) = 13.8 min.

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Chapter 3. Development of an *N*-Sulfinyl Prolinamide for the Asymmetric Aldol Reaction.

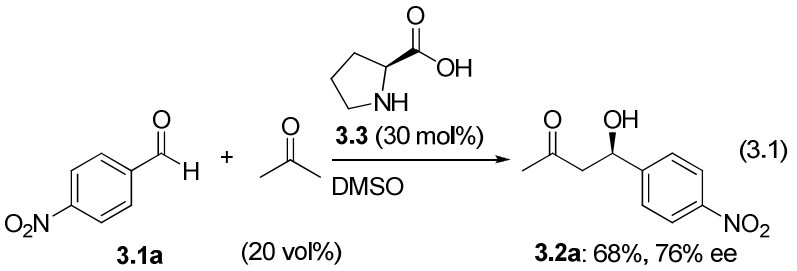
A new organocatalyst is reported that incorporates an N-sulfinyl amide as a hydrogen-bond donor, replacing the carboxylic acid of proline. The application of this catalyst to the asymmetric aldol reaction is described.

Authorship

This project was conducted in collaboration with Melissa Herbage. Melissa synthesized *N*-sulfinyl amides **3.15** and **3.16** and assisted with the characterization of **3.9** and **3.10**.

Introduction

The proline-catalyzed enantioselective intermolecular aldol reaction was first reported by List, Lerner, and Barbas in 2000 (eq 3.1).[1] This reaction, a prototypical example of enamine-based organocatalysis, proceeds via reversible condensation of the catalytic amine with a ketone to provide a nucleophilic enamine intermediate. In this reaction, the carboxylic acid functionality on proline was found to be important and is postulated to activate and orient the aldehyde acceptor via a hydrogen-bonding interaction.



The high catalyst loading required and the moderate enantioselectivities obtained with aryl aldehyde substrates in this reaction have led many researchers to investigate the replacement of the carboxylic acid of proline (**3.3**) with other H-bond donors (Figure 1).[2,3] Achiral acid replacements such as tetrazole (**3.4**),[4-14] initially reported for the aldol reaction by the Arvidsson group,[4] or sulfonyl amides (**3.5**),[8,15-19] initially reported by Berkessel and coworkers,[15] have been described. The prolinamide scaffold (**3.6**) is less acidic but provides opportunity for incorporation of additional chiral centers as well as additional tethered hydrogen bond donors or amines.[20-40] Worch and Bolm recently detailed replacement of the carboxylic acid with a chiral sulfonimidamide (**3.7**), which represents the first example of a carboxylic acid derivative that is both chiral and acidic.[41] In their study of the aldol condensation of cyclohexanone with aromatic aldehydes, evaluation of each diastereomer of the catalyst revealed that for most substrates, the configuration of the stereogenic sulfur in the catalyst had only a minor impact on the ee of the products obtained.

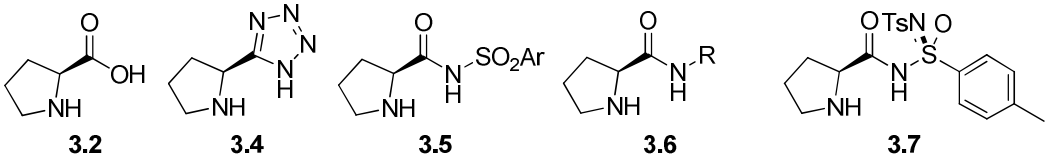


Figure 3.1. Selected organocatalysts for the aldol reaction

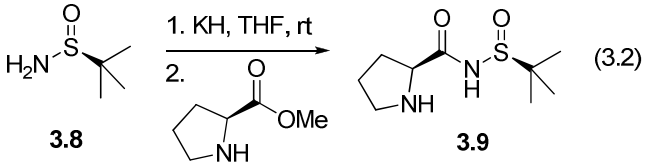
As described in Chapter 2, the utility of the *N*-sulfinyl group as both a chiral directing group and acidifying element in hydrogen-bonding organocatalysts has been demonstrated by the successful application of *N*-sulfinyl ureas, initially in the addition of nitroalkanes to imines (the aza-Henry reaction),[42] and more recently the addition of thioacetic acid to nitroalkenes.[43] In these

reactions, the sulfinyl N-H is postulated to activate the substrates by the formation of key hydrogen bonding interactions. The inductive electron-withdrawing effect of the sulfinyl group acidifies this N-H bond, helping to strengthen the hydrogen bonding interactions. Additionally, close proximity of the stereogenic sulfur to the active site of the catalysts contributes to high levels of stereocontrol in these reactions (vide infra).

On the basis of the success of *N*-sulfinyl ureas in hydrogen-bonding organocatalysis, we sought to extend this concept to enamine-based organocatalysis. Specifically, we postulated that the incorporation of an *N*-sulfinyl amide in place of the carboxylic acid of proline would maintain the level of acidity required to act as an efficient hydrogen bond donor, while at the same time the chiral nature of the sulfinamide substituent could contribute to the achievement of high levels of stereocontrol in the aldol reaction.

Results and Discussion

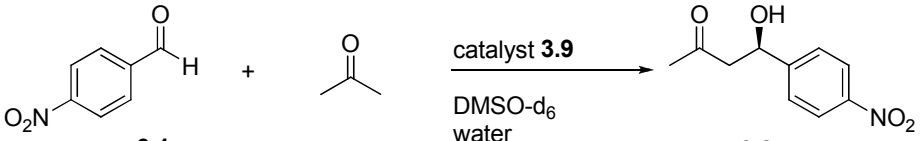
In order to test this hypothesis, a panel of *N*-sulfinyl amides was synthesized. A simple procedure was developed for the synthesis of these catalysts from the reaction of enantiomerically pure sulfinamides with either enantiomer of the commercially available amino acid methyl esters. For example, catalyst **3.9** was obtained in 82% yield by deprotonating (*S*)-*tert*-butanesulfinamide with KH, followed by addition of L-proline methyl ester (eq 3.2). Several different sulfinamide substituents were incorporated, and both diastereomers of each catalyst were prepared in order to systematically evaluate the effect of the sulfinyl substituent and stereocenter on the selectivity of the aldol reaction.



(3.2)

In initial studies, *N*-sulfinyl amide **3.9** was identified as a promising catalyst, and a survey of solvents revealed that the highest enantioselectivities were obtained in DMSO. Therefore, optimization of the reaction parameters was undertaken with catalyst **3.9** in DMSO-d_6 (Table 3.1). Importantly, it was discovered that addition of a small amount of water to the reaction mixture was important for both the reactivity and selectivity (entries 1-5), while larger amounts of water were detrimental (entry 6). The catalyst loading could be decreased at the expense of reaction rate (entries 7-9). The reaction was relatively independent of the amount of DMSO used, allowing the reaction to be conducted at higher concentrations (entries 8, 10, and 11). A direct correlation was observed between the reaction rate and the amount of acetone added (entries 10 vs. 12).

Table 3.1. Optimization of Reaction Conditions



3.1a **3.2a**

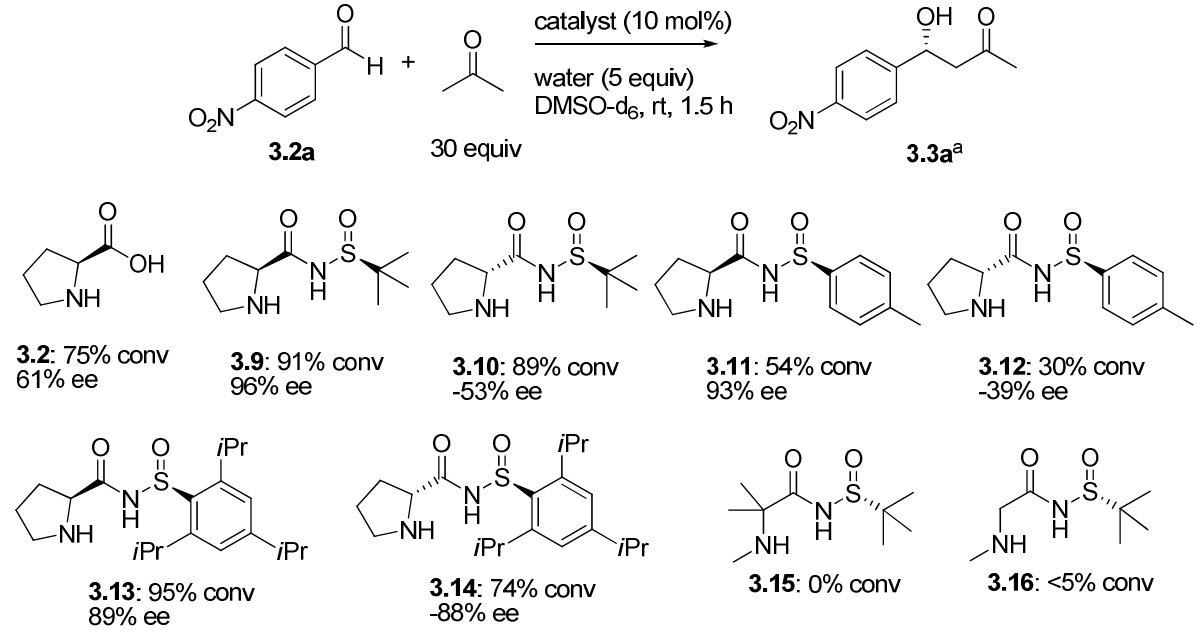
entry	equiv catalyst	[**3.1a**] in DMSO (M)	equiv acetone	equiv water	time [a] (h)	conv [a] (%)	ee [b] (%)
1	0.20	0.125	30	0	>1.5 [c]	45	89
2	0.20	0.125	30	1	0.5	89	92
3	0.20	0.125	30	2	0.5	88	94
4	0.20	0.125	30	5	0.5	86	96
5	0.20	0.125	30	10	0.5	83	96
6	0.20	0.125	30	30	>1.5 [d]	66	93
7	0.10	0.125	30	5	4	88	95
8	0.05	0.125	30	5	48	87	96
9	0.025	0.125	30	5	> 96 [e]	77	94
10	0.05	0.25	30	5	48	92	95
11	0.05	0.50	30	5	48	91	94
12	0.05	0.25	15	5	96	94	95

[a] Time required for >97% consumption of **3.1a** and conversion to **3.2a** at that time was determined by ^{1}H NMR relative to trimethoxybenzene as an internal standard. [b] Enantioselectivity was determined by chiral HPLC. [c] 29% of **3.1a** remains after 1.5 h. [d] 14% of **3.1a** remains after 1.5 h. [e] 18 % of **3.1a** remains after 96 h.

With optimal reaction conditions established, the performance of each of the *N*-sulfinyl amide catalysts was evaluated (Scheme 3.1). While a dramatic difference in enantioselectivity was observed for the *tert*-butanesulfinyl amide diastereomers **3.9** and **3.10**, very little effect of the sulfur stereocenter was observed for trisylsulfinyl amides **3.13** and **3.14**. Additionally, the reaction was significantly slower in the presence of the arenesulfinyl amide derivatives. The performance of catalysts **3.15** and **3.16**, which incorporate achiral secondary amino acids, clearly demonstrate the importance of the proline scaffold for good reaction efficiency. This is consistent with the report by List and coworkers,[1] in which N-methyl valine provided poor conversion for this aldol reaction.

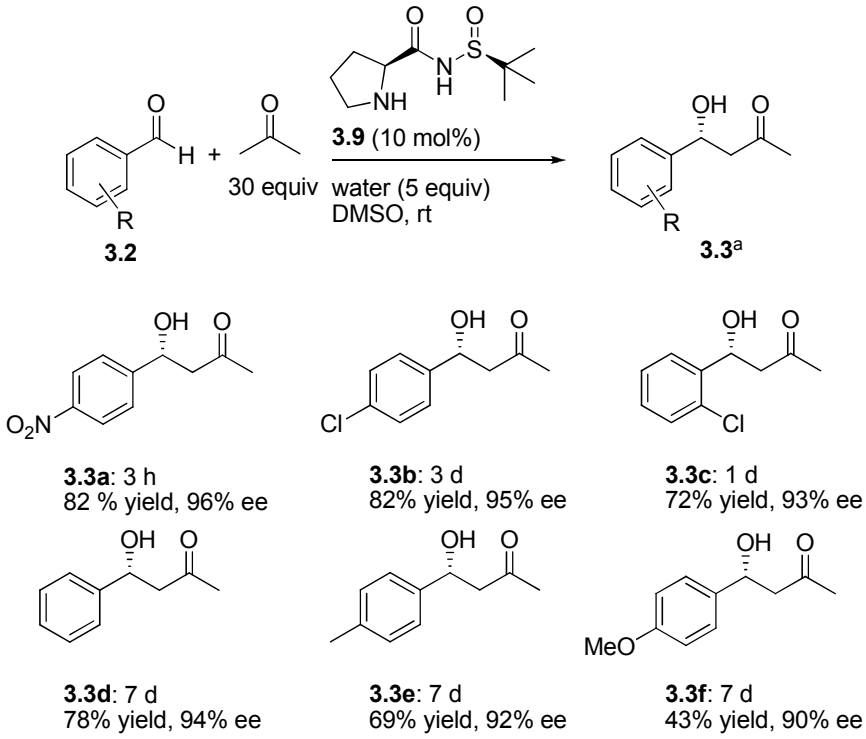
Next, the scope of the reaction was evaluated (Scheme 3.2). The aldol reaction of acetone with a variety of aryl aldehydes proceeded smoothly, providing the products with 90-96% ee. For aldehydes with electron withdrawing substituents the reaction proceeded in high conversion within 3 d, and the aldol products were isolated in high yields (**3.3a** – **3.3c**). However, in the case of the less reactive aldehydes much longer reaction times were necessary (1 week) to achieve reasonable conversion (**3.3d** – **3.3f**).

Scheme 3.1. Catalyst Evaluation for Enantioselective Aldol Reaction.



[a] Conversion to product was determined by ^{1}H NMR analysis relative to trimethoxybenzene as an internal standard. Enantioselectivity was determined by chiral HPLC analysis.

Scheme 3.2. Substrate Scope



[a] Products were isolated by extraction and purified by silica gel chromatography after the indicated time. Enantioselectivity was determined by chiral HPLC analysis.

Conclusions

We have demonstrated the utility of the *N*-sulfinyl amide as a chiral carboxylic acid replacement in the proline scaffold for the highly enantioselective intermolecular aldol reaction. The dramatic difference in stereoselectivity between the diastereomeric *N*-*tert*-butanesulfinyl amides demonstrates that the chirality of the sulfinyl substituent in addition to its acidifying nature is important for reactivity.

Experimental

General Methods.

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was carried out either with Merck 60 230-240 mesh silica gel, or using a Biotage SP Flash Purification System (Biotage No. SP1-B1A) with Flash+ cartridges (Biotage No. FPK0-1107-16046). ^{1}H and $^{13}C\{^{1}H\}$ NMR chemical shifts are reported in ppm relative to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. IR spectra were recorded as thin films on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory or as KBr pellets on a Nicolet MAGNA-IR 850 spectrometer, and only partial data are listed. Mass spectrometry (HRMS) was carried out by the University of California at Berkeley Mass Spectrometry Facility.

The syntheses of catalysts **3.9-3.14** were carried out under nitrogen in flame-dried glassware, using dry tetrahydrofuran (THF) that was passed through columns of activated alumina under nitrogen pressure immediately prior to use. Enantiomerically pure proline methyl esters were purchased as the corresponding hydrochloride salts and were isolated as the free bases by extraction with CH_2Cl_2 and aqueous K_2CO_3. The proline methyl esters contained up to 1 equiv of residual CH_2Cl_2 after concentration (as determined by ^{1}H NMR) and the mass of material used was adjusted in each case to account for the presence of the CH_2Cl_2. The aldol reactions were carried out using commercial solvents and reagents without further drying, and were set up in vials without any precautions to exclude air.

Catalyst Synthesis

3.9. A solution of (S)-*tert*-butanesulfinamide (1.21 g, 10.0 mmol) in THF (40 mL) was added to a stirred suspension of KH (0.420 g, 10.5 mmol) in THF (40 mL), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt, providing a white slurry. (L)-Proline methyl ester (10.8 mmol) was added via syringe, and the white slurry dissolved within 3 min to provide a clear solution. After 30 min, the reaction was quenched by addition of acetic acid (0.630 g, 10.5 mmol) and water (1 mL). The crude mixture was concentrated to remove the THF and then purified by reverse phase chromatography without buffers (Biotage 40+M C_{18} column, 1% to 100% MeOH in H_2O). The product was concentrated to remove the water, then recrystallized from hot EtOAc in the presence of a trace amount of MeOH. The crystals were collected by vacuum filtration and rinsed with additional EtOAc and hexanes, to yield 1.79 g (82%) of **3.9** as a white crystalline solid, mp 149.5 – 150.0 °C (phase change at 139 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.86 (m, 2H), 2.03 (m, 1H), 2.25 (m, 1H), 3.24 (m, 1H), 3.33 (m, 1H), 4.16 (m, 1H). ^{13}C

NMR (126 MHz, $CDCl_3$): δ 22.1, 25.4, 30.9, 47.0, 53.6, 61.3, 178.0. IR (neat): 3646, 3451, 3095, 2659, 1586, 1537, 1367, 1369, 1321, 811, 546 cm^{-1}. Exact mass calcd for $C_9H_{18}N_2O_2S$ requires m/z 219.1162, found m/z 219.1165 ($M+H^+$, ESI).

3.10. A solution of (R)-*tert*-butanesulfinamide (0.303 g, 2.50 mmol) in THF (10 mL) was added to a stirred suspension of KH (0.105 g, 2.63 mmol) in THF (10 mL), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt, providing a white slurry. (D)-Proline methyl ester (3.0 mmol) was added via syringe, and the white slurry dissolved within 3 min to provide a clear solution. After 30 min, the reaction was quenched by addition of acetic acid (0.158 g, 2.63 mmol) and water (1 mL). The crude mixture was concentrated to remove most of the THF, and the resulting white precipitate was collected by vacuum filtration and then rinsed on the filter with small amounts of water and Et_2O. The crude product was dissolved in 100 mL of hot EtOAc, and the resulting solution was filtered twice to remove insoluble white solids. The filtrate was concentrated, then recrystallized from approximately 5 mL of EtOAc. The solids were collected by vacuum filtration and rinsed with additional EtOAc, to yield 0.22 g (41%) of **3.10** as a white powder, mp 149.5 – 150.0 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 9H), 1.75 (m, 2H), 1.96 (m, 1H), 2.19 (m, 1H), 2.95 (m, 1H), 3.09 (m, 1H) 3.89 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.1, 26.2, 30.8, 47.2, 56.1, 61.1, 176.5. IR (neat): 3651, 3368, 2981, 2888, 1566, 1298, 1270, 935, 599 cm^{-1}. Exact mass calcd for $C_9H_{18}N_2O_2S$ requires m/z 219.1162, found m/z 219.1162 ($M+H^+$, ESI).

3.11. A solution of (S)-toluenesulfinamide (0.388 g, 2.50 mmol) in THF (10 mL) was added to a stirred suspension of KH (0.105 g, 2.63 mmol) in THF (10 mL) resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt. (L)-Proline methyl ester (3.0 mmol) was added via syringe. After 30 min, the reaction was quenched by addition of acetic acid (0.158 g, 2.63 mmol) and water (8 mL). The crude mixture was concentrated to remove the THF, and the resulting white precipitate was collected by vacuum filtration and rinsed on the filter with small amounts of water. The crude product was recrystallized from EtOAc in the presence of trace amounts of MeOH. The solids were collected by vacuum filtration and rinsed with additional EtOAc to yield 0.30 g (48%) of **3.11** as a white crystalline solid, mp 126.0 – 127.0 °C . ^1H NMR (600 MHz, $CDCl_3$): δ 1.80 (m, 1H), 1.90 (m, 1H), 2.08 (m, 1H), 2.26 (m, 1H), 2.39 (s, 3H), 3.23 (m, 1H), 3.35 (m, 1H), 4.21 (m, 1H), 7.27 (d, J = 8.0, 2H), 7.61 (d, J = 8.0, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 25.6, 30.7, 47.1, 61.4, 125.0, 129.7, 141.3, 142.8, 177.5. Exact mass calcd for $C_{12}H_{16}N_2O_2SNa$ requires m/z 275.0825, found m/z 275.0832 ($M+Na^+$, ESI).

3.12. THF (10 mL) was added to a flask containing (S)-toluenesulfinamide (0.388 g, 2.50 mmol) and KH (0.100 g, 2.50 mmol), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 1.5 h at rt. (D)-Proline methyl ester (3.0 mmol) was added via syringe. After 2 h, the reaction was quenched by addition of acetic acid (0.150 g, 2.50 mmol), and resulting mixture was stirred for 20 min. The crude mixture in THF was loaded onto a silica plug and side products were eluted with 100% EtOAc. The mobile phase was switched to 50:40:10 EtOAc:MeOH:NH_4OH, resulting in rapid elution of the product. Fractions containing the desired product were concentrated several times from EtOAc, and then the white solid was dissolved in CH_2Cl_2 and filtered to remove a white solid byproduct. The filtrated was concentrated and then recrystallized from EtOAc. The solids were

collected by vacuum filtration and rinsed with additional EtOAc, to yield 0.21 g (34%) of **3.12** as a white powder, mp 115.0 – 117.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.70 (m, 2H), 1.99 (m, 1H), 2.20 (m, 1H), 2.43 (s, 3H), 2.79 (m, 1H), 2.98 (m, 1H), 3.88 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 26.1, 30.7, 47.1, 61.0, 124.6, 130.0, 141.3, 142.2, 176.6. Exact mass calcd for $C_{12}H_{16}N_2O_2SNa$ requires m/z 275.0825, found m/z 275.0836 ($M+Na^+$, ESI).

3.13. A solution of (S)-(1,3,5)-triisopropylbenzenesulfinamide (0.669 g, 2.50 mmol) in THF (10 mL) was added to a flask containing a suspension of KH (0.105 g, 2.63 mmol), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt. (L)-Proline methyl ester (3.0 mmol) was added via syringe. After 30 min, the reaction was quenched by addition of acetic acid (0.160 g, 2.66 mmol) and water (8 mL), and the resulting mixture was concentrated to remove the THF. The crude product was extracted into EtOAc, and the organic layer from the extraction was loaded onto a silica plug and side products were eluted with 100% EtOAc. The product was eluted using a mobile phase gradient of 20% to 50% MeOH in EtOAc. Fractions containing the desired product were concentrated several times from EtOAc and the resulting residue was redissolved in warm EtOAc and filtered. The filtrate was concentrated, and then the white solid was recrystallized from 5 mL of hexanes. The solids were collected by vacuum filtration and rinsed with additional hexanes, to yield 0.66 g (73%) of **3.13** as a white powder, mp 170.5 – 172.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.23 (m, 12H), 1.35 (d, J = 6.9 Hz, 6H), 1.83 (m, 2H), 2.07 (m, 1H), 2.26 (m, 2H), 2.88 (m, 1H), 3.15 (m, 1H), 3.22 (m, 1H), 3.98 (m, 1H), 4.05 (m, 2H), 7.08 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 23.6, 24.0, 24.4, 25.7, 28.6, 30.8, 34.2, 46.9, 61.0, 122.8, 137.1, 148.7, 151.9, 176.3. Exact mass calcd for $C_{20}H_{32}N_2O_2SNa$ requires m/z 387.2077, found m/z 387.2087 ($M+Na^+$, ESI)..

3.14. A solution of (S)-(1,3,5)-triisopropylbenzenesulfinamide (0.669 g, 2.50 mmol) in THF (10 mL) was added to a flask containing a suspension of KH (0.105 g, 2.63 mmol), resulting in the evolution of hydrogen gas as the sulfinamide was deprotonated. The reaction mixture was stirred for 3 h at rt. (D)-Proline methyl ester (3.0 mmol) was added via syringe. After 30 min, the reaction was quenched by addition of acetic acid (0.160 g, 2.66 mmol) and water (8 mL), and the resulting mixture was concentrated to remove the THF. The crude product was extracted into EtOAc, and the organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was loaded onto a silica plug and side products were eluted with 100% EtOAc. The product was eluted using 50% MeOH in EtOAc. Fractions containing the desired product were concentrated several times from EtOAc, and then the material was redissolved in warm EtOAc and filtered. The filtrate was concentrated, and then the white solid was recrystallized from 1 mL of EtOAc. The solids were collected by vacuum filtration and rinsed with additional EtOAc (3 x 0.3 mL) to yield 0.52 g (57%) of **3.14** as a white crystalline solid , mp 152.5 – 154.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.25 (m, 12 H), 1.35 (d, J = 6.9 Hz, 6H), 1.60 (m, 1H), 1.69 (m, 1H), 1.90 (m, 1H), 2.17 (m, 1H), 2.76 (m, 1H), 2.91 (m, 1H), 2.98 (m, 1 H), 3.90 (m, 1 H), 3.97 (m, 2H), 7.12 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 23.6, 24.0, 24.4, 26.0, 28.5, 30.5, 34.2, 47.1, 60.8, 123.1, 136.0, 148.7, 152.8, 176.1. Exact mass calcd for $C_{20}H_{32}N_2O_2SNa$ requires m/z 387.2077, found m/z 387.2086 ($M+Na^+$, ESI).

Representative Procedure for Catalyst Screen (Scheme 3.1)

A reaction vial was equipped with a stirbar and charged with catalyst **3.9** (4.4 mg, 0.020 mmol, 0.10 equiv), acetone (0.44 mL, 6.0 mmol, 30 equiv), water (18 μL, 1.0 mmol, 5 equiv), and DMSO-d_6 (0.40 mL). After stirring for 15 min, a freshly prepared stock solution (0.40 mL) containing 4-nitrobenzaldehyde (0.20 mmol, 1.0 equiv) and 1,3,5-trimethoxybenzene (0.067 mmol, 0.33 equiv) was added, and the vial was sealed with a cap. The resulting mixture was stirred for 90 min, and then a 0.8 mL aliquot was transferred to an NMR tube and analyzed by ^{1}H NMR. The conversion to product was determined to be 91% by integration of the product peak at 5.2 ppm relative to the trimethoxybenzene peak at 6.1 ppm. No remaining aldehyde was observed. A second aliquot of the reaction mixture (approx. 100 μL) was diluted with 1 mL of EtOAc and washed with 1 mL of water. The organic layer was filtered through a plug of silica, eluting with EtOAc and then concentrated. The ee of this sample was determined to be 96% by chiral HPLC analysis (Chiralpak AS-H, hexanes/iPrOH 70/30, 1 mL min^{-1}): t_R (major) = 12.6 min, t_R (minor) = 16.3 min.

General Procedure for the Preparation of Products Listed in Scheme 3.2

The aldehyde (1.0 mmol) was weighed into a reaction vial. A freshly prepared stock solution containing catalyst **3.9** (0.20 mmol), acetone (30.0 mmol), water (5.0 mmol), and DMSO (4.0 mL) was added by mass, and then the vial was sealed with an airtight cap. The mixture was stirred for the indicated amount of time. The reaction mixture was diluted with EtOAc (40 mL), washed with water (10 mL) and brine (10 mL), and then dried over Na_2SO_4, filtered, and concentrated. The product was purified by silica gel chromatography (EtOAc/Hexanes).

The ee of each product was determined by chiral HPLC analysis. Authentic racemic standards for the HPLC analysis were synthesized using pyrrolidine as a catalyst according to a literature procedure.[44]

3.3a: The general procedure was followed using 4-nitrobenzaldehyde. After 3 h, 0.17 g (82%) of the desired product was isolated. The ee of this sample was determined to be 96% by chiral HPLC analysis (Chiralpak AS-H, hexanes/iPrOH 70/30, 1 mL min^{-1}): t_R (major) = 11.7 min, t_R (minor) = 15.3 min. The ^{1}H NMR is consistent with literature reports.[21]

3.3b: The general procedure was followed using 4-chlorobenzaldehyde. After 3 d, 0.17 g (82%) of the desired product was isolated. The ee of this sample was determined to be 95% by chiral HPLC analysis (Chiralpak AS-H, hexanes/iPrOH 90/10, 1 mL min^{-1}): t_R (major) = 14.1 min, t_R (minor) = 18.4 min. The ^{1}H NMR is consistent with literature reports.[21]

3.3c: The general procedure was followed using 2-chlorobenzaldehyde. After 1 d, 0.14 g (73%) of the desired product was isolated. The ee of this sample was determined to be 93% by chiral HPLC analysis (Chiralpak AS-H, hexanes/iPrOH 90/10, 1 mL min^{-1}): t_R (minor) = 10.4 min, t_R (major) = 13.9 min. The ^{1}H NMR is consistent with literature reports.[21]

3.3d: The general procedure was followed using benzaldehyde. After 7 d, 0.13 g (78%) of the desired product was isolated. The ee of this sample was determined to be 94% by chiral

HPLC analysis (Chiralpak AS-H, hexanes/iPrOH 90/10, 1 mL min^{-1}): t_R (major) = 14.4 min, t_R (minor) = 16.9 min. The ^1H NMR is consistent with literature reports.[21]

3.3e: The general procedure was followed using 4-tolualdehyde. After 7 d, 0.12 g (69%) of the desired product was isolated. The ee of this sample was determined to be 92% by chiral HPLC analysis (Chiralpak AS-H, hexanes/iPrOH 90/10, 1 mL min^{-1}): t_R (major) = 13.4 min, t_R (major) = 17.0 min. The ^1H NMR is consistent with literature reports.[21]

3.3f: The general procedure was followed using 4-methoxybenzaldehyde. After 7 d, 0.082 g (43%) of the desired product was isolated. The ee of this sample was determined to be 90% by chiral HPLC analysis (Chiralpak AS-H, hexanes/iPrOH 90/10, 1 mL min^{-1}): t_R (minor) = 31.0 min, t_R (major) = 35.8 min. The ^1H NMR is consistent with literature reports.[45]

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