

N-*tert*-Butanesulfinyl Imines: Versatile Intermediates for the Asymmetric Synthesis of Amines

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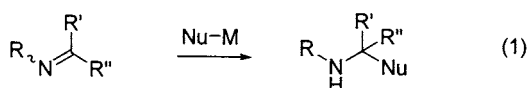
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ABSTRACT

N-*tert*-Butanesulfinyl aldimines **3** and ketimines **4** are exceedingly versatile intermediates for the asymmetric synthesis of amines. The *N*-*tert*-butanesulfinyl imines are prepared in high yields by condensing enantiomerically pure *tert*-butanesulfinamide **1**, which is readily available in either configuration, with a wide range of aldehydes and ketones. The *tert*-butanesulfinyl group activates the imines for the addition of many different classes of nucleophiles, serves as a powerful chiral directing group, and after nucleophilic addition is readily cleaved by treatment of the product with acid. A wide range of highly enantioenriched amines, including α -branched and α,α -dibranched amines, α - and β -amino acids, 1,2- and 1,3-amino alcohols, and α -trifluoromethyl amines, are efficiently synthesized using this methodology. In addition, *N*-*tert*-butanesulfinyl imine derivatives provide a new family of ligands for asymmetric catalysis.

A large majority of drugs and drug candidates incorporate amine functionality. Despite this fact, efficient methods are not available for the asymmetric synthesis of many structural classes of amines. In principle, one of the most versatile methods for the asymmetric synthesis of amines is the 1,2-addition of nucleophiles to imines (eq 1).¹ A wide



range of imines may be prepared from readily available amines, aldehydes, and ketones. Furthermore, many different classes of amines may be prepared by the addition of different types of nucleophiles. For example, α -branched

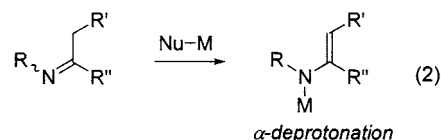
Jonathan Ellman was born in Los Angeles in 1962. He received his undergraduate degree in chemistry from Massachusetts Institute of Technology, working with K. Barry Sharpless, and his Ph.D. in chemistry from Harvard University, working with David A. Evans. After carrying out postdoctoral research with Peter G. Schultz at the University of California at Berkeley, he joined the faculty at University of California at Berkeley in 1992, where he is currently a Professor of Chemistry. His laboratory is engaged in the development of new synthesis methods and chemical tools for applications in chemistry and biology.

Timothy D. Owens was born in Santa Clara, CA, in 1972. As an undergraduate at the University of California at San Diego, he worked in the Medicinal Chemistry Department at Corvas International, where he remained for two years upon completing his degree. He is currently pursuing a Ph.D. degree in chemistry at the University of California at Berkeley under the guidance of Professor Ellman.

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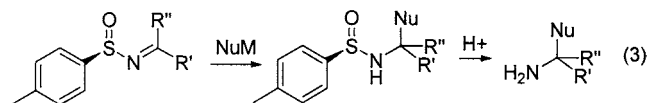
amines may be prepared by adding organometallic reagents, β -amino acids may be prepared by adding enolates, and α -amino acids may be prepared by adding acyl anion equivalents.

Unfortunately, many factors can compromise the successful addition of nucleophiles to imines. In particular, the steric and electronic properties of the substituent on nitrogen play a critical role and have to be considered in developing this approach. Nitrogen substitution is almost always required to prevent rapid imine oligomerization, and although the majority of *N*-substituted imines are unstable and inconvenient to store or manipulate, modulating the electronic properties of the substituent on nitrogen can provide stable compounds. Moreover, when reacted with basic nucleophiles, electron-withdrawing substituents on nitrogen are necessary to activate imines toward nucleophilic addition relative to α -deprotonation (eq 2).



To achieve the general and straightforward asymmetric synthesis of amines, an appropriate nitrogen substituent must therefore be identified that enables the preparation of stable imines and that activates the imine for the addition of a wide range of nucleophiles. Clearly, to be generally useful, the nitrogen substituent also must be inexpensive and straightforward to remove from the amine product.

A chiral substituent on nitrogen that satisfies all of these criteria while providing high diastereofacial selectivity for nucleophilic addition would provide a very general approach for the asymmetric synthesis of a broad range of amine-containing compounds. The *N*-*p*-toluenesulfinyl substituent pioneered by Davis satisfies many of these criteria (eq 3).² *p*-Toluenesulfinyl imines are stable and

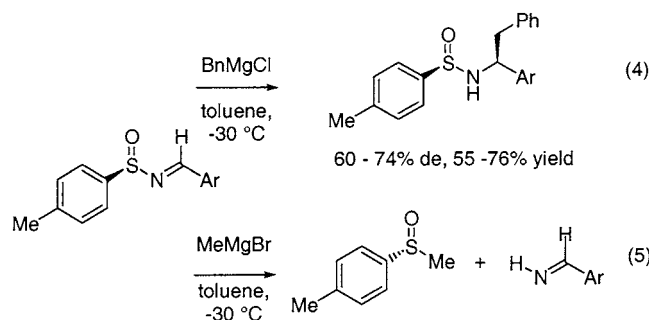


isolable compounds. The sulfinyl group also activates the imine, and the configurationally stable stereocenter at sulfur can provide diastereofacial selectivity for nucleophilic addition. Moreover, the sulfinyl group is readily cleaved by brief treatment with acid.

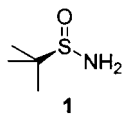
Unfortunately, there are limitations to using the *p*-toluenesulfinyl group as an imine substituent for amine synthesis. At the time we initiated our efforts, the direct condensation of *p*-toluenesulfinamide with aldehydes and ketones had not successfully provided the desired sulfinyl imines, except for the condensation of activated 4-nitro-

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benzaldehyde.³ Instead, less direct methods for *p*-toluenesulfinyl imine synthesis had been developed and these had provided only modest yields for imines capable of forming enamine tautomers. Stabilized organometallic reagents, such as benzyl magnesium chloride, were also reported to add with only moderate diastereofacial selectivity (eq 4).⁴ Most seriously, unstabilized organometallic reagents, such as methyl magnesium bromide, were reported to attack at sulfur rather than at the desired carbon site (eq 5).

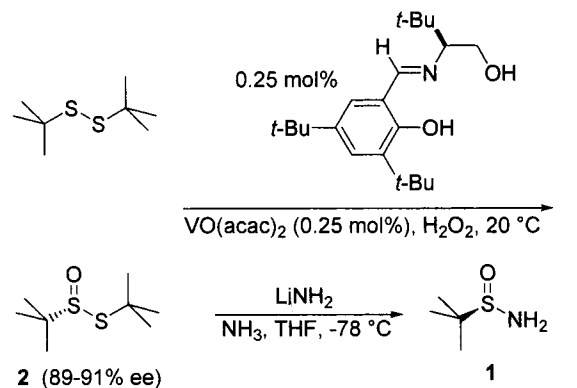


In efforts to develop a new linker for solid-phase synthesis, we were the first to isolate enantiomerically pure *tert*-butanesulfinamide **1**,^{5,6} and we found reagent **1** to be a white crystalline solid that is stable indefinitely at room temperature. This result prompted us to explore



nucleophilic additions to *N*-*tert*-butanesulfinyl imines for amine synthesis because we envisioned that the *tert*-butanesulfinyl group would preserve the desirable characteristics of the *p*-toluenesulfinyl group while overcoming its liabilities. We envisioned that *tert*-butanesulfinamide should be significantly more nucleophilic than *p*-toluenesulfinamide for direct condensation with aldehydes and ketones due to the electron-donating characteristics of the *tert*-butyl versus the *p*-tolyl group. Additions to *tert*-butanesulfinyl imines also should generally proceed with higher selectivity, based upon the higher selectivity observed for the chemistry of *tert*-butyl versus *p*-tolyl sulfoxides.⁷ In a limited study on the preparation of aziridines, additions to *tert*-butanesulfinyl imines were also reported to proceed with higher selectivity than for the corresponding *p*-toluenesulfinyl imines.⁸ Most importantly, competitive nucleophilic attack at sulfur should also be minimized for additions to *tert*-butanesulfinyl versus *p*-toluenesulfinyl imines due to the greater steric hindrance and reduced electronegativity of the *tert*-butyl group relative to the *p*-tolyl group.

As described in this Account, the *N*-*tert*-butanesulfinyl group does, indeed, overcome the limitations of the *N*-*p*-toluenesulfinyl group and serves as an ideal *N*-substituent for nucleophilic additions to imines, providing a highly efficient and versatile approach to the asymmetric synthesis of many different types of amines.



71-78% overall yield of enantiomerically pure material with single recrystallization

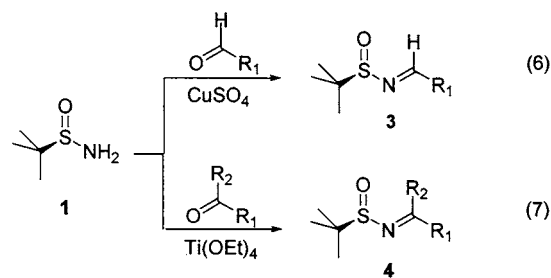
FIGURE 1. Asymmetric synthesis of *tert*-butanesulfinamide **1**.

Asymmetric Synthesis of *tert*-Butanesulfinamide

We realized that for *tert*-butanesulfinyl imine chemistry to be useful, it was essential that we develop a highly efficient method to prepare enantiomerically pure *tert*-butanesulfinamide. Several potential methods could be considered; however, we felt that the most practical approach would be the two-step process of catalytic asymmetric oxidation of *tert*-butyl disulfide, followed by reaction of the *tert*-butanethiosulfinate product **2** with an amide anion (Figure 1).^{5,9} *tert*-Butyl disulfide is an oil waste product and therefore serves as an extremely inexpensive starting material. In addition, oxidation of *tert*-butyl disulfide to **2** proceeds with good conversion and in 89–91% ee when H₂O₂ is used as an inexpensive stoichiometric oxidant and with only 0.25 mol % of VO(acac)₂ and chiral ligand. Because the reaction is performed in air at a high concentration (1.5 M), the reaction can easily be carried out on a one-mole scale in any standard laboratory setting. Furthermore, since both antipodes of the chiral ligand are accessible, either enantiomer of *tert*-butanethiosulfinate **2** may be readily prepared. Addition of lithium amide in ammonia to **2** provides the desired sulfonamide **1** with complete inversion at sulfur. After a single crystallization, enantiomerically pure **1** is obtained in 72–78% overall yield from *tert*-butyl disulfide.¹⁰

Synthesis of *tert*-Butanesulfinyl Imines

High-yielding and general methods for the preparation of *tert*-butanesulfinyl aldimines **3** and ketimines **4** are



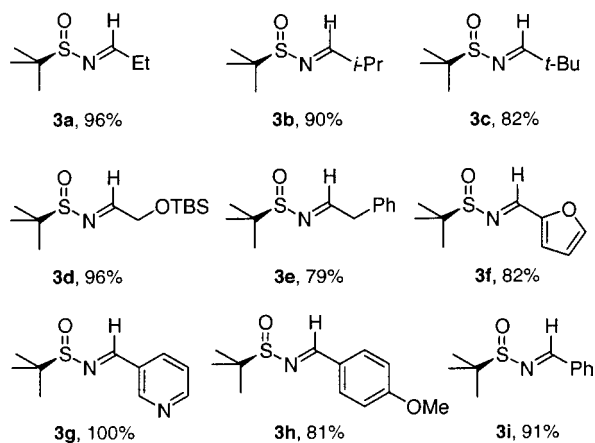


FIGURE 2. Sulfinyl aldimine synthesis.

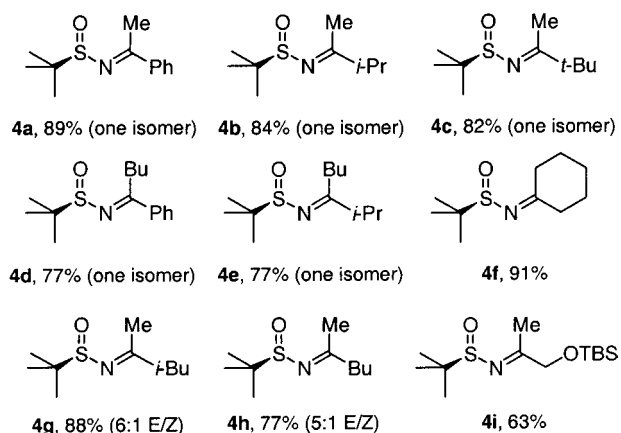
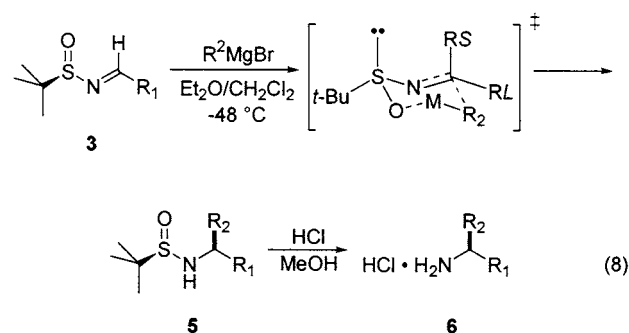


FIGURE 3. Sulfinyl ketimine synthesis.

critical to the successful application of *tert*-butanesulfinamide to the asymmetric synthesis of amines. The most straightforward method for the preparation of aldimines **3** is the condensation of aldehydes and *tert*-butanesulfinamide with CuSO_4 as a Lewis acid catalyst and water scavenger (eq 6).^{11,12} For the preparation of ketimines **4**, $\text{Ti}(\text{OEt})_4$ is the preferred Lewis acid and water scavenger (eq 7).^{12–14}

A wide range of sulfinyl aldimines **3** may be prepared in high yields (Figure 2). For example, the aldimines **3** can even be prepared in very high yields from unreactive aldehydes, such as sterically hindered aldimine **3c** or electronically deactivated aldimines **3f** and **3g**. For these aldimines, $\text{Ti}(\text{OEt})_4$ instead of CuSO_4 is the preferred catalyst and water scavenger. Significantly, phenylacetaldimine **3e** can also be prepared in good yield, despite the strong tendency for phenylacetaldimines to tautomerize to the corresponding enamines followed by further side reactions.

A wide range of sulfinyl ketimines **4** may also be prepared with diverse steric and electronic properties, even though ketones have reduced electrophilicity relative to aldehydes (Figure 3). Even sterically hindered ketimines such as **4c–e** may be prepared in good yields. An additional complicating feature of ketimines is the possibility of forming two imine isomers, which directly impacts the diastereoselective addition of nucleophiles.

Table 1. Asymmetric Synthesis of α -Branched Amines

entry	sulfinyl imine 3 , R ₁	R ² M	yield (%)		
			sulfinamide 5	amine hydrochloride 6	dr 5
1	Et	MeMgBr	96	97	93:7
2	Et	<i>i</i> -PrMgBr	97	92	98:2
3	Et	PhMgBr	quant.	90	96:4
4	<i>i</i> -Pr	MeMgBr	97	97	98:2
5	<i>i</i> -Pr	EtMgBr	quant.	93	97:3
6	<i>i</i> -Pr	PhMgBr	98	91	89:11
7	<i>i</i> -Pr	vinylMgBr	90	78	88:12
8	Ph	MeMgBr	96	88	97:3
9	Ph	EtMgBr	98	94	92:8
10	Ph	<i>i</i> -PrMgBr	29	—	—
11	Ph	vinylMgBr	79	93	94:6
12	Bn	MeMgBr	89	95	95:5
13	Bn	EtMgBr	85	98	92:8
14	Bn	vinylMgBr	81	97	91:9
15	Bn	PhMgBr	81	99	95:5
16	<i>p</i> -MeOPh	EtMgBr	88	quant.	99:1

Fortunately, due to the steric properties of the *tert*-butanesulfinyl group, only the *E* imine isomer is observed if there is differential branching at the α - and α' -positions of the ketimine. Surprisingly good *E:Z* imine ratios are observed even for imines **4h** and **4i**, considering the very similar sterics of the two substituents.

Synthesis of α -Branched Amines

The addition of Grignard reagents to sulfinyl aldimines **3** proceeds in high yields and diastereoselectivities for a diverse range of substrates (Table 1).^{5,15} Aliphatic and aromatic aldimines and alkyl, aryl, and vinyl Grignard reagents all serve as successful coupling partners.¹⁶ It is notable that even aldimines having α -protons, including highly acidic arylacetaldimines (entries 12–15), provide products in good yields. To our knowledge, the addition of basic organometallic reagents to arylacetaldimines has not previously been reported. A six-membered cyclic transition state with Mg coordinated to the sulfinyl oxygen is consistent with the observed sense of induction (eq 8). The reaction also proceeds with highest selectivities in noncoordinating solvents, further supporting the metal-chelated transition state.

The sulfinyl group is removed from sulfinamide **5** by brief treatment (<30 min) with stoichiometric quantities of HCl in a protic solvent to provide the desired amine hydrochloride **6** in nearly quantitative yields (Table 1). Enantiomerically pure material may be obtained by crystallization of the amine hydrochloride salt **6** or by

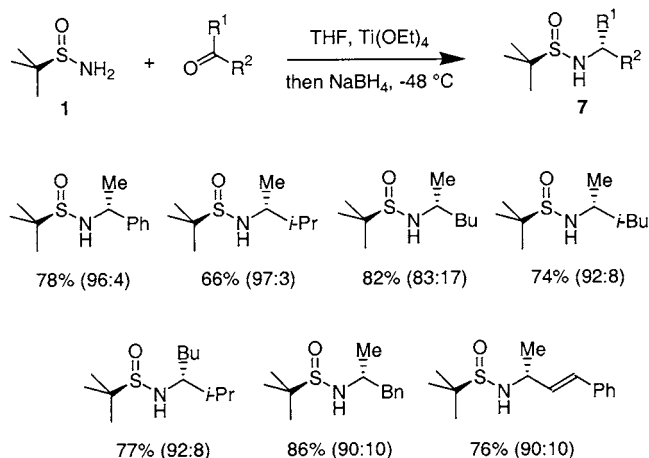


FIGURE 4. One-pot asymmetric synthesis of *N*-sulfinyl α -branched amines from ketones.

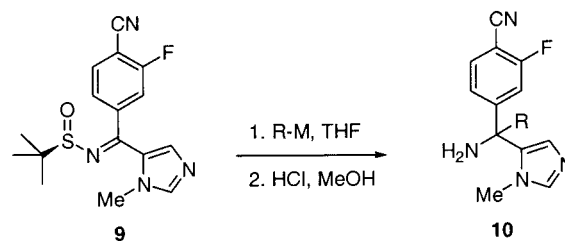
chromatography or crystallization of sulfinamide **5** prior to sulfinyl group removal.

As a second general method for the preparation of α -branched amines that complements the Grignard addition chemistry, we have also reported the one-pot asymmetric synthesis of *tert*-butanesulfinyl-protected amines **7** from ketones (Figure 4).¹⁷ In this procedure, ketones are condensed with *tert*-butanesulfinamide using $\text{Ti}(\text{OEt})_4$, followed by addition of NaBH_4 to the reaction solution at -48°C . Sulfinamides **7** are obtained in 66–86% yields and with good to excellent diastereoselectivities for both aryl alkyl ketones and dialkyl ketones. Notably, $\text{Ti}(\text{OEt})_4$ not only serves to mediate the imine condensation step, but also serves as a Lewis acid to provide enhanced reduction rates and diastereoselectivities.

Synthesis of Tertiary Carbinamines

Tertiary carbinamines are important components of natural products, synthetic pharmaceuticals, and catalysts, yet general and efficient methods are not available for the asymmetric synthesis of this class of amines.¹⁸ The 1,2-addition of organolithium reagents to *tert*-butanesulfinyl ketimines **4** provides the first direct method for the asymmetric synthesis of a broad range of tertiary carbinamines (Table 2).^{13,15} While the direct addition of organolithium reagents to ketimines **4** generally proceeds in acceptable yields and diastereoselectivities (data not shown),¹⁵ precomplexation of ketimine **4** with Me_3Al results in higher yields and diastereoselectivities for aryl and alkyl lithium additions to both aliphatic and aromatic ketimine substrates (Table 2). The high selectivity (89:11) observed in entry 6 is particularly noteworthy, considering the minimal steric difference of the methyl and butyl substituents. The sense of induction and requirement for noncoordinating solvents is again consistent with a six-membered transition state (eq 9). Precomplexation of the aluminum reagent to the imine is required, since no reaction occurs if the aluminum reagent is first mixed with the organolithium to form an aluminate complex.

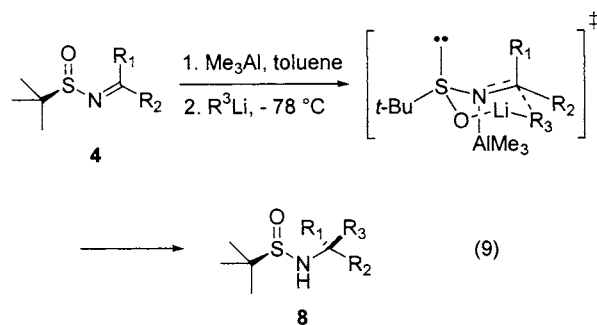
Shaw and deSolms at Merck have reported an impressive application of this method to the synthesis of farnesyl



R-M	Ratio (-):(+)	Yield (%)
PhLi	94:6	83
PhMgBr	6:94	78
CH_3Li	13:87	82
CH_3MgBr	80:20	74

FIGURE 5. Asymmetric synthesis of ras farnesyl transferase inhibitors.

Table 2. Asymmetric Synthesis of Tertiary Carbinamines



entry	R ₁	R ₂	R ³ Li	yield of 8 (%)	dr
1	Me	<i>i</i> -Pr	Bu	61	99:1
2	Me	<i>i</i> -Pr	Ph	93	97:3
3	Bu	<i>i</i> -Pr	Me	82	91:9
4	Bu	<i>i</i> -Pr	Ph	82	91:9
5	Me	Ph	Bu	86	98:2
6	Me	Bu	Ph	93	89:11
7	Me	<i>i</i> -Bu	Ph	62	85:15
8	Me	2-Npth	Ph	62	99:1
9	Bu	Ph	Me	quant.	99:1

protein transferase inhibitors.¹⁹ As shown in the representative examples in Figure 5, they established that the addition of organometallic reagents to sulfinyl ketimine **9** generally proceeds in high yields and with high diastereoselectivities. The selectivity is particularly impressive, considering the similar steric properties of the two aryl substituents. The reversal in selectivity observed for organolithium versus Grignard reagents for these specialized substrates is also noteworthy, considering that both transformations are performed in the coordinating solvent THF.²⁰

Synthesis of Highly Substituted β -Amino Acids

β -Amino acids are components of numerous natural products and therapeutic agents.²¹ Recently, oligomers of β -amino acids have received considerable attention due to their unique structural properties.²² Although a number of methods are available for the synthesis of monosubstituted β -amino acids,²³ efficient, general methods to

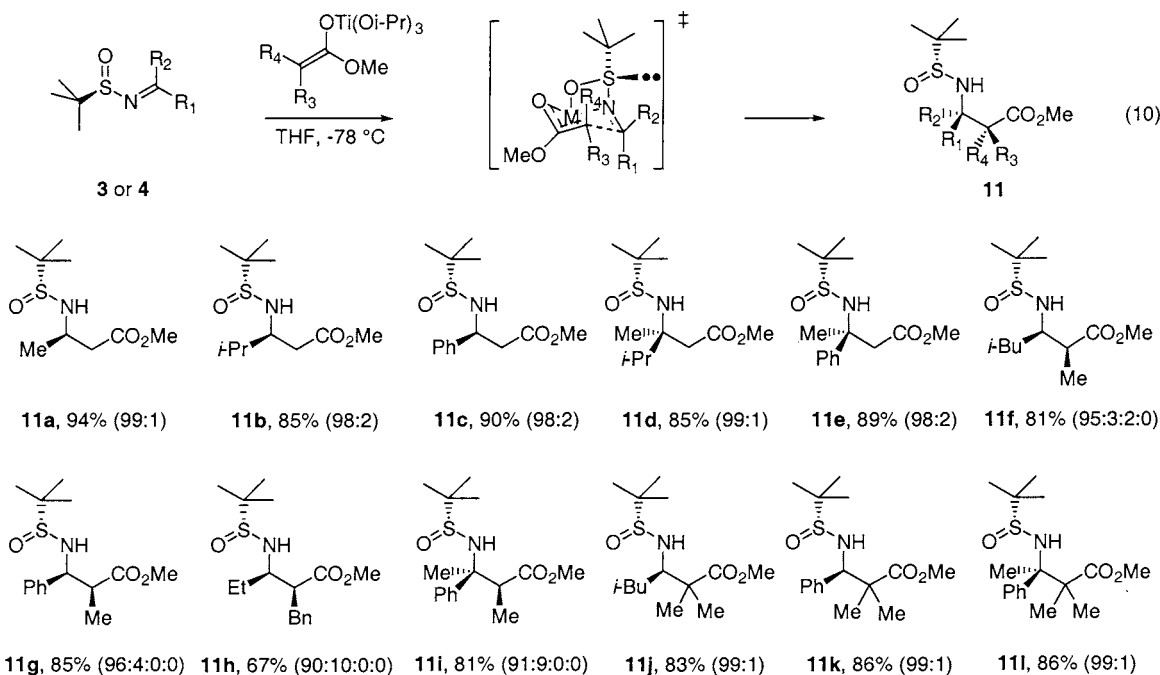


FIGURE 6. Asymmetric synthesis of β -amino acid derivatives.

prepare highly substituted derivatives are not available.²⁴ The addition of titanium enolates to *tert*-butanesulfinyl aldimines and ketimines provides the first general method for the asymmetric synthesis of highly substituted β -amino acid derivatives (Figure 6).^{25,26} The addition of acetate enolates to sulfinyl aldimines **3** and ketimines **4** provides β -substituted amino acid derivatives, e.g., **11a–c**, and β,β -disubstituted β -amino acid derivatives which are difficult to access, e.g., **11d** and **11e**, respectively, in extremely high yields and diastereoselectivities. The addition of α -substituted enolates to aldimines **3** and ketimines **4** also proceeds with good yields and diastereoselectivities to provide α,β -disubstituted β -amino acid derivatives, e.g., **11f–h**, and α,β,β -trisubstituted β -amino acid derivatives, e.g., **11i**, respectively. Finally, α,α -disubstituted enolates may even be added to aldimines **3** and ketimines **4** to give exceptional diastereoselectivities and high yields, as exemplified by α,α,β -trisubstituted β -amino acid derivatives **11j** and **11k** and the $\alpha,\alpha,\beta,\beta$ -tetrasubstituted β -amino acid derivative **11l**.

The sense of induction can be predicted for every substrate combination by invoking a six-membered Zimmerman–Traxler-type transition state where the sulfinyl imine nitrogen and oxygen both interact with the highly coordinatively unsaturated Ti(IV) (eq 10). The high level of preorganization presumably contributes to the very high selectivity for attack opposite to the large *tert*-butyl group.

The *N*-Sulfinyl Protecting Group. The *tert*-butanesulfinyl group not only is an ideal chiral directing group for the asymmetric synthesis of β -amino esters but also can serve as a versatile, low-molecular-weight protecting group analogous to the Boc protecting group.^{25,26} Like the Boc group, the *tert*-butanesulfinyl group is stable to basic conditions. For example, *N*-sulfinyl amino esters may be saponified to provide *N*-sulfinyl amino acids.²⁷ In addition,

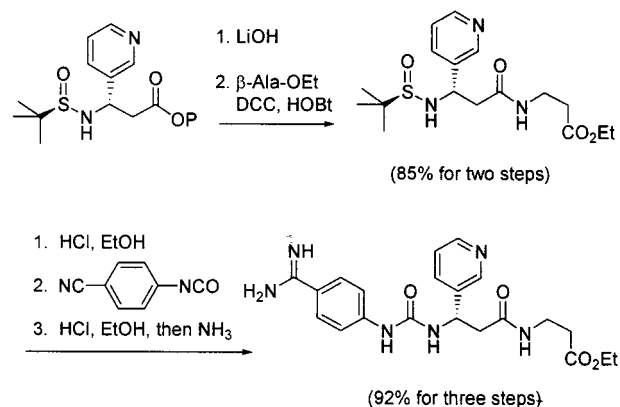


FIGURE 7. Application of *N*-sulfinyl-protected β -amino acids in the synthesis of a IIb/IIIa antagonist.

the sulfinyl protecting group renders the nitrogen non-nucleophilic, such that activation and amide bond coupling of the *N*-sulfinyl-protected β -amino acid may be accomplished. Finally, like a Boc group, the sulfinyl group is readily cleaved with acid to provide the free amine that may undergo further acylation reactions. These transformations are illustrated in the synthesis of an intermediate to a IIb/IIIa antagonist reported by workers at Monsanto (Figure 7).

Solid-Phase Synthesis of Foldamers. There is increasing interest in the properties of foldamers to design ordered secondary structures and to identify structures with significant biological activities.²² For example, Gellman and DeGrado have recently identified β -peptides that are potent antimicrobial agents, and Seebach has reported on low nanomolar, specific β -peptide-derived somatostatin antagonists.²² Unfortunately, progress on the study of foldamers is hindered by the relative difficulty of synthesis of many of these oligomers. This is due to the lack of accessibility of many of the desired β -amino acids

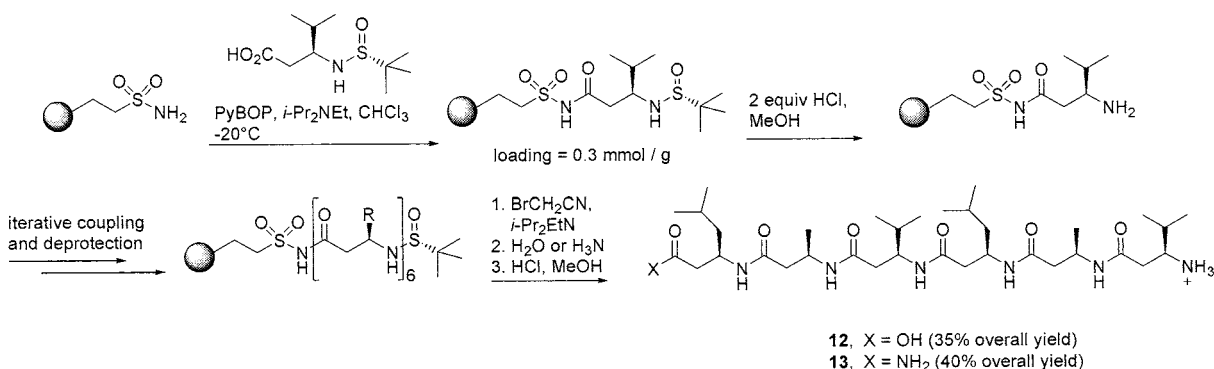


FIGURE 8. Solid-phase synthesis of β -peptides from *N*-sulfinyl-protected β -amino acids.

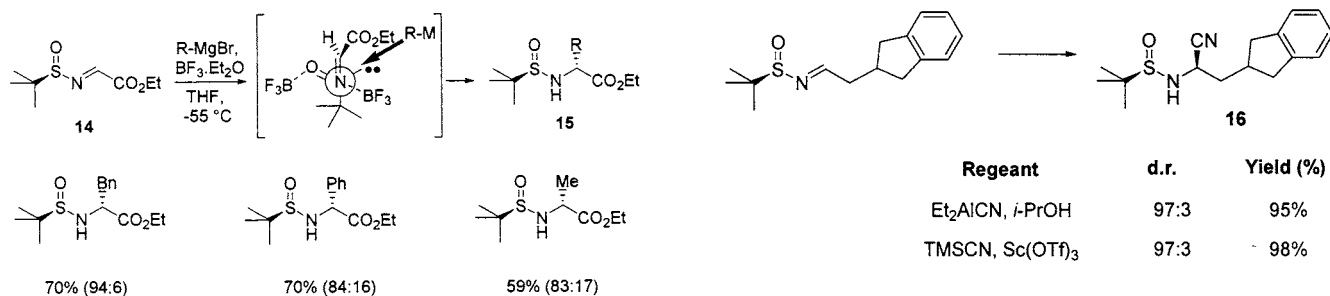


FIGURE 9. Addition of organometallic reagents to *N*-sulfinyl α -imino esters.

in suitably protected form for solid-phase synthesis. Significantly, *N*-sulfinyl- β -amino acids serve as versatile building blocks for the solid-phase synthesis of β -peptides, as demonstrated by the preparation of hexameric β -peptides **12** and **13** in 35% and 40% overall yields, respectively (Figure 8). Note that, at the end of the synthesis, cyanomethylation of the *N*-acysulfonamide “safety catch” linker results in activation for nucleophilic displacement to provide access to diverse ester and amide derivatives.^{26,28}

Synthesis of α -Amino Acid Derivatives

α -Amino acids constitute one of the most heavily used building blocks in pharmaceutical research and natural product synthesis. While a number of methods are available for the preparation of these compounds, efficient new methods are still of value. Two versatile approaches to this compound class have been developed, based upon additions to *tert*-butanesulfinyl imines. Davis and co-workers have reported the addition of Grignard and dialkylzinc reagents to *N*-*tert*-butanesulfinyl α -imino esters **14** (Figure 9).²⁹ To achieve good yields for Grignard reagent addition, it is important to add 2 equiv of BF₃·OEt₂ to activate the imine. The sense of induction is successfully predicted by a non-chelation-controlled addition to give the Cram product **15**. Notably, Davis found that benzyl Grignard addition to the corresponding *p*-toluenesulfinyl aldimine proceeded in significantly lower yields (31%) and with reduced stereoselectivity (63:37).

Davis and co-workers have also reported an efficient alternative route to enantioenriched α -amino acids by the asymmetric addition of cyanide to *p*-toluenesulfinyl aldimines followed by acidic hydrolysis.³⁰ A number of groups have subsequently applied this method to the

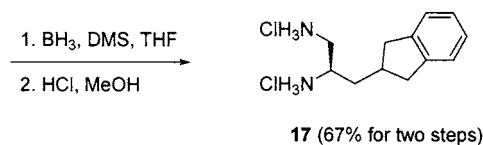
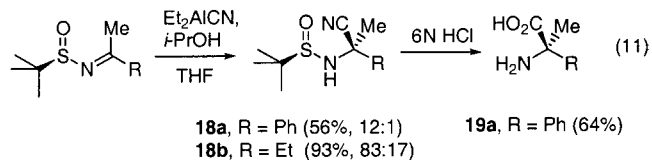


FIGURE 10. Asymmetric synthesis of α -aminonitriles as intermediates to α -amino acids and 1,2-diamines.

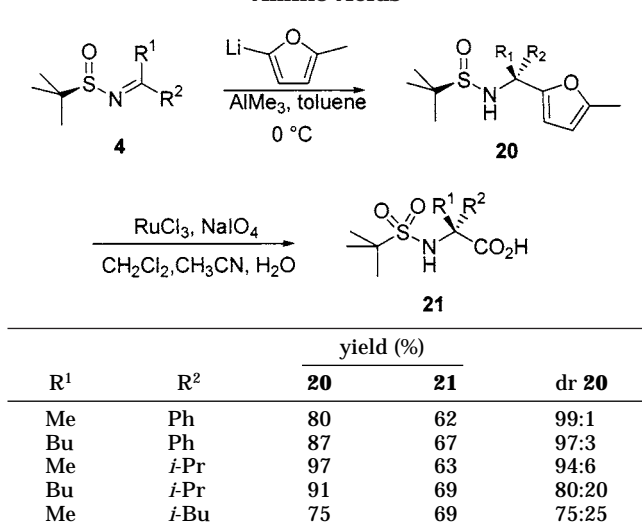
asymmetric synthesis of α -amino acids. Mabic and Cordi have reported the first example of the asymmetric addition of cyanide to *tert*-butanesulfinyl aldimines, achieving high yields and diastereoselectivities by using either Et₂AlCN or TMSCN catalyzed by Sc(OTf)₃ (Figure 10).³¹ They have further demonstrated that *N*-sulfinyl α -aminonitriles not only are useful precursors to the corresponding α -amino acid but can also be readily converted to the 1,2-diamines (Figure 10).

Davis has also explored the reaction of Et₂AlCN with *tert*-butanesulfinyl ketimines for the preparation of α,α -disubstituted α -amino acids (eq 11).³² These structures



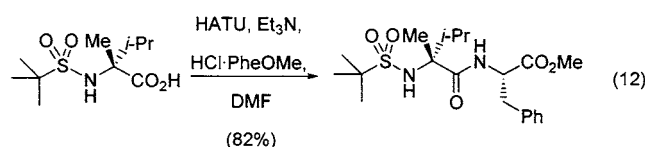
have significant effects on the conformation and on the biological activity of molecules in which they are incorporated. In contrast to α -substituted α -amino acids, few methods are available for the synthesis of α,α -disubstituted α -amino acids. The α -aminonitrile products **18a** and **18b** are obtained in good diastereoselectivities, especially considering the minimal steric difference of the methyl and ethyl substituents in **18b**. Notably, additions to the corresponding *p*-toluenesulfinyl ketimines provided the products in significantly lower diastereoselectivities, 4:1 and 3:1, respectively.

Table 3. Asymmetric Synthesis of α,α -Disubstituted Amino Acids



We have also reported an alternative, efficient method for the asymmetric synthesis of the difficult-to-prepare α,α -disubstituted α -amino acids.³³ In particular, the 1,2-addition of furyllithium to *N*-sulfinyl ketimines **4** followed by oxidative cleavage provides *N*-*tert*-butanesulfonyl (Bus)-protected α,α -disubstituted amino acids **21** (Table 3).

As previously reported by Sun and Weinreb,³⁴ the Bus group is a versatile nitrogen-protecting group that is stable to basic conditions but can be cleaved under acidic conditions. Significantly, even for hindered α,α -disubstituted amino acids, the Bus-protected derivative undergoes efficient peptide coupling under standard conditions (eq 12).



Synthesis of α -Trifluoromethylamines

α -Trifluoromethylamines are important building blocks for drug development due to the strongly electron-withdrawing nature of the trifluoromethyl group. Amides that incorporate these amines often are resistant to nonspecific proteolysis and have modified solubility and desolvation properties. Olah has reported a highly stereoselective and general method for the synthesis of this difficult-to-prepare amine class by the addition of "CF₃⁻" to *tert*-butanesulfinyl aldimines **3** (Figure 11).³⁵ Extremely high selectivities are observed for a range of aromatic, alkenyl, and aliphatic aldimines. The sense of induction can be predicted by applying a non-chelation-controlled model to provide Cram products. Significantly, Olah found that additions to *tert*-butanesulfinyl aldimines proceed with higher selectivity than that found for additions to the corresponding *p*-toluenesulfinyl aldimines.

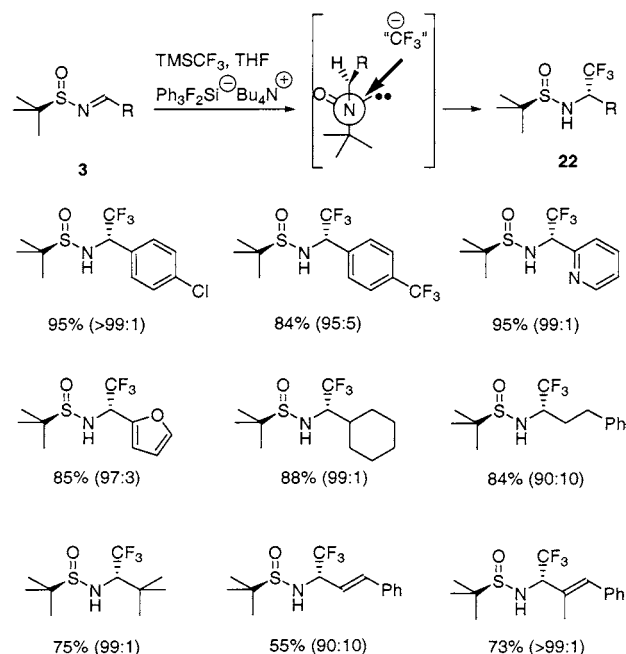


FIGURE 11. Asymmetric synthesis of α -trifluoromethylamine derivatives.

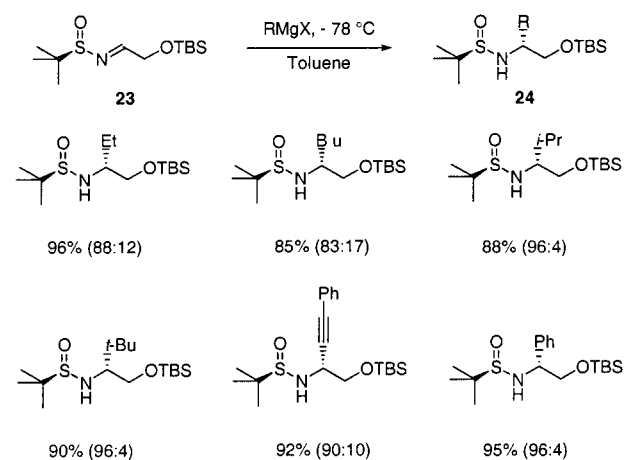


FIGURE 12. Grignard additions to α -silyloxy *N*-sulfinyl aldimine **23**.

Synthesis of 1,2-Amino Alcohols

1,2-Amino alcohols are prevalent in drugs and natural products and serve as important precursors to many chiral ligands for asymmetric catalysis. For this reason, both my group³⁶ and Barrow and co-workers at Merck³⁷ have explored the asymmetric synthesis of this compound class by the 1,2-addition of organometallic reagents to α -alkoxy sulfinyl imines. Addition of Grignard reagents to α -silyloxy sulfinyl aldimine **23** proceeds in high yields and selectivities in the noncoordinating solvents toluene and CH₂Cl₂ (Figure 12). Organometallic reagents may also be added to α -benzyloxy sulfinyl aldimines in high yields (80–99%) and with good to high selectivities (90:10 to 99:1 dr).³⁶ Interestingly, the sense of induction is opposite to that observed for Grignard addition to sulfinyl aldimines lacking an α -coordinating group. Presumably, metal chelation to the α -alkoxy group alters the transition state for the reaction. Treatment of the addition product **24** with HCl and methanol cleanly cleaves the sulfinyl group and

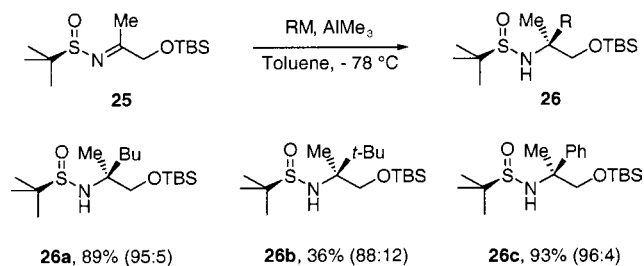


FIGURE 13. Addition of organometallic reagents to α -silyloxy *N*-sulfinyl ketimines.

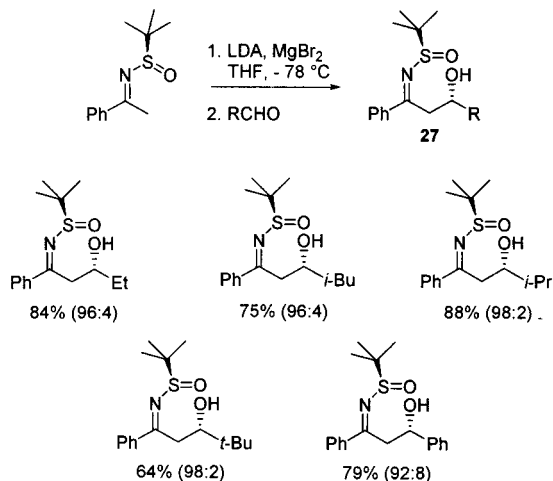


FIGURE 14. Asymmetric synthesis of β -hydroxy sulfinyl ketimines.

the silyl group to provide the corresponding 1,2-amino alcohols in nearly quantitative yields.

Organometallic reagents may also be successfully added to α -silyloxy ketimine **25** (Figure 13). Only a few limited examples of the successful addition to α -alkoxy ketimines have been reported due to the high propensity for competitive α -deprotonation to occur.³⁸ Addition of butyllithium provides sulfinamide **26a** in good yields and with good diastereoselectivity, while addition of the sterically hindered *tert*-butyllithium provides **26b** in reduced yields due to competitive methyl transfer from AlMe_3 . Interest-

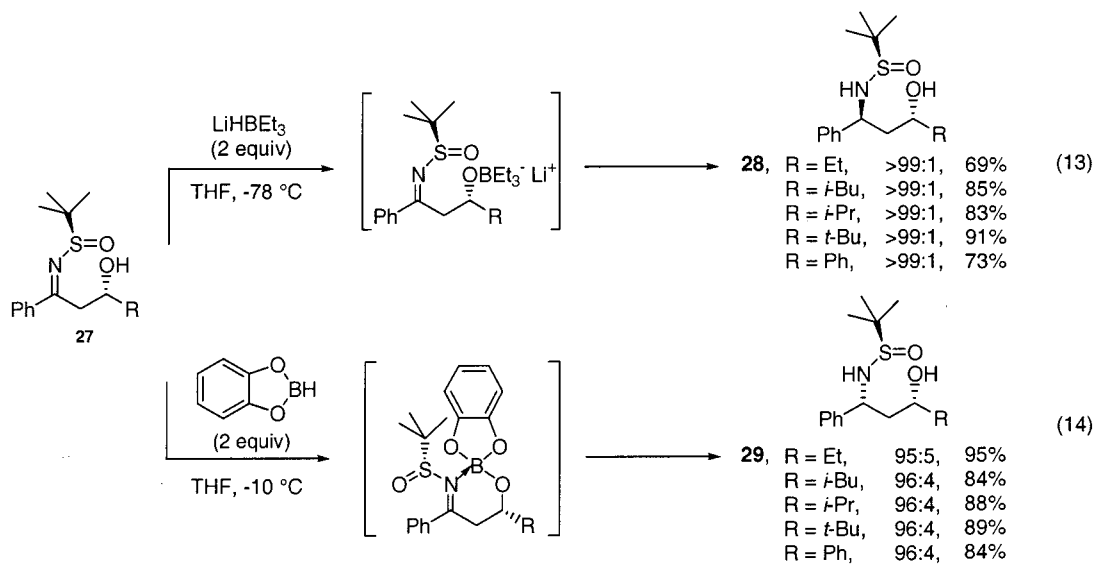
ingly, in contrast to the selectivity trend observed for aliphatic organometallic reagents, sulfinamide **26c** is obtained in higher yield when phenyl magnesium bromide is employed rather than phenyllithium. For organometallic additions to α -silyloxy ketimines, the same sense of induction is observed as for the addition of organolithium reagents to sulfinyl ketimines lacking an α -coordinating group (see Table 2).

Synthesis of 1,3-Amino Alcohols

As described previously, nucleophilic additions to sulfinyl imines have been explored extensively by a number of researchers. In contrast, α -deprotonation of sulfinyl imines to provide metalloenamines followed by reaction with electrophiles has not been explored. We have recently determined that metalloenamines react with aldehydes to provide β -hydroxy *N*-sulfinyl ketimines **27** in high yields and with high diastereoselectivities (Figure 14).³⁹

The β -hydroxy ketimines **27** are versatile intermediates for the preparation of either syn- or anti-1,3-amino alcohols. Reduction of **27** with LiBHET_3 provides the anti product **28** with $\geq 99:1$ selectivity (eq 13, Scheme 1), while reduction with catecholborane provides the syn product **29** with $\geq 95:5$ selectivities (eq 14, Scheme 1). To our knowledge, this is the first method to be reported for the stereoselective synthesis of both the syn- and anti-1,3-amino alcohols from a common synthetic intermediate. The high selectivity results primarily from the *tert*-butanesulfinyl group, since reduction of the hydroxyl epimer of **27** ($\text{R} = \text{Ph}$) with LiBHET_3 provided the syn-1,3-amino alcohol with 90:10 diastereoselectivity, while reduction with catecholborane provided the anti-1,3-amino alcohol product with 86:14 diastereoselectivity. The opposite selectivity observed for the reduction with catecholborane relative to LiBHET_3 can be rationalized by considering the geometry of the *N*-sulfinyl imine during the reduction step (eqs 13 and 14). The *E* geometry of β -hydroxy *N*-sulfinyl imine **27** is based upon the X-ray crystal structure of **27**

Scheme 1



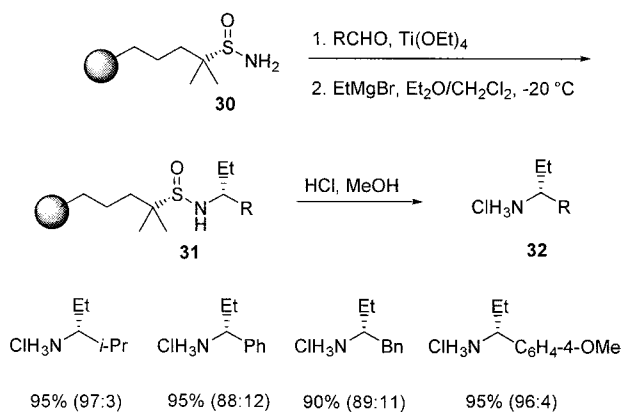


FIGURE 15. Asymmetric synthesis of amines on solid support.

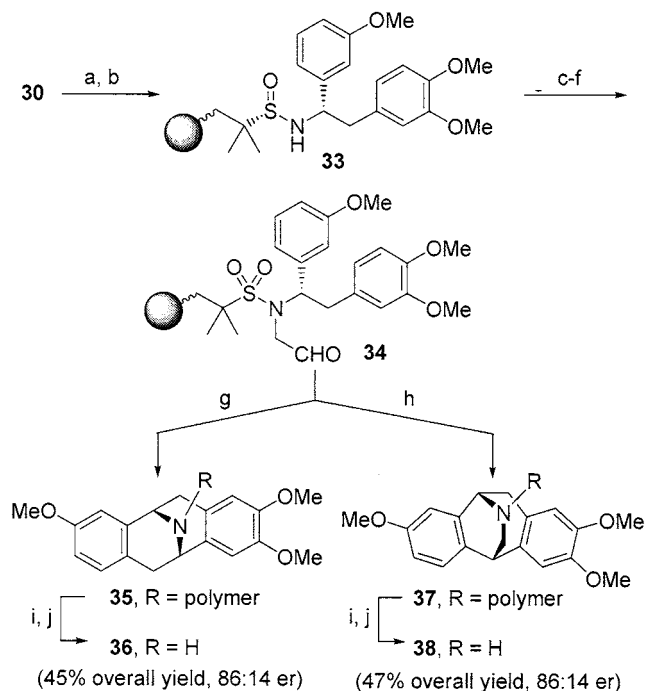
(R = Ph). The addition of LiBHET_3 is unlikely to change the *N*-sulfinyl imine geometry (eq 13). In contrast, addition of catecholborane may provide the stable six-membered-ring intermediate, in analogy to the stereoselective reduction of β -hydroxy ketones reported by Evans and Hoveyda (eq 14).⁴⁰ Isomerization from the *E*- to the *Z*-imine presumably results in the opposite face selectivity for the catecholborane reduction.

Parallel Multistep Synthesis on Solid Support

Because amines are present in the majority of drugs, the synthesis of amine-containing compounds is a major focus of solid-phase parallel synthesis, and a number of extensively utilized linkers have been developed for this purpose.⁴¹ However, linkers for the *asymmetric* synthesis of amines have undergone only limited development, despite their potential importance for the multistep asymmetric synthesis of drug leads and natural-product-like compounds.⁴² We have recently developed an efficient synthesis of a support-bound *tert*-butanesulfinamide derivative **30** (SBS linker) and demonstrated the utility of this linker for the asymmetric synthesis of enantioenriched amines **32**,⁴³ which can be obtained in nearly quantitative yields over the three-step process (Figure 15).

The SBS linker **30** potentially can be applied to the asymmetric synthesis of a range of different bioactive amines. To demonstrate this point, we designed an efficient synthesis of the pavine and isopavine alkaloids **36** and **38** (Scheme 2). Both alkaloid classes have a range of interesting biological activities; for example, they are potential neuroprotective agents for the treatment of ischemia and are inhibitors of TNF production. The key step in the synthesis of each alkaloid is the completely selective bis-cyclization of a common intermediate, **34**, to either the pavine skeleton **35** or the isopavine skeleton **37**. After release from support, pavine derivative **36** and the corresponding isopavine derivative **38** were isolated in 45 and 47% overall yields, respectively, based upon the starting resin **30**. Notably, only solid-phase extraction with support-bound sulfonic acid followed by elution with ammonia was necessary to provide completely pure material.

Scheme 2. Asymmetric Multistep Synthesis of Pavine and Isopavine Alkaloids



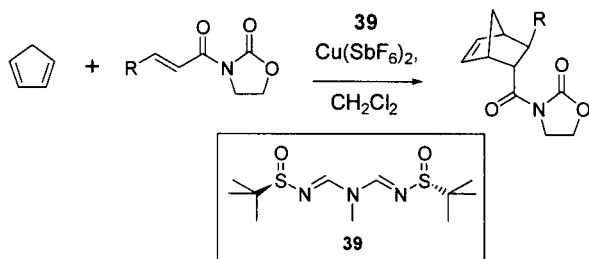
^a Reagents and conditions: (a) 3,4-(MeO)₂PhCH₂CHO, Ti(OEt)₄, THF; (b) 3-MeOPhMgBr, CH₂Cl₂, -48 °C; (c) KO-*t*-Bu, NMP, allyl bromide; (d) *m*CPBA, CH₂Cl₂/DMF; (e) 2.5% OsO₄/*t*-BuOH, NMO, THF; (f) Pb(OAc)₄, 10:1 CH₂Cl₂/AcOH; (g) diluted HCl, CH₂Cl₂; (h) 3:1 CH₂Cl₂/HCO₂H; (i) 0.1 N TfOH, 1,4-dimethoxybenzene, CH₂Cl₂; (j) sulfonic acid resin and then NH₃/MeOH.

New Privileged Ligands for Asymmetric Catalysis

The C=N bond serves as a key coordinating group for several of the most important ligands for asymmetric catalysis, including the salens, bisoxazolines, and salicylaldimines.⁴⁴ The straightforward preparation of stable sulfinyl imines enables the synthesis of a new class of C=N donor ligands. The sulfinyl imine ligands are distinct relative to the aforementioned ligand classes in that chirality resides at sulfur rather than carbon. In addition, metal coordination can occur not only through nitrogen but also through sulfur or oxygen. Despite the ready availability of enantiomerically pure sulfinamides, the preparation of metal complexes of sulfinamide derivatives and catalysis by these complexes have not been explored. In very recent efforts, we have obtained crystal structures of sulfinyl imine-based ligands complexed to Cu,⁴⁵ Zn,⁴⁶ Rh,⁴⁷ and Pd⁴⁸ and, depending upon the complex, have observed coordination to the sulfur, oxygen, and nitrogen of the *N*-sulfinyl group. Furthermore, as shown in the following example, we have established that sulfinyl-based ligands can provide exceptional levels of enantio- and diastereoselectivity in Lewis acid-catalyzed reactions.

Metal complexes of sulfinyl-based ligands were first evaluated as Lewis acid catalysts in the Diels–Alder reaction because this reaction provides a benchmark for measuring the new ligand class against previously developed ligands.⁴⁴ The Cu(II) complex of a C₂-symmetric bis-sulfinyl(imidoamidine) ligand, **39**, which is available in

Table 4. Substrate Generality in the Diels–Alder Reaction^a

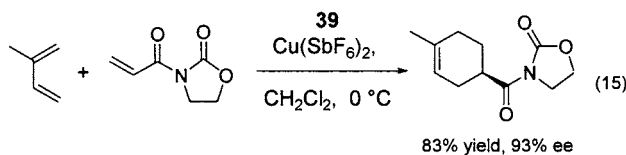


entry	dienophile, R	time (h)	temp (°C)	yield (%)	ee	dr
1	H	0.1	-78	96	>98	>99:1
2 ^b	H	8	-78	96	>98	>99:1
3	CH ₃	8	-40	76	97	98:2
4	Ph	16	0	58	94	95:5
5	CO ₂ Et	2	-78	85	96	97:3

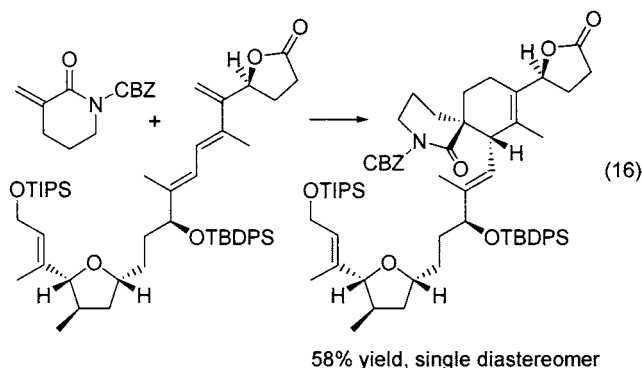
^a Unless otherwise noted, reactions are performed with 10 mol % catalyst. ^b Reaction performed with 1% catalyst.

three steps from **1**, provides exceptional levels of enantio- and diastereoselectivity that are competitive with or superior to those of all previously reported asymmetric Lewis acid-catalyzed reactions with these substrates (Table 4).⁴⁹ The catalyst is highly efficient, as demonstrated for entry 2, where a low catalyst loading (1%) was used.

We have further demonstrated that the catalyst is effective for Diels–Alder reactions with much less reactive acyclic dienes. For example, the Diels–Alder reaction of 2-methylbutadiene and *N*-acryloyl oxazolidinone proceeds with very high levels of stereoselectivity (eq 15).⁵⁰ In



contrast, the best bisoxazoline metal complex provides only 60% ee for the same reaction.⁴⁹ Furthermore, Ishiwara and Murai have recently utilized the sulfinamide-based catalyst in studies toward the synthesis of gymnodimine, demonstrating that this catalyst is effective even for highly complex substrates (eq 16).⁵¹ Studies are ongoing to



further establish the scope of this catalyst system for Diels–Alder transformations and to determine the mechanism through which high selectivities are achieved. In

addition, this ligand class and other ligand classes are actively being explored in a wide range of asymmetric catalytic transformations.

Conclusion

N-*tert*-Butanesulfinyl imines are extremely versatile intermediates for the asymmetric synthesis of amines. There are several factors that contribute to the utility of these compounds. First, either configuration of enantiomerically pure *tert*-butanesulfinamide **1** is commercially available or is readily prepared on a mole scale in two steps from inexpensive starting materials. Second, isolable and stable *N*-*tert*-butanesulfinyl imines may be easily prepared in high yield by condensing a wide range of aldehydes and ketones with *tert*-butanesulfinamide **1**. Third, the *tert*-butanesulfinyl group activates the imine for nucleophilic addition and serves as a powerful chiral directing group. Finally, the *tert*-butanesulfinyl group acts as a Boc surrogate that is stable to basic conditions but may be readily cleaved with acid. As a result of these favorable properties, *tert*-butanesulfinyl imines have now been successfully applied to the asymmetric synthesis of α -branched and α,α -dibranched amines, α -substituted and α,α -disubstituted α -amino acids, β -amino acids with a wide range of substitution patterns, α -trifluoromethylamines, and 1,2- and 1,3-amino alcohols. The generality of the aforementioned chemistry has rapidly led to the extensive use of *tert*-butanesulfinyl imines in academics and industry.

We gratefully acknowledge the researchers who carried out the work described herein. They are individually identified in the references. We also thank the National Science Foundation for support of this work.

References

- (1) For recent reviews, see: (a) Bloch, R. Additions of Organometallic Reagents to C=N Bonds: Reactivity and Selectivity. *Chem. Rev.* **1998**, *98*, 1407–1438. (b) Enders, D.; Reinhold, U. Asymmetric Synthesis of Amines by Nucleophilic 1,2-Addition of Organometallic Reagents to the CN-Double Bond. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (c) Kobayashi, S.; Ishitani, H. Catalytic Enantioselective Addition to Imines. *Chem. Rev.* **1999**, *99*, 1069–1094.
- (2) For recent reviews, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. Syntheses and Reactions of Sulfinimines. In *Advances in Sulfur Chemistry*; Raynor, C. M., Ed.; JAI Press: Stamford, CT, 2000; Vol. 2, pp 249–282. (b) Davis, F. A.; Reddy, R. E. Asymmetric Synthesis Using Sulfinimines (Thiooxime S-Oxides). *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *120/121*, 291–303.
- (3) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. Asymmetric Synthesis and Properties of Sulfinimines (Thiooxime S-Oxides). *J. Org. Chem.* **1997**, *62*, 2555–2563.
- (4) Moreau, P.; Essiz, M.; Merour, J.-Y.; Bouzard, D. Stereoselective Addition Reactions to Chiral *N*-benzylidene-*p*-Toluenesulfinamides. Application to the Synthesis of Optically Active 1,2-Diphenylethylamines. *Tetrahedron: Asymmetry* **1997**, *8*, 591–598.
- (5) Liu, G.; Cogan, D. A.; Ellman, J. A. Catalytic Asymmetric Synthesis of *tert*-Butanesulfinamide. Application to the Asymmetric Synthesis of Amines. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.
- (6) One report of racemic *tert*-butanesulfinamide **1** had appeared in a patent. Chambers, M. S.; Matassa, V. G.; Fletcher, S. R. Benzodiazepine Derivatives, Compositions Containing Them and Their Use in Therapy. U.S. Patent 5,360,802, 1994.
- (7) For leading references, see: Casey, M.; Mukherjee, I.; Trabsa, H. Stereoselective Additions of Sulphoxides to Carbonyl Compounds. *Tetrahedron Lett.* **1992**, *33*, 127–130.

- (8) Ruano, J. L. G.; Fernandez, I.; Catalina, M.; Cruz, A. A. Asymmetric Aziridination by Reaction of Chiral N-Sulfinylimines with Sulfur Ylides: Stereoselective Improvement by Use of *tert*-Butylsulfinyl Group as Chiral Auxiliary. *Tetrahedron: Asymmetry* **1996**, *7*, 3407–3414.
- (9) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. A.; Ellman, J. A. Catalytic Asymmetric Oxidation of *tert*-Butyl Disulfide. Synthesis of *tert*-Butanesulfinamides, *tert*-Butyl Sulfoxides, and *tert*-Butanesulfinimines. *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019.
- (10) Racemic **1** is also extremely straightforward to prepare. Reaction of *tert*-butyl disulfide with hydrogen peroxide followed by chlorine provides *tert*-butanesulfinyl chloride. Subsequent addition of ammonium hydroxide provides racemic **1** in 93% overall yield. See ref 5.
- (11) Liu, G.; Cogan, D. A.; Ellman, J. A. Catalytic Asymmetric Synthesis of *tert*-Butanesulfinamide. Application to the Asymmetric Synthesis of Amines. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.
- (12) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. The Synthesis of Enantiomerically Pure *N*-*tert*-Butanesulfinyl Imines (*tert*-Butanesulfinimines) by the Direct Condensation of *tert*-Butanesulfinamide with Aldehydes and Ketones. *J. Org. Chem.* **1999**, *64*, 1278–1284.
- (13) Cogan, D. A.; Ellman, J. A. The Asymmetric Synthesis of α,α -Dibranched Amines by the Trimethylaluminum Mediated 1,2-Addition of Organolithiums to *tert*-Butanesulfinyl Ketimines. *J. Am. Chem. Soc.* **1999**, *121*, 268–269.
- (14) After our initial reports on the direct condensation of *tert*-butanesulfinamide **1** with aldehydes (ref 5) and ketones (ref 13), Davis reported on the direct condensation of toluenesulfinamide with carbonyl compounds. Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. Improved Synthesis of Enantiopure Sulfinimines (Thioxime S-Oxides) from *p*-Toluenesulfinamide and Aldehydes and Ketones. *J. Org. Chem.* **1999**, *64*, 1403–1406.
- (15) Cogan, D. A.; Liu, G.; Ellman, J. A. Asymmetric Synthesis of Chiral Amines by Highly Diastereoselective 1,2-Additions of Organometallic Reagents to *N*-*tert*-Butanesulfinyl Imines. *Tetrahedron* **1999**, *55*, 8883–8904.
- (16) For recent applications of *tert*-butanesulfinamide chemistry to the asymmetric synthesis of diarylmethylamines, see: (a) Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. Asymmetric Synthesis of Cetirizine Dihydrochloride. *Tetrahedron Lett.* **2002**, *43*, 923–926. (b) Plobeck, N.; Powell, D. Asymmetric Synthesis of Diarylmethylamines by the Diastereoselective Addition of Organometallic Agents to Chiral *N*-*tert*-Butanesulfinimines: Switchover of Diastereofacial Selectivity. *Tetrahedron: Asymmetry* **2002**, *13*, 303–310.
- (17) Borg, G.; Cogan, D. A.; Ellman, J. A. One-Pot Asymmetric Reductive Amination of Ketones to Prepare *tert*-Butanesulfinyl Protected Amines. *Tetrahedron Lett.* **1999**, *40*, 6709–6712.
- (18) For the special case of additions to α -pyridyl-substituted ketones, see: Spero, D. M.; Kapadia, S. R. A Novel Method for the Asymmetric Synthesis of α,α -Disubstituted Alkylamines via Grignard Additions to Ketimines. *J. Org. Chem.* **1997**, *62*, 5537–5541.
- (19) Shaw, A. W.; deSolms, S. J. Asymmetric Synthesis of α,α -Diaryl and α -Aryl- α -heteroarylalkylamines by Organometallic Additions to *N*-*tert*-Butanesulfinyl Ketimines. *Tetrahedron Lett.* **2001**, *42*, 7173–7176.
- (20) Two research groups have very recently reported that either diastereomer of *N*-*tert*-butanesulfinyl diarylmethylamines may be accessed in additions of organometallic agents to *tert*-butanesulfinyl imines by changing the solvent or counterion and by addition of Lewis acids (see ref 16).
- (21) For a review on the biology and synthesis of β -amino acids, see: *Enantioselective Synthesis of β -Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.
- (22) For a very recent comprehensive review, see: Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. β -Peptides: From Structure to Function. *Chem. Rev.* **2001**, *101*, 3219–3232.
- (23) For leading references, see: Juaristi, E.; Lopez-Ruiz, H. Recent Advances in the Enantioselective Synthesis of β -Amino Acids. *Curr. Med. Chem.* **1999**, *6*, 983–1004.
- (24) For a recent review on the synthesis of substituted β -amino acids, see: Abele, S.; Seebach, D. Preparation of Achiral and of Enantiopure Geminally Disubstituted β -Amino Acids for β -Peptide Synthesis. *Eur. J. Org. Chem.* **2000**, 1–15.
- (25) Tang, T. P.; Ellman, J. A. The *tert*-Butanesulfinyl Group: An Ideal Chiral Directing Group and Boc-Surrogate for Asymmetric β -Amino Acid Synthesis and Applications. *J. Org. Chem.* **1999**, *64*, 12–13.
- (26) Tang, T. P.; Ellman, J. A. Applications of *N*-*tert*-Butanesulfinyl Imines Toward the Asymmetric Synthesis of β -Amino Acids. *J. Org. Chem.* **2002**, *67*, in press.
- (27) α -Substituted *N*-sulfinyl β -amino esters racemize under standard saponification conditions; however, Bu_3SnO -mediated saponification may be accomplished without racemization. In addition, PMB ester enolates may be used in place of the Me ester enolate in the initial condensation step. The PMB ester may be conveniently cleaved in the presence of the sulfinyl group by treatment with TFA in CH_2Cl_2 (see ref 26 for details).
- (28) For details on the *N*-acylsulfonamide safety-catch linker, see: Backes, B. J.; Ellman, J. A. An Alkanesulfonamide “Safety-Catch” Linker for Solid-Phase Synthesis. *J. Org. Chem.* **1999**, *64*, 2322–2330.
- (29) Davis, F. A.; McCoull, W. Concise Asymmetric Synthesis of α -Amino Acid Derivatives from *N*-Sulfinylimino Esters. *J. Org. Chem.* **1999**, *64*, 3396–3397.
- (30) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. Asymmetric Strecker Synthesis Using Enantiopure Sulfinimines and Diethyl Aluminum Cyanide: The Alcohol Effect. *J. Org. Chem.* **1996**, *61*, 440–441.
- (31) In their studies, Mabic and Cordi also found that, while the reaction of Et_2AlCN with the corresponding toluenesulfinyl imine proceeded in similar yields and stereoselectivity, the TMSCN addition proceeded with reduced yields (77%) and stereoselectivity (83:17). As well, the authors reported that the synthesis of the *p*-toluenesulfinyl imine proceeded in significantly lower yield (51% versus 89%). Mabic, S.; Cordi, A. A. Synthesis of Enantiomerically Pure Ethylenediamines from Chiral Sulfinimines: A New Twist to the Strecker Reaction. *Tetrahedron* **2001**, *57*, 8861–8866.
- (32) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. Application of the Sulfinimine-Mediated Asymmetric Strecker Synthesis to the Synthesis of α -Alkyl- α -Amino Acids. *J. Org. Chem.* **2000**, *65*, 8704–8708.
- (33) Borg, G.; Chino, M.; Ellman, J. A. Asymmetric Synthesis of Pre-Protected α,α -Disubstituted Amino Acids from *tert*-Butanesulfinyl Ketimines. *Tetrahedron Lett.* **2001**, *42*, 1433–1436.
- (34) Sun, P.; Weinreb, S. M. *tert*-Butylsulfonyl (Bus), a New Protecting Group for Amines. *J. Org. Chem.* **1997**, *62*, 8604–8608.
- (35) (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. Stereoselective Nucleophilic Trifluoromethylation of *N*-(*tert*-Butylsulfinyl)imines by Using Trimethyl(trifluoromethyl)silane. *Angew. Chem., Int. Ed.* **2001**, *40*, 589–590. (b) Prakash, G. K. S.; Mandal, M.; Olah, G. A. Asymmetric Synthesis of Trifluoromethylated Allylic Amines Using α,β -Unsaturated *N*-*tert*-Butanesulfinimines. *Org. Lett.* **2001**, *3*, 2847–2850.
- (36) Tang, T. P.; Volkman, S. K.; Ellman, J. A. Asymmetric Synthesis of 1,2-Amino Alcohols Using *tert*-Butanesulfinyl Aldimines and Ketimines. *J. Org. Chem.* **2001**, *66*, 3707–3709.
- (37) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. A Facile Three-Step Synthesis of 1,2-Amino Alcohols Using the Ellman Homochiral *tert*-Butylsulfinamide. *Tetrahedron Lett.* **2001**, *42*, 2051–2054.
- (38) Steinig, A. G.; Spero, D. M. Highly Diastereoselective Addition of Grignard Reagents to Aliphatic, Enolizable N-Alkylketimines and 2,2-Disubstituted 1,3-Oxazolidines. Asymmetric Synthesis of the Antidepressant Cericlamine. *J. Org. Chem.* **1999**, *64*, 2406–2410.
- (39) Kochi, T.; Tang, T. P.; Ellman, J. A. Asymmetric Synthesis of *Syn*- and *Anti*-1,3-Amino Alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 6518–6519.
- (40) Evans, D. A.; Hoveyda, A. H. Reduction of β -Hydroxy Ketones with Catecholborane. A Stereoselective Approach to the Synthesis of *syn*-1,3-Diols. *J. Org. Chem.* **1990**, *55*, 5190–5192.
- (41) For a recent review of solid-phase linkers, see: James, I. W. Linkers for Solid Phase Organic Synthesis. *Tetrahedron* **1999**, *55*, 4855–4946.
- (42) Enders, D.; Kirchoff, J. H.; Kobberling, J.; Peiffer, T. H. Asymmetric Synthesis of Alpha-Branched Primary Amines on Solid Support via Novel Hydrazine Resins. *Org. Lett.* **2001**, *3*, 1241–1244.
- (43) Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. Design, Synthesis, and Utility of Support-Bound *tert*-Butanesulfinamide. *J. Am. Chem. Soc.* **2001**, *123*, 10127–10128.
- (44) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer: New York; 1999.
- (45) Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. Synthesis, Utility, and Structure of Novel Bis(sulfinyl)imidoamidate Ligands for Asymmetric Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2001**, *123*, 1539–1540.
- (46) Owens, T. D.; Ellman, J. A., unpublished results.
- (47) Souers, A. J.; Owens, T. D.; Oliver, A. G.; Hollander, F. J.; Ellman, J. A. Synthesis and Crystal Structure of a Unique and Homochiral *N,S*-Bonded *N,N'*-Bis(*tert*-butanesulfinyl)amidinate Rhodium(I) Complex. *Inorg. Chem.* **2001**, *40*, 5299–5301.
- (48) Schenkel, L.; Ellman, J. A., unpublished results.

- (49) (a) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. Chiral Bis-(oxazoline)copper(II) Complexes as Lewis Acid Catalysts for the Enantioselective Diels–Alder Reaction. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573. (b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. A.; Shaughnessy, E. A.; Campos K. R. Bis(oxazoline) and Bis-(oxazoliny)pyridine Copper Complexes as Enantioselective Diels–Alder Catalysts: Reaction Scope and Synthetic Applications. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.
- (50) Owens, T. D.; Ellman, J. A., unpublished results.
- (51) Tsujimoto, T.; Ishihara, J.; Horie, M.; Murai, A. Asymmetric Construction of the Azaspiro[5.5]undec-8-ene System Towards Gymnodimine Synthesis. *Synlett* **2002**, 399–402.

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