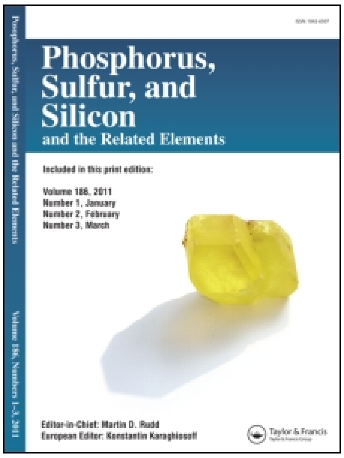

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Franklin A. Davis[a]; Bin Yang[a]; Jianghe Deng[a]; Yongzhong Wu[a]; Yulian Zhang[a]; Ashwin Rao[a]; Tianan Fang[a]; Rajesh Goswami[a]; Kavirayani R. Prasad[a]; M. Brad Nolt[a]; Gopinathan Anilkumar[a]
[a] Department of Chemistry, Temple University, Philadelphia, Pennsylvania

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Department of Chemistry, Temple University, Philadelphia, Pennsylvania

Sulfinimine-derived polyfunctionalized chiral building blocks, often prepared in one pot, provide efficient access, with a minimum of chemical manipulation, to enantiopure, multifunctional amine derivatives including piperidines and pyrrolidines.

Keywords Alkaloids; amines; asymmetric synthesis; *N*-sulfinylimines; piperidine; pyrrolidine

INTRODUCTION

The availability of small, easily manipulated chiral building blocks and templates continues to have a significant impact on the asymmetric syntheses of biologically and pharmaceutically valuable molecules. Examples of such building blocks include carbohydrates, amino acids, hydroxy acids, and terpenes. Because they are often derived from the ”chiral pool” they usually require extensive manipulation and protecting-group chemistry to transform them into the desired target.

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Address correspondence to Franklin A. Davis, Department of Chemistry, Temple University, Philadelphia, PA 19122. E-mail: fdavis@temple.edu

Furthermore, access to both enantiomers is usually limited. Many of these limitations can be avoided using polyfunctionalized chiral building blocks designed specifically for this purpose. Ideally these types of compounds are both easily prepared in enantiomerically pure forms and require a minimum of chemical manipulation to transform them into the target molecules.

The emergence of simple, easily prepared, sulfinimine-derived polyfunctionalized chiral building blocks—including *N*-*p*-toluenesulfinyl δ-amino β-ketoesters for piperidine[1] and pyrrolidine[2] alkaloid syntheses; *N*-*p*-toluenesulfinyl β-amino Weinreb amides for β-amino carbonyl synthesis;[3] *N*-*p*-toluenesulfinyl β-amino aldehydes and ketones for alkaloid synthesis;[3–5] *N*-sulfinyl aziridine 2-carboxylates[6] and phosphonates for the syntheses of α- and β-amino acids and phosphonates;[6] and 2*H*-azirine 3-phosphonates[7] for piperidine phosphonate synthesis—is expected to further facilitate the asymmetric syntheses of increasingly complex biologically active nitrogen containing molecules for both industrial and academic applications (Figure 1).

Sulfinimines (*N*-sulfinyl imines **1**) first synthesized in our laboratory provide a general solution to the problem of the addition of

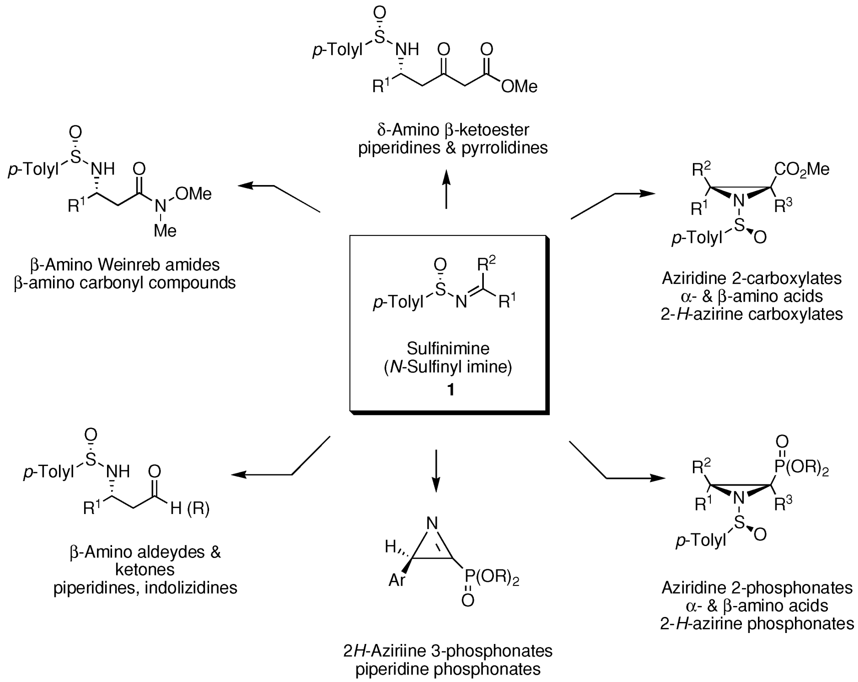


FIGURE 1 Sulfinimine-derived polyfunctionalized chiral building blocks.

organometallic reagents to the C—N double bond of chiral imines.[8] In **1** the electron-attracting sulfinyl group activates the C=N bond for nucleophilic addition and exerts powerful stereodirecting effects, which results in the addition of enolates and organometallic reagents to both enolizable and nonenolizable sulfinimines with high diastereoselectivities, and predictable asymmetric induction. Unlike other imine *N*-auxiliaries, the sulfinyl group can be removed under comparatively mild conditions. Moreover, sulfinimines are stable and easily prepared from diverse aldehydes and ketones by condensation of commercially available (*R*)- and (*S*)-*p*-toluenesulfinamide. The utility of sulfinimines **1** in highly diastereoselective asymmetric syntheses of amine derivatives has been demonstrated and is the subject of several reviews.[8] Recent applications of sulfinimine-derived chiral building blocks are presented below.

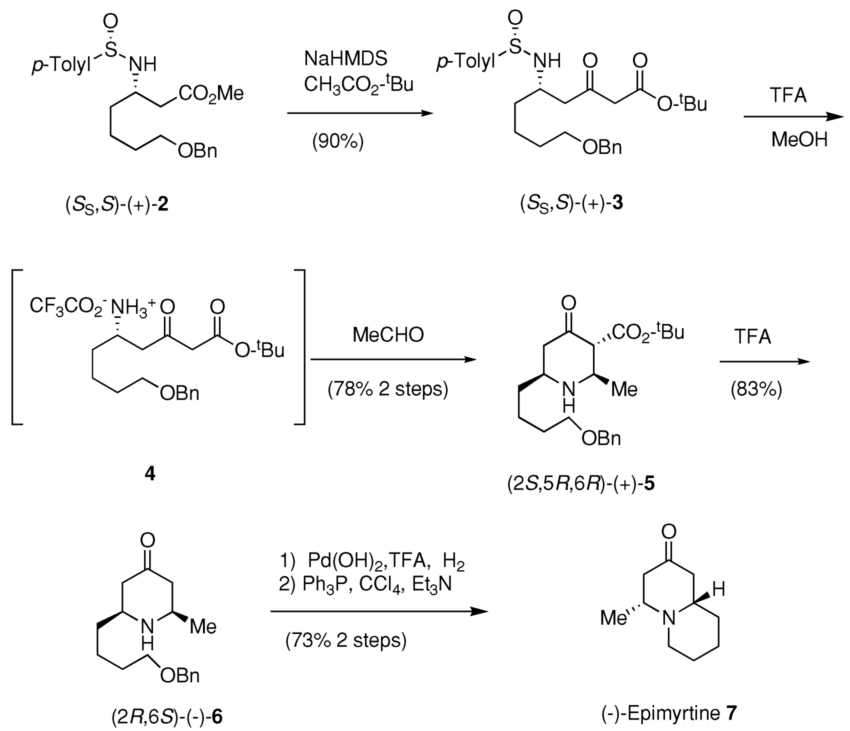
RESULTS

N-Sulfinyl δ-Amino β-Ketoesters

N-sulfinyl δ-amino β-ketoesters can be prepared in one pot by condensing an excess of the sodium enolate of methyl acetate with a sulfinimine or in a two-step sequence involving reaction of the enolate with an *N*-sulfinyl β-amino ester. The sulfinimine building block provides general access to mono substitute piperidines such as (*R*)-(+)-2-phenylpiperidine; disubstituted piperidines such as the four isomers of 4-hydroxypipecolic acid[1c] and (−)-SS20846A;[1a] and trisubstituted piperidines including the frog skin toxin (+)-241D[1d] and the quinolizidine alkaloid (+)-Lasubine II.[1e] Newer applications of this building block are discussed in the following sections.

(−)-Epimyrtine

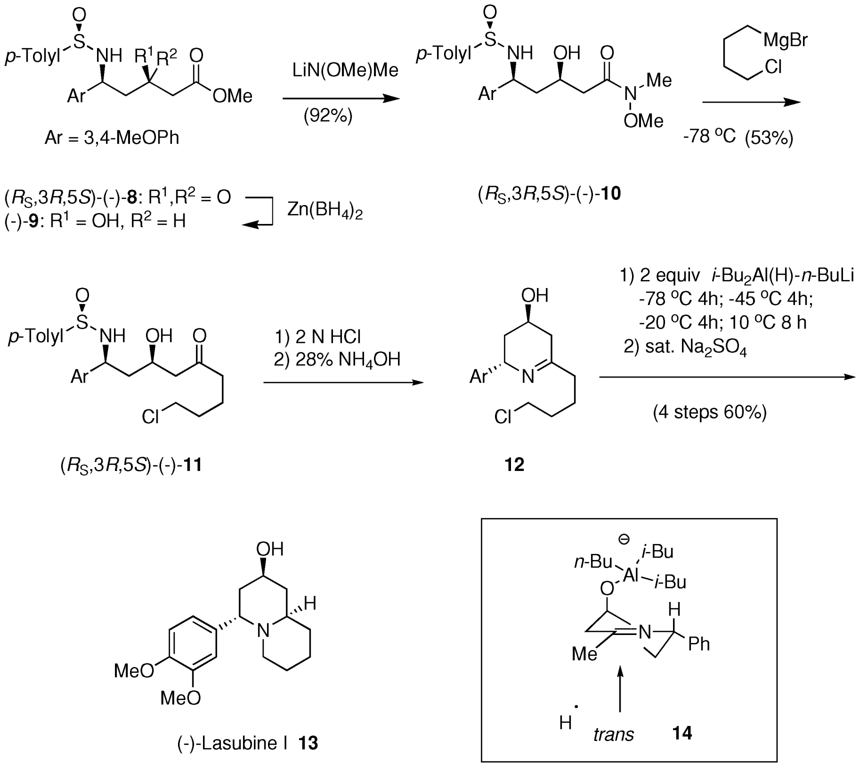
The asymmetric synthesis of the quinolizidine alkaloid (−)-epimyrtine **7** from δ-amino β-ketoesters **3** was accomplished using a novel intramolecular Mannich reaction (Scheme 1).[1f] Removal of the *N*-sulfinyl group in **3** with TFA/MeOH gave the intermediate amine salt **4** that, on treatment with acetaldehyde, resulted in 2,3,4,6-tetrasubstituted piperidine (+)-**5**. The intramolecular Mannich cyclization was highly stereoselective, producing only the isomer with the 2,6-substitutents in the *cis* geometry. Decarboxylation of **5** gave **6**, which was then deprotected and cyclized to form (−)-epimyrtine **7**. This sequence represents the most concise asymmetric synthesis of this alkaloid reported to date.



SCHEME 1

(−)-Lasubine I

The synthesis of piperidines using δ-amino β-ketoesters generally results in formation of *cis*-2,6-disubstituted examples; i.e. (−)-7.$^{1a-d,f}$ New methodology was developed, employing δ-amino β-ketoesters, for the asymmetric synthesis of the more difficult to prepare 2,6-trans disubstituted piperidines. This new chemistry was highlighted in the asymmetric synthesis of (−)-lasubine I **13** as outlined in Scheme 2.^{1e} Stereoselective reduction of the β-keto group in **8** gave **9**, which was converted into the Weinreb amide **10** with excess LiN(OMe)Me. Hydrolysis of *N*-sulfinyl ketone **11** afforded 1,2-dehydropiperidine **12**, which underwent a highly stereoselective reduction by the "ate" complex prepared from DIBAL-H and *n*-BuLi. Slow warming of the reaction mixture to 10°C gave exclusively (−)-lasubine I **13** in 60% yield for the four steps. This result can be explained by assuming that the alkoxy aluminum in intermediate **14** shields the top face of the C—N double bond, which would favor the approach of hydride from the bottom face (Scheme 2).

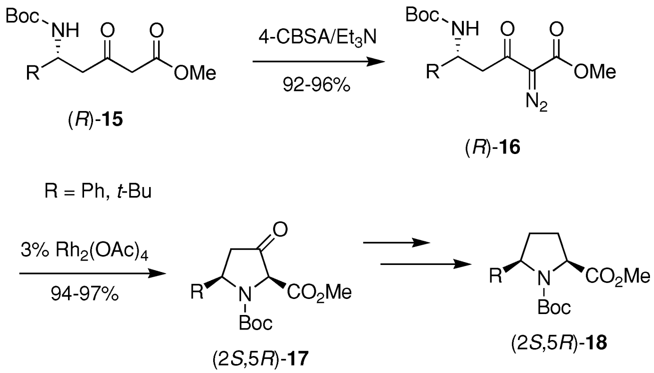


SCHEME 2

cis-2,5-Disubstituted Prolines

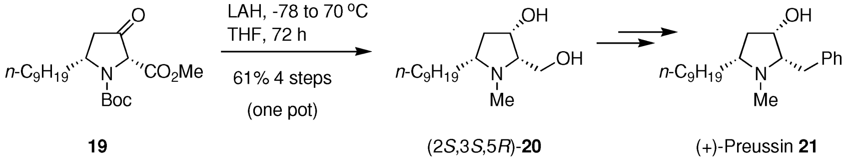
The sulfinimine-derived δ-amino β-ketoester polyfunctionalized chiral building block not only provides efficient access to multisubstituted piperidine alkaloids but to pyrrolidines as well.

Upon treatment with 4-carboxybenzenesulfonylazide (4-CBSA) and Et_3N the *N*-Boc-δ-amino β-ketoester (*R*)-**15** afforded the δ-amino-β-ketone-α-diazoesters **16** in 92–96% yield (Scheme 3).[2a,b] With 3 mol% of $Rh_2(OAc)_4$ in DCM, **16** gave 3-oxo prolines (2*S*, 5*R*)-**17** in excellent yield. The intramolecular metal carbenoid NH insertion reaction was highly stereospecific, affording the *cis* isomers exclusively. Removal of the 3-oxo group via hydrogenation of the vinyl triflate or enol phosphonate gave *cis*-5-phenylproline 18 (R = Ph)[2a] and *cis*-5-*tert*-butylproline 18 (R = *t*-Bu),[2b] respectively. *cis*-5-Phenylproline is a component of (+)-RP 66803, a nonpeptide cholecystokinin antagonist, while *cis*-5-*tert*-butylproline has been used in probing peptide conformations.



SCHEME 3

In a similar manner, 3-oxo proline **19** was prepared from the corresponding α-diazoester and was elaborated to the potent antifungal pyrrolidine alkaloid (+)-preussin **21** (Scheme 4).[2c] A key step in the synthesis was the highly stereoselective one pot reduction of **19** to diol (2*S*, 3*S*, 5*R*)-**20** with LAH in 61% yield for the four-step sequence.



SCHEME 4

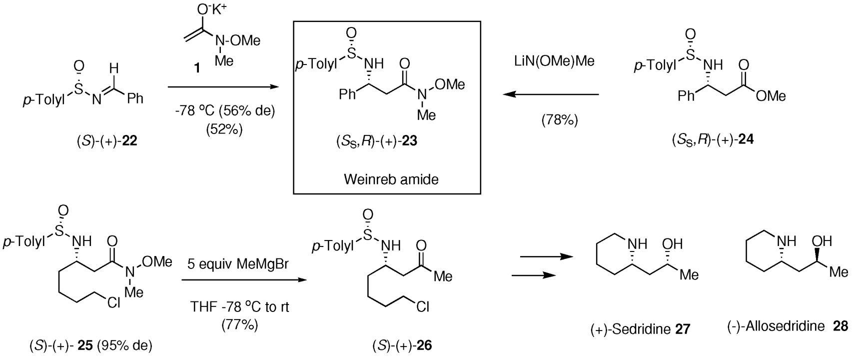
β-Amino Carbonyl Compounds

β-Amino carbonyl compounds are found in natural products and are precursors of 1,3-amino alcohols. However, β-amino aldehydes and ketones have been underutilized because of the lack of general methods for their preparation. Furthermore, unless suitably *N*-protected, they are unstable as they undergo self-condensation or β-elimination of the amino group. A new and general methodology for the asymmetric synthesis of stable β-amino aldehydes and ketones is presented next.

β-Amino Weinreb Amides

Weinreb amides are important carbonyl equivalents that, on reaction with organometallic reagents, afford carbonyl derivatives.[3] *N*-Sulfinyl

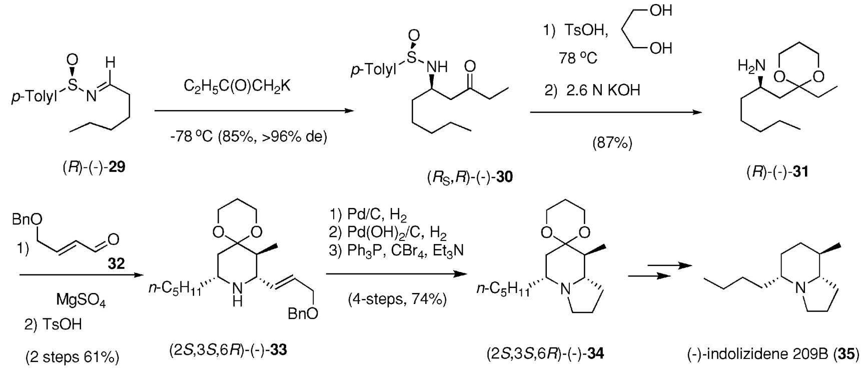
β-amino Weinreb amide **23** was prepared by reaction of the potassium enolate of *N*-methoxy *N*-methylacetamide with sulfinimine (*S*)-(+)-**22** or lithium *N*,*O*-dimethylhydroxylamine with the corresponding β-amino ester (+)-**24** (Scheme 5). This Weinreb amide reacts with DIBAL-H and Grignard reagents to give excellent yields of the corresponding, stable, β-amino aldehydes and ketones. For example, reaction of (*S*)-(+)-**25** with methylmagnesium bromide gave methyl ketone (+)-**26** in 77% yield. This ketone was further manipulated into the sedrum alkaloids (+)-sedridine **27** and (−)-allosedridine **28** (Scheme 5).[3]



SCHEME 5

β-Amino Ketones

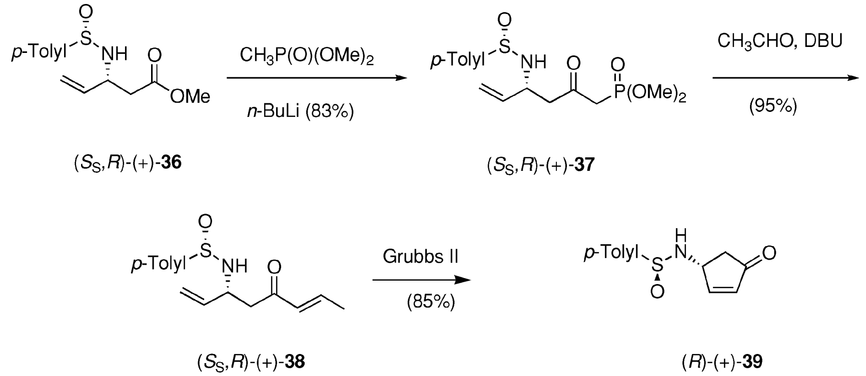
β-Amino ketones can be prepared directly, with excellent diastereoselectivity, by reacting the potassium enolates of methyl ketones with sulfinimines.[4] For example, the potassium enolate of methyl ethyl ketone reacted with sulfinimine (*R*)-(−)-**29** to give β-amino ethyl ketone (−)-**30** in >96% de (Scheme 6). One-pot deprotection/protection of **30** with TsOH and 1,3-propanediol afforded the corresponding β-amino ketal (−)-**31** in 87% isolated yield. This protected amino ketone is a valuable chiral building block in the asymmetric synthesis of polysubstituted, *cis*-2,6-disubstitute piperidines, because on reaction with aldehydes such as **32** it undergoes a facile, highly stereoselective intramolecular Mannich to give piperidine (−)-**33** in 61% yield for the two steps (Scheme 6). Deprotection, cyclization gave (−)-**4**, and removal of the keto group gave the dendrobatid frog skin toxin (−)-indolizidine 209B **35** and our synthesis represents the most efficient asymmetric synthesis of this alkaloid to date.



SCHEME 6

δ-Amino β-Ketophosphonates

N-Sulfinyl amino keto-2,7-diene (+)-**38** was prepared from *N*-sulfinyl δ-amino β-ketophosphonate (+)-**37**, a new sulfinimine chiral building block (Scheme 7).[9] The phosphonate was prepared by reaction of



SCHEME 7

lithium dimethyl methylphosphonate with β-amino ester **36**. Horner–Wadworth–Emmons chemistry with DBU and acetaldehyde gave the amino ketodiene (+)-**38** in excellent yield. Ring closing metathesis on treatment of (+)-**38** with 5 mol% Grubbs II (second-generation) catalyst afford (*R*)-(+)-4-aminocyclopentenone **39**. This amino-cyclopentenone is a valuable chiral building block for the asymmetric synthesis of structurally diverse antiviral and anticancer carbocyclic nucleosides.[9]

SUMMARY

Simple, easily prepared, sulfinimine-derived chiral building blocks such as *N*-sulfinyl δ-amino β-ketoesters and β-amino carbonyl compounds provide efficient access to enantiomerically pure biorelevant nitrogen-containing compounds.

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