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Asymmetric Synthesis of *syn*-α-Substituted β-Amino Ketones by Using Sulfinimines and Prochiral Weinreb Amide Enolates

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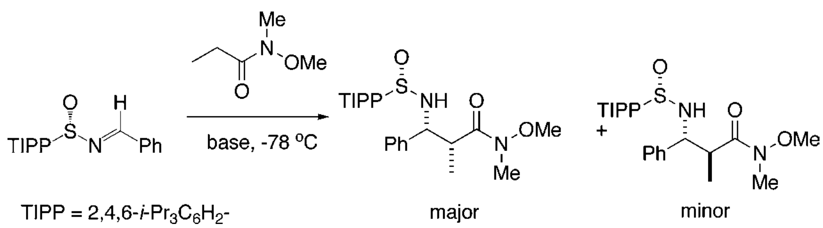
ABSTRACT



***syn*-α-Substituted β-amino Weinreb amides are new chiral building blocks for asymmetric synthesis of *syn*-α-substituted β-amino acids, aldehydes, and ketones and are prepared by addition of prochiral lithium enolates of Weinreb amides to sulfinimines (*N*-sulfinyl imines).**

β-Amino aldehydes and ketones are important chiral building blocks for the asymmetric synthesis of nitrogen-containing biologically active molecules.[1,2] For example, they have been employed in the synthesis of β-amino acids[3] and 1,3-amino alcohols.[4−6] They undergo Wittig-type condensations[3,4,7] to give homoallylic amines which were employed in the asymmetric synthesis of (−)-197B, a *trans*-2,5-disubstituted pyrrolidine.[8] The intramolecular Mannich cyclization of β-amino ketones with aldehydes is a particularly useful protocol for the asymmetric synthesis of stereodefined ring functionalized piperidines,[9] indolizidines,[10] and other alkaloids.[11] However, there are few methods reported for the synthesis of enantiopure β-amino aldehydes and ketones, and most of these are of limited scope.[12] We recently disclosed a general procedure for the asymmetric synthesis of β-amino aldehydes and ketones via the addition of organometallic reagents to *N*-sulfinyl β-amino Weinreb amides.[13] The

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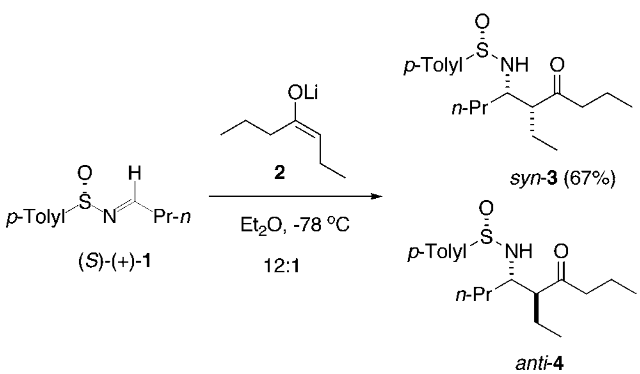
Weinreb amides were prepared in good to excellent yields and high de values by addition of the potassium enolate of *N*-methoxy-*N*-methylacetamide to sulfinimines (*N*-sulfinyl imines) or reaction of lithium *N*,*O*-dimethylhydroxylamine with *N*-sulfinyl β-amino esters.[13]

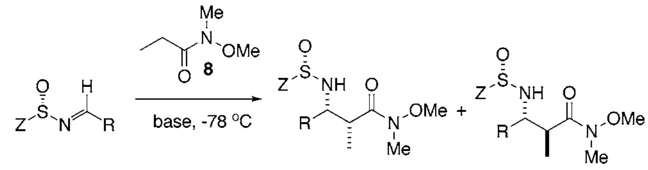
Methods for the asymmetric synthesis of α-substituted β-amino ketones that are required for the synthesis of architecturally complex piperidine alkaloids via the Mannich cyclization protocol are limited. Several racemic syntheses of α-substituted β-amino ketones[14] and a number of asymmetric syntheses of α-substituted β-amino esters have been reported.[15] To the best of our knowledge, the only asymmetric synthesis of an α-substituted β-amino ketone is our highly diastereoselective addition of the *E*-lithium enolate of 4-heptanone **2** to sulfinimine (*S*)-(+)-**1**.[10b] A 12:1 separable mixture of β-amino ketones *syn*-**3** and *anit*-**4** was obtained (Scheme 1). A limitation of this procedure is that the ketone needs to be symmetrical. A more general way of preparing α-substituted β-amino ketones would be the reaction of organometallic reagents with a sulfinimine-derived α-substituted β-amino Weinreb amide. We describe here a study of the asymmetric synthesis of α-substituted β-amino Weinreb amides and their conversion into α-substituted β-amino acids, aldehydes, and unsymmetrical α-substituted β-amino ketones.

Scheme 1



Conceptually the most direct way for preparing α-substituted β-amino Weinreb amides is the addition of a prochiral Weinreb amide enolate to a sulfinimine (Scheme 2). Weinreb amides, introduced by Nahm and Weinreb in 1981,[16] are valuable carbonyl equivalents and are widely used for the synthesis of carbonyl compounds.[17] Only a few studies on the addition of prochiral enolate and carbanion species to sulfinimines[18] exist where the formation of four diastereoisomers is possible.[19] The chemistry of prochiral Weinreb amide enolates has not been described.[20,21]

Scheme 2



(*S*)-**4a**: Z = 4-MeC$_6$H$_4$-, R = Ph
b: Z = 4-MeC$_6$H$_4$-, R = Et
(*S*)-**5**: Z = *t*-Me$_3$C-, R = Ph
(*S*)-**6a**: Z = 2,4,6-Me$_3$C$_6$H$_2$-, R = Ph
b: Z = 2,4,6-Me$_3$C$_6$H$_2$-, R = Et
(*S*)-**7a**: Z = 2,4,6-*i*-Pr$_3$C$_6$H$_2$, R = Ph
b: Z = 2,4,6-*i*-Pr$_3$C$_6$H$_2$, R = Et

syn:anti-**9**: Z = 4-MeC$_6$H$_4$-, R = Ph
syn:anti-**10**: Z = 4-MeC$_6$H$_4$-, R = Et
syn:anti-**11**: Z = 2,4,6-Me$_3$C$_6$H$_2$-, R = Ph
syn:anti-**12**: Z = 2,4,6-Me$_3$C$_6$H$_2$-, R = Et
syn:anti-**13**: Z = 2,4,6-*i*-Pr$_3$C$_6$H$_2$-, R = Ph
syn:anti-**14**: Z = 2,4,6-*i*-Pr$_3$C$_6$H$_2$-, R = Et

The prochiral Weinreb amide enolate of *N*-methoxy-*N*-methylpropylamide (**8**) was generated at −78 °C by addition of 1 equiv of the appropriate base at −78 °C (Scheme 2). After 2 h 0.5 equiv of sulfinimine (*S*)-**4** (Z = 4-MePh) was added to the preformed enolate and TLC monitored the progress for completion (typically 30 min). Products were isolated by chromatography and are recorded in Table 1. These results reveal that good levels of stereoinduction were observed for formation of the *syn*-α-methyl β-amino Weinreb amides, *syn*-**9** and *syn*-**10**, regardless of the base (Table 1, entries 1−4 and 6). Optimum results were noted for LiHMDS in THF (Table 1, entries 1 and 6). However, all four diastereoisomers were detected and they were not separable by conventional chromatography. This phenomenon has occasionally been observed for the addition of carbanion species to sulfinimines and can usually be overcome by changing the *N*-sulfinyl group.[22] Diverse *N*-sulfinyl imines

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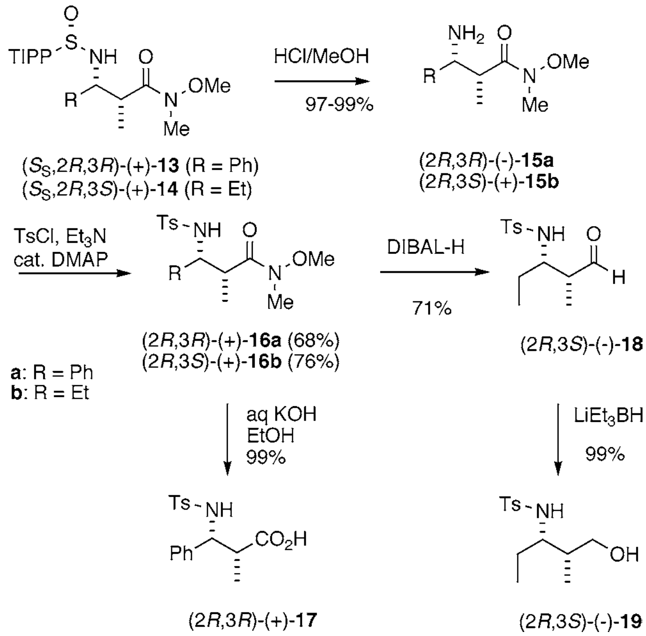
Table 1. Synthesis of α-Substituted *β*-Amino Weinreb Amides at −78 °C

entry	Z	R	base[a]	solvent	% yield[b] (dr syn:anti)[c]
1	**4a**	Ph	LiHMDS	THF	99 (87:13:<1:trace)
2			LiHMDS	THF:Et_2O (1:1)	35 (93:7:trace)
3			NaHMDS	THF	67 (91:6:3:0)
4				Et_2O	99 (73:17:9:1)
5			KHMDS	THF	NR
6	**4b**	Et	LiHMDS	THF	67 (75:11:10:4)
7	**5**	Ph	LiHMDS	THF	NR
8	**6a**	Ph	LiHMDS	THF	99 (96:4:0:0)
9	**6b**	Et	LiHMDS	THF	72 (80:17:3:0)
10	**7a**	Ph	LiHMDS	THF	74 (92:5:3:0) [*syn*-**13**, 68%][d]
11	**7b**	Et	LiHMDS	THF	95 (4:1:0:0) [*syn*-**14**,76%], [*anti*-**14**,19%][d]

[a] Ratio of base to **8**. [b] Combined yield of diastereoisomers that were not separable unless otherwise noted. [c] Determined by ^1H NMR on the crude reaction mixture. [d] Isolated yields.

Scheme 3



can be prepared with use of the *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide chiral auxiliary introduced by Senanayake and co-workers.[23] These workers also reported that for the addition of Grignards to sulfinimines the stereoinduction improves as the steric size of the *N*-sulfinyl moiety increases.[23b]

To improve the separation of the diastereoisomers and to explore the effect of the sulfinimine *N*-sulfinyl moiety on the stereoselectivity, the prochiral enolate of **8** was added to sulfinimines (*S*)-**5**, (*S*)-**6**, and (*S*)-**7** where the *N*-sulfinyl group was *tert*-butyl (TB), 2,4,6-mesityl (TMP), and 2,4,6-triisopropylphenyl (TIPP), respectively. These sulfinimines were prepared by condensation of the corresponding enantiopure sulfinamides (Z-S(O)NH_2)[23] with the appropriate aldehydes, using Ti$(OEt)_4$ as previously described.[24]

Unexpectedly, addition of the lithium enolate of **8** to *N*-*tert*-butanesulfinyl imine (*S*)-**5** resulted in no reaction and recovery of starting material (Table 1, entry 7). The reason for this result may be related to the larger size of the *tert*-butyl moiety that inhibits addition of the bulky amide enolate. Both the less bulky *N*-(2,4,6-mesitylsulfinyl) and the *N*-(2,4,6-triisopropylphenylsulfinyl) imines, (*S*)-**6** and (*S*)-**7**, gave results similar to those of (*S*)-**4** with the *syn*-isomers predominating (Table 1, entries 8−11). Importantly, both the *N*-(2,4,6-triisopropylphenylsulfinyl)amides, *syn*-**13** and *syn*-**14**, could be isolated in 68% and 76% yield, respectively (Table 1, entries 10 and 11). The minor *anti*-**14** isomer was obtained in 19% yield (Table 1, entry 11).

The absolute configurations of the α-substituted *β*-amino Weinreb amides (+)-**13** and (+)-**14** were determined by conversion to products of known stereochemistry as outlined in Scheme 3. Selective removal of the *N*-sulfinyl groups in (+)-**13** and (+)-**14** gave amines (−)-**15a** and (+)-**15b** in excellent yield, which when treated with TsCl/Et_3N gave the corresponding *N*-tosyl *β*-amino Weinreb amides (+)-**16a** and (+)-**16b** in 68% and 76% isolated yields, respectively. Hydrolysis of (+)-**16a** with aqueous KOH gave the known acid (2*R*,3*R*)-(+)-**17** in 99% yield.[25] When (+)-**16b** was subjected to DIBAL-H reduction, aldehyde (−)-**18** was obtained in 71% yield and reduction of the aldehyde with Super hydride gave the known 1,3-amino alcohol (2*R*,3*S*)-(−)-**19** in quantitative yield.[23] Both amino acid (+)-**17** and amino alcohol (−)-**19** have properties identical with those of authentic samples. These results establish that the major diastereoisomer formed in the addition of the prochiral lithium enolate of **8** to sulfinimines has the *syn* stereochemistry. Importantly these α-substituted *β*-amino Weinreb amides exhibit high configuration stability under the chemical transformations shown in Scheme 3.

The stereochemistry of the minor product isolated in the addition of the enolate of **8** to (*S*)-**7b** is shown to be *anti* as shown in Scheme 4. Weinreb amide (S_S,2*S*,3*S*)-(+)-**14** was converted to the *N*-tosyl derivative (−)-**20**, which was hydrolyzed to the *β*-amino acid (−)-**21**. Treatment of the acid with DCC/cat. 4-pyrrolidinopyridine afforded the *β*-lactam (−)-**22** in 67% yield. The proton $J_{3,4}$ coupling constant in (−)-**22** of 6.4 Hz is suggestive of a *cis*-relationship for these protons.[26] However, the large NOE (4.5%) for the C-3 proton and C-4 methyl group indicates that they have the expected *anti*-relationship.

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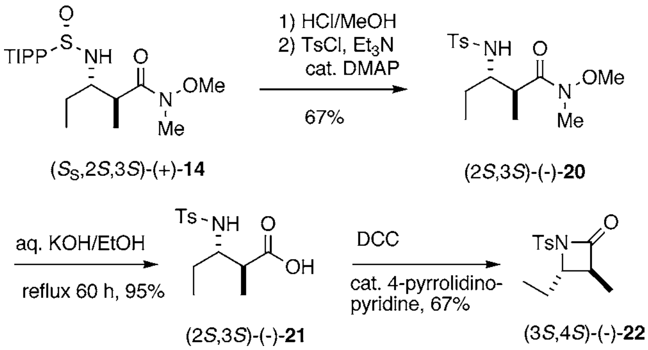
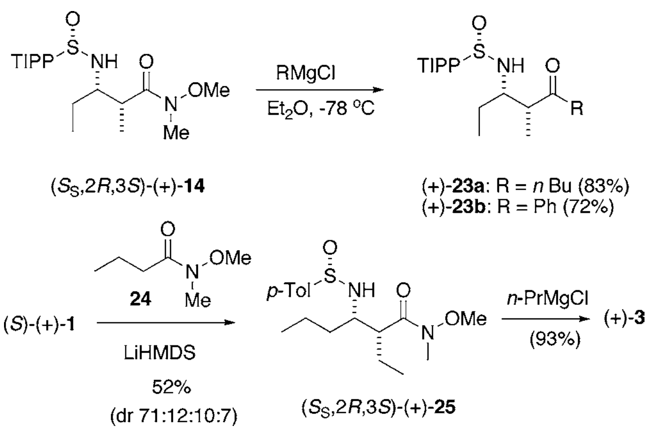
Scheme 4



Reaction of 5 equiv of *n*-butyl and phenylmagnesium chloride with (S_S,2*R*,3*S*)-(+)-**14** gave the corresponding unsymmetrical α-methyl *β*-amino ketones (+)-**23a** and (+)-**23b** in 83% and 72% yields, respectively (Scheme 5).

Scheme 5



α-Ethyl *β*-amino ketone *syn*-(+)-**3** was obtained in 93% yield by treating (+)-**25** with *n*-propylmagnesium chloride. This Weinreb amide was prepared by reaction of the lithium enolate of *N*-methoxy-*N*-methylbutyrylamide with sulfinimine (*S*)-(+)-**1** and isolated in 52% yield from the diastereomeric mixture of isomers.

Addition of the prochiral enolates of esters,[19c] glycine esters,[19e,f] α-bromoesters,[27] ketones,[10b] and *O*-Boc-α-hydroxy esters[19h] to sulfinimines gives *syn*-2,3-disubstituted *β*-amino carbonyl derivatives as the major product. These results are rationalized as involving addition of the *E*-enolate species to the sulfinimine via the usual six-membered chairlike transition states. A similar transition state **TS-1** explains the formation of the major *syn* product observed in the addition of lithium Weinreb amide enolates to sulfinimines (Figure 1). However, lithium enolates of amides are known to have

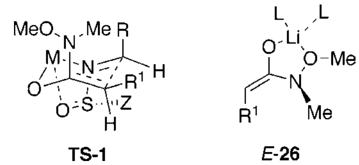


Figure 1. Transition state for enolate addition.

the *Z*-geometry, because $A^{1,3}$ interactions are thought to be lower than in the E-form.[28] This dichotomy is not easily explained and attempts to determine the geometry of the lithium enolate of **8** have failed. Perhaps because a Weinreb amide enolate is likely to exist in an intramolecular chelated form, the $A^{1,3}$ interactions in *E*-**26** are not as important as they would be in a nonchelated amide.[29]

In summary, of four possible diastereoisomers the *syn*-α-substituted *β*-amino Weinreb amide is the major product observed in the addition of lithium prochiral Weinreb amide enolates to sulfinimines. These new sulfinimine-derived chiral building blocks are important precursors of *syn*-α-substituted *β*-amino acids, aldehydes, and ketones on hydrolysis, reduction, and reaction with Grignard reagents, respectively.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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