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Direct Asymmetric Synthesis of β-Amino Ketones from Sulfinimines (*N*-Sulfinylimines). Synthesis of (–)-Indolizidine 209B

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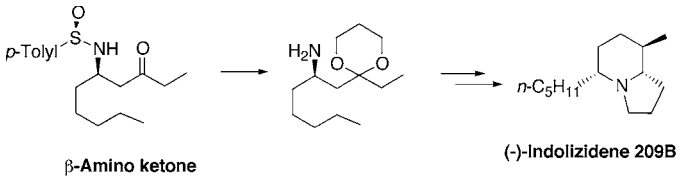
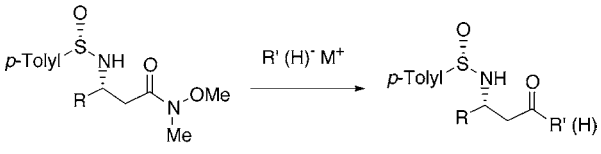
ABSTRACT



***N*-Sulfinyl β-amino ketones, prepared directly from the potassium enolates of methyl ketones and enantiopure sulfinimines, are transformed in one pot to protected amino ketones, which are valuable chiral building blocks for the assembly of piperidines. The utility of this methodology is illustrated in a concise asymmetric synthesis of (–)-indolizidine 209B.**

Recently, we introduced a new and general methodology for the asymmetric syntheses of β-amino aldehydes and ketones **2** via the addition of hydride and Grignard reagents to nonracemic *N*-sulfinyl β-amino Weinreb amides **1** (Scheme 1).[1] The Weinreb amides **1** were prepared either by the addition of the potassium enolate of *N*-methoxy-*N*-methylacetamide to enantiopure sulfinimines (*N*-sulfinylimines) or by the reaction of the corresponding β-amino ester with lithium *N*,*O*-dimethylhydroxyamine.[1] β-Amino carbonyl moieties are found not only as structural units of natural products[2] but also as useful chiral building blocks for Wittig-type condensations[3−7] and natural product,[1,4,5] 1,3-amino alcohol,[1,8] and β-amino acid syntheses. We describe herein a direct method for the asymmetric synthesis of β-amino ketones via the addition of the methyl ketone enolates to sulfinimines and its application to the concise synthesis of piperidine and indolizidine alkaloids.

Scheme 1



The methyl ketone enolates were generated from the corresponding ketones, acetophenone, acetone, 2-butanone, and 2-hexanone and the appropriate base at −78 °C. A solution of 1.0 equiv of (*S*)-(+)-*N*-benzylidine-*p*-toluene-

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(2) Davis, F. A.; Szewczyk J. M. *Tetrahedron Lett.* **1998**, *39*, 5951.
(3) Louis, C.; Mill, S.; Mancuso, V.; Hootele, C. *Can. J. Chem.* **1994**, *72*, 1347.
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(5) (a) Rodriguez, M.; Aumelas, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 5153. (b) Rodriguez, M.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 7319. (c) Limal, D.; Quesnel, A.; Briand, J.-P. *Tetrahedron Lett.* **1998**, *39*, 4239.
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(7) For a review see Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957.
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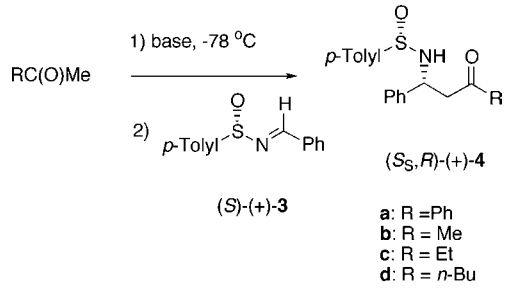
Scheme 2



sulfinamide (**3**)[9] was added, via cannula and at −78 °C, to 1.8 equiv of the enolates. The reaction mixture was quenched after 30 min by addition of saturated NH_4Cl solution. Flash chromatography afforded the *N*-sulfinyl *β*-amino ketones (S_S,*R*)-(+)-**4a**−**d** as single diastereoisomers (Scheme 2). These results are summarized in Table 1.

Table 1. Addition of Methyl Ketone Enolates to Sulfinimine (*S*)-(+)-**3** at −78 °C

entry	ketone (R =)	base	solvent	% isolated yield[a] (% de)[b]
1	Ph	LDA	THF	(S_S,*R*)-(+)-**4a** 53 (>96)
2		LiHMDS	THF	59 (>96)
3		NaHMDS	THF	<10
4		KHMDS	THF	95 (>96)
5	Me	NaHMDS	THF	(S_S,*R*)-(+)-**4b** <10
6		KHMDS	THF	40 (62)
7		KHMDS	Et_2O	72(70)
8	Et	KHMDS	Et_2O	(S_S,*R*)-(+)-**4c** 90 (90)
9	*n*-Bu	KHMDS	THF	(S_S,*R*)-(+)-**4d** 65 (80)
10		KHMDS	Et_2O	83 (90)

[a] Isolated yield of major diastereoisomer. [b] Determined from the ^1H NMR of the crude reaction mixture.

The results summarized in Table 1 reveal that the potassium enolates of the methyl ketones afford the highest yields and diastereoselectivity. While the lithium enolate of acetophenone gave high diastereoselectivity (>96% de), the yields were modest (Table 1, entries 1 and 2). Sodium enolates gave complex reaction mixtures (Table 1, entries 3 and 5). Improved diastereoselectivities and yields were also noted in ether solvent (Table 1, entries 7, 8, and 10). The absolute stereochemistry of the newly created stereocenter for the addition of enolates to (*S*)-(+)-**3** was established as *R* by comparison of the rotation of (+)-**4a** with an authentic sample.[1] These results are consistent with the usual model for addition of organometallic reagents to sulfinimines: the metal ion coordinates to the sulfinyl oxygen and addition to the C−N double bond occurs via six-membered chairlike transition states.[11]

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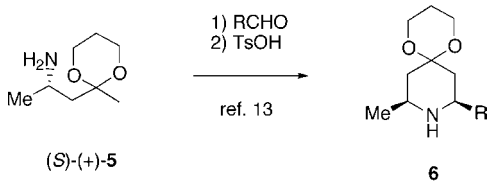
The availability of small, easily manipulated chiral building blocks and templates has had a significant impact on the asymmetric syntheses of biologically and pharmaceutically valuable molecules.[11,12] Toward this objective, Troin and coworkers introduced the ketal of (*S*)-(+)-4-amino-2-pentanone **5** and its enantiomer for the asymmetric synthesis of *cis*-2,6-disubstituted protected 4-oxo piperidines **6**.[13] On treatment with various aldehydes, followed by acid, **5** undergoes a facile intramolecular Mannich reaction to afford **6** in good yield and high diastereoselectivity (Scheme 3). However, the

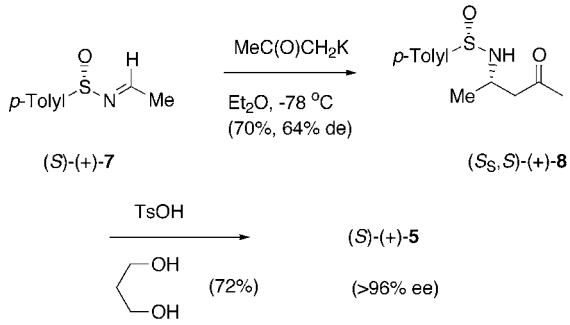
Scheme 3



multistep synthesis of **5** requires either a classical resolution or a microbiological reduction as key steps.[13a,e] Moreover, their methodology does not provide convenient access to diversely substituted derivatives, which are needed for the synthesis of more complex piperidines.

The Troin chiral building block is readily prepared using our new *β*-amino ketone synthesis. Thus, treatment of (*S*)-(+)-acetylidene-*N*-*p*-toluenesulfinimide (**7**)[9] with the potassium enolate of acetone in ether gave (S_S,*S*)-(+)-*N*-(*p*-toluenesulfinyl)-4-aminopentane-2-one (**8**) in 70% isolated yield of the major diastereoisomer following chromatography (Scheme 4). The diastereoselectivity of the addition was 64%.

Scheme 4



Initial attempts to convert (+)-**8** into (+)-**5** using 1,3-propanediol and catalytic *p*-toluenesulfonic acid (TsOH, 5

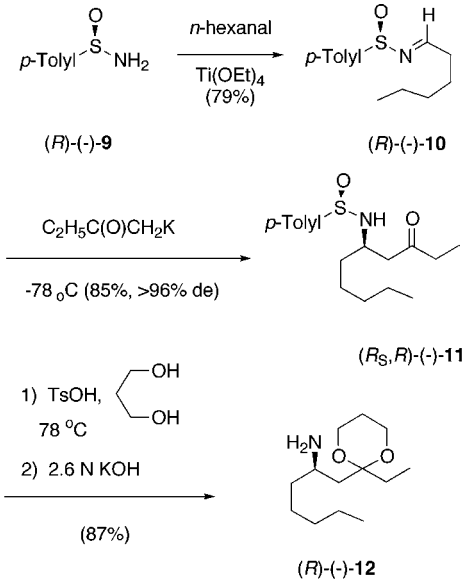
(10) For reviews on the chemistry of sulfinimines, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. In *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI Press: Stamford, CT, 2000; Vol. 2, pp 249−282. (b) Davis, F. A.; Zhou, P.; Chen. B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(11) For a review on sulfinimine derived polyfunctionalized chiral building blocks, see: Davis, F. A.; Chao, B.; Andemichael, Y. W.; Mohanty, P. K.; Fang, T.; Burns, D. M.; Rao, A.; Szewczyk, J. M. *Heteroto. Chem.* **2002**, *13*, 48.

mol %) resulted in low conversions. However, when (+)-**8** was heated in benzene or toluene with 1.5 equiv of TsOH and 5.0 equiv of 1,3-propanediol, (+)-**5** was obtained directly in 72% yield for the two-step, one-pot reaction. Comparison of its rotation with literature values indicated that epimerization had not occurred.[13a]

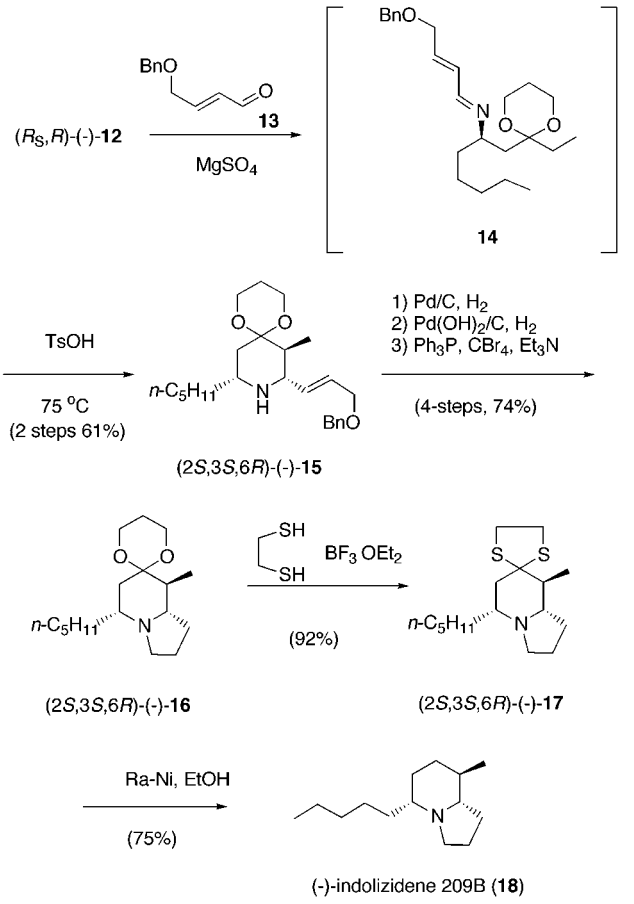
A further illustration of the utility of our methodology is the asymmetric synthesis of (−)-indolizidine 209B (**18**).[14] This 5,8-disubstituted indolizidine is member of a large family of indolizidine alkaloids isolated from the toxic skin of the dendrobatide frog and many of these alkaloids exhibit interesting biological activities.[15] Our synthesis begins with the preparation of (*R*)-(−)-*N*-(hexanylidine)-*p*-toluenesulfinamide (**10**), in 79% yield, by condensation of hexanal with commercially available (*R*)-(−)-*p*-toluenesulfinamide (**9**) using $Ti(OEt)_4$ (Scheme 5).[9] Next, treatment of the sulfinimine with the potassium enolate of 2-butanone afforded the β-amino ketone (R_S,*R*)-(−)-**11** in 85% yield and >96% de. The one-pot deprotection−protection sequence gave (*R*)-(−)-**12** in 87% yield following chromatography.

Scheme 5



With the requisite protected β-amino ketone (−)-**12** in hand, heating it with 4-benzyloxybutanal in the presence of anhydrous $MgSO_4$ in DCM was attempted, but complex mixtures occurred, apparently from aldol condensation of the aldehyde. Alternatively, treating this aldehyde with 4 Å molecular sieves without heating did seem to give some of the imine, but the aldol product was also present. This problem was avoided by stirring (−)-**12** at room temperature with anhydrous $MgSO_4$ and (*E*)-4-benzyloxy-but-2-enal (**13**) for 2−3 h (Scheme 6). The crude imine **14**, obtained in nearly quantitative yield was heated with dry TsOH, 2.0 equivalents, in benzene at 75 °C for 3 h to afford the Mannich product (−)-**15** as a single diastereoisomer in 61% yield for the two steps. The relative configuration was unambiguously assigned based on the ^{1}H NMR and COSY spectra and is consistent with a transition state where all the substituents occupy equatorial positions.[13b] Initial attempts to hydrogenate the alkene and remove the benzyl group using Pd/C/H_2 resulted

Scheme 6



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(14) For earlier syntheses of (−)-indolizidine 209B and leading references, see: (a) Ma, D.; Pu, X.; Wang, J. *Tetrahedron: Asymmetry* **2002,** *13*, 2257. (b) Song, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 8635. (c) Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477. (d) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543. (e) Michael, J. P.; Gravestock, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1919.

(15) For a review, see Daly, J. W.; Carraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical & Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: Oxford, 1999; Vol. 13, pp 1−161.

in only reduction of the alkene even after 3 days. Subsequent reaction of the crude alkane with $Pd(OH)_2/H_2$ gave the alcohol, which was subjected to cyclization using $CBr_4/Ph_3P/Et_3N$ and afforded the indolizidine (−)-**16** in 74% yield for the four steps. With ethane dithiol/BF_3, (−)-**16** gave the thioketal (−)-**17**, which on Ra−Ni desulfurization gave (−)-indolizidene 209B (**18**) with properties consistent with literature values.[14]

In summary, the direct asymmetric synthesis of *N*-sulfinyl *β*-amino ketones **4** from the potassium enolate of methyl ketones and sulfinimines is described. These compounds are efficiently transformed in one pot to protected *β*-amino ketones, which are valuable chiral building blocks for the assembly of piperidines. The utility of this methodology was demonstrated in the asymmetric synthesis of (−)-indolizidene 209B (**18**).

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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