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N-Sulfinyl Metalloenamine Conjugate Additions: Asymmetric Synthesis of Piperidines

Hillary M. Peltier and Jonathan A. Ellman*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

jellman@berkeley.edu

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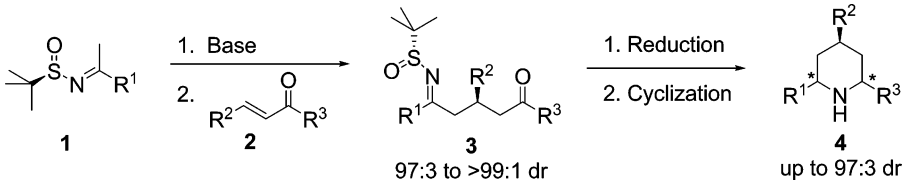
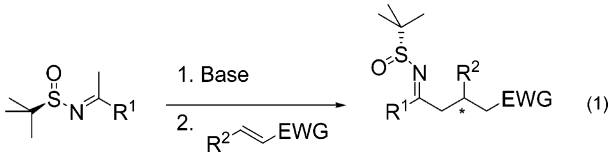


The first examples of conjugate additions of *N*-*tert*-butanesulfinyl metalloenamines are reported. Highly stereoselective conjugate additions (97:3 to 99:1 dr) were observed between metalloenamines derived from *N*-sulfinyl ketimines and α,β-unsaturated ketones bearing either alkyl or aryl substituents. The conjugate addition products could rapidly be converted with high diastereoselectivity to 2,4,6-trisubstituted piperidines, which are difficult to access by other methods.

Introduction

N-Sulfinyl metalloenamines have been employed in the rapid asymmetric syntheses of *syn*- and *anti*-1,3-amino alcohols through highly diastereoselective additions to aldehydes, followed by subsequent reduction of the *N*-sulfinylimino alcohol products.[1] Recently, the self-condensation of *N*-*tert*-butanesulfinyl aldimines has also been reported for the rapid production of biologically important amine-containing compounds.[2] We anticipated that the scope of the *N*-sulfinyl metalloenamine additions could be substantially broadened to include a more diverse set of electrophiles.[3−5] In particular, Michael additions could provide entry into a variety of functionalized compounds (eq 1).



Successful Michael additions to α,β-unsaturated ketones **2** would be of particular value because the addition products **3** could potentially be converted to 2,4,6-trisubstituted piperidines **4** by stereoselective reduction and cyclization (Scheme 1). While piperidines are a very important class of compounds commonly found in natural products and drugs,[6] methods for the asymmetric synthesis of 2,4,6-trialkyl-substituted piperidines have not previously been reported.[7,8]

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(2) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 3621.

(3) For alkylation of *N*′-*tert*-butanesulfinyl amidines, see: Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.

(4) For leading references on applications of *tert*-butanesulfinyl imines, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Pflum, D. A.; Krishnamurthy, D.; Han, Z. X.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 923. (c) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303. (d) Han, Z. X.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. *Tetrahedron Lett.* **2003**, *44*, 4195. (e) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666. (f) Cooper, I. R.; Grigg, R.; Hardie, M. J.; MacLachlan, W. S.; Sridharan, V.; Thomas, W. A. *Tetrahedron Lett.* **2003**, *44*, 2283. (g) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495. (h) Jung, P. M. J.; Beaudegnies, R.; De Mesmaeker, A.; Wendeborn, S. *Tetrahedron Lett.* **2003**, *44*, 293. (i) Chemla, F.; Ferreira, F. *Synlett* **2004**, 983. (j) Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641. (k) Jayathilaka, L. P.; Deb, M.; Standaert, R. F. *Org. Lett.* **2004**, *6*, 3659. (l) Weix, D. J.; Shi, Y. L.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (m) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747.

(5) For a leading reference on applications of arenesulfinyl imines, see: Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

(6) (a) Michael, J. P.*Nat. Prod. Rep.* **2001**, *18*, 520. (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (d) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (e) *Alkaloids: Chemical and Biological Perspectives;* Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3.

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SCHEME 1. Planned Route to Piperidines

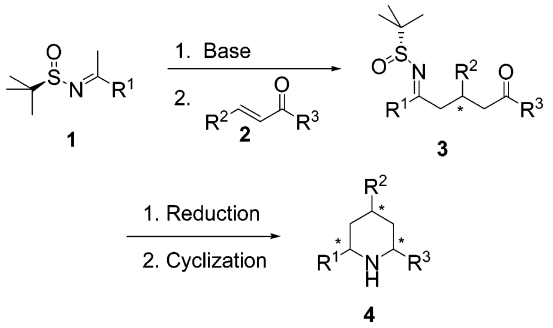
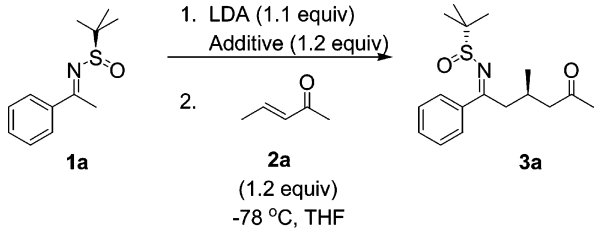


TABLE 1. Additive Screen of Addition of 1a to 2a



entry	additive	yield[a] (%)	dr[b,c]
1	none	<60	96:4
2	$MgBr_2$	69	97:3
3	$ZnBr_2$	84	97:3

[a] Isolated yield. [b] Determined by LCMS. [c] The sense of induction was established by X-ray analysis of the piperidine product **4a** (vida infra).

Results and Discussion

For the initial investigation of conjugate additions of *N*-sulfinyl metalloenamines to Michael acceptors, *N*-sulfinyl ketimine **1a**[9] was chosen as a model substrate because it forms a single metalloenamine upon deprotonation, thereby eliminating regioselectivity issues (Table 1). The addition of **1a** to ketone **2a**, using LDA as a base, provided product **3a** with a 96:4 diastereomeric ratio, albeit in modest yield (entry 1). Competitive deprotonation of the Michael acceptor has been reported for lithium enolate conjugate additions[10] and was likely responsible for the modest yield observed in the metalloenamine addition. It was anticipated that a metal that forms a more covalent bond might favor conjugate addition over deprotonation, and therefore, the reaction was repeated with $MgBr_2$ and $ZnBr_2$ as additives (entries 2 and 3). The improvement in yield was most dramatic when $ZnBr_2$ was employed (entry 3). Consequently, this additive was used in all subsequent metalloenamine additions to α,*β*-unsaturated ketones.

To explore the reaction scope for the Michael acceptor, compound **1a** was added to ketones **2b** and **2c** (Table 2, entries 1 and 2). Compounds **3b** and **3c** were obtained in good yields (82% and 60%) and with high selectivity (>99:1 dr), demonstrating that this method is general for both alkyl- and aryl-substituted α,*β*-unsaturated ketones. The scope of the additions to α,*β*-unsaturated ketones was further extended from metalloenamines derived from *N*-sulfinyl aryl ketimines to those derived from aliphatic ketimines (entries 3 and 4). Addition of compound **1b** to ketone **2b** yielded the desired product **3d** in 61% isolated yield with >99:1 dr, and compound **3e** was obtained in 72% yield with >99:1 dr from the addition of **1c** to ketone **2b**. Use of the metalloenamine formed from the unbranched ketimine **1d** resulted in a complex mixture of products (entry 5).

Diastereoselective additions of *N*-sulfinyl metalloenamines to nitro olefins were also investigated (Table 3). Deprotonation of **1a** with LDA in THF, followed by addition to commercially available *trans*-*β*-nitrostyrene **5a**, provided compound **6a** in 88% yield with a diastereomeric ratio of 75:25 (entry 1). Imine hydrolysis with aqueous acetic acid provided the corresponding ketone in 80% yield, which by comparison with literature data[11] defined the major diastereomer as having the (*S*)-configuration. Previous work had shown that $ZnBr_2$ and $MgBr_2$ provide increased selectivity for the addition of **1a** to aldehydes;[1] however, neither the zinc nor magnesium metalloenamines enhanced the diastereoselectivity in this case (entries 2 and 3). Altering the solvent (entry 4) and the base (entry 5) resulted in a reversal in the sense of induction but did not improve the selectivity. The scope of the Michael addition was next examined by evaluating additions to the aliphatic nitroalkene **5b**.[12] Addition of **1a** to **5b** without any additive resulted in only trace amounts of the desired product **6b** (entry 6). The reaction was repeated with $ZnBr_2$ and $MgBr_2$ as additives to minimize competitive deprotonation of **5b** (entries 7 and 8). Although the additions proceeded with dramatically improved yields, only moderate selectivity was observed.

Asymmetric Synthesis of 2,4,6-Trisubstituted Piperidines. Conversion of the *N*-sulfinylimino ketones **3** to piperidines began with stereoselective reductions of **3** (Scheme 2). Similar to reductions of *β*-hydroxy-*N*-sulfinyl imines,[1] appropriate selection of the reducing agent allows access to either diastereomeric imine reduction product from a common intermediate. Treatment of compounds **3a** and **3e** with L-Selectride, followed by selective alcohol oxidation with Dess−Martin periodinane, gave the *syn*-*N*-sulfinylamino ketones **7a**,**b** in good to high yields over the two steps as 97:3 and 96:4 mixtures of diastereomers, respectively. Conversely, treatment of **3a** with $NaBH_4$ and $Ti(OEt)_4$,[13] followed by oxidation with Dess−Martin periodinane, gave the *anti*-*N*-sulfinylamino ketone **7c** in 95% yield over the two steps as a 87:13 mixture of diastereomers.

The *N*-sulfinylamino ketones **7a**−**c** were then readily converted to the 2,4,6-trisubstituted piperidines **4a**−**c** (Scheme 3). Treatment of **7a**−**c** with HCl resulted in cleavage of the sulfinyl group and cyclization to compounds **8a**−**c**. Subsequent reduction[14] with DIBAL-H provided the desired piperidines **4a**−**c** in moderate to good yields and with high selectivity. The absolute configuration of compound **4a** was determined by X-ray

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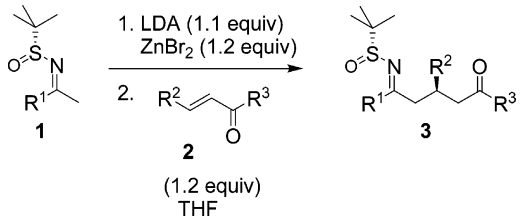
(13) Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709.
(14) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am.Chem. Soc.* **1983**, *105*, 2831.

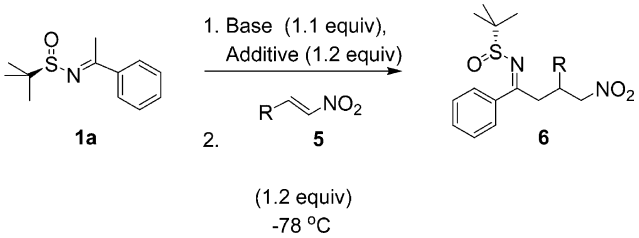
TABLE 2. Generality of Michael Addition to α,β-Unsaturated Ketones



entry	imine	R^1	ketone	R^2	R^3	*T* (°C)	time (h)	yield[a] (%)	dr[b]	product
1	**1a**	Ph	**2b**	Me	Ph	−78	1.0	82	>99:1	**3b**[c]
2	**1a**	Ph	**2c**	Ph	Me	−78 to −20	22	60	>99:1	**3c**
3	**1b**	*t*-Bu	**2b**	Me	Ph	−78	6.0	61	>99:1	**3d**
4	**1c**	*i*-Pr	**2b**	Me	Ph	−78	4.5	72	>99:1	**3e**
5	**1d**	Et	**2a**	Me	Me	−78	6.0	<50	n.d.	**3f**

[a] Isolated yield. [b] Determined by LCMS. [c] 85% yield, >99:1 dr obtained without use of $ZnBr_2$.

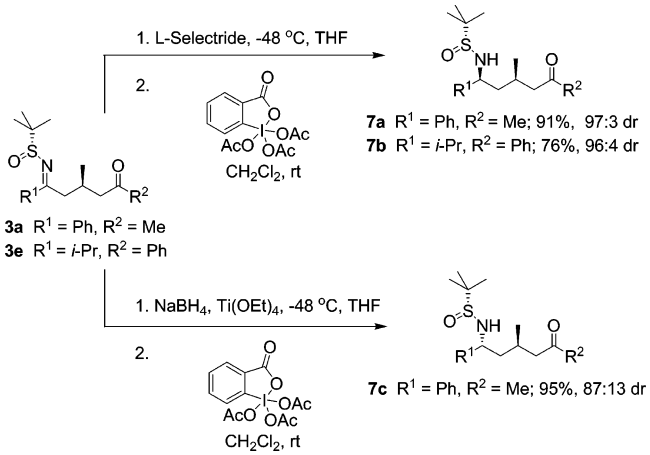
TABLE 3. Addition of 1a to Nitroalkenes 5



entry	solvent	nitroalkene	R	base	additive	dr[a]	yield[b] (%)	product
1	THF	**5a**	Ph	LDA	none	75:25	88	**6a**
2	THF	**5a**	Ph	LDA	$ZnBr_2$	75:25	n.d.	**6a**
3	THF	**5a**	Ph	LDA	$MgBr_2$	75:25	n.d.	**6a**
4	Et_2O	**5a**	Ph	LDA	none	42:58	n.d.	**6a**
5	THF	**5a**	Ph	NaHMDS	none	40:60	n.d.	**6a**
6	THF	**5b**	Me	LDA	none	n.d.	n.d.	**6b**
7	THF	**5b**	Me	LDA	$ZnBr_2$	76:24	70	**6b**
8	THF	**5b**	Me	LDA	$MgBr_2$	79:21	92	**6b**

[a] Determined by LCMS. [b] Isolated yield of analytically pure material.

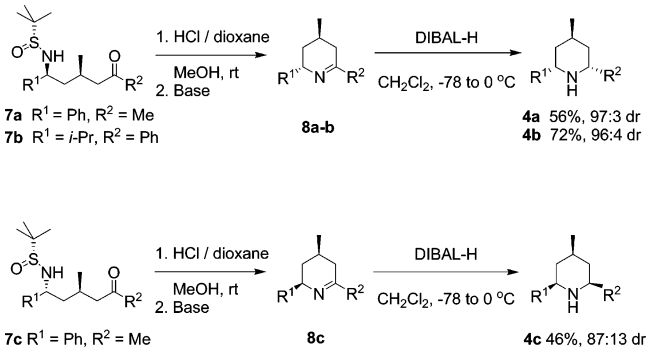
SCHEME 2. Stereoselective Reduction of *N*-Sulfinyl Imines



analysis of the corresponding Mosher amide, which also served to define the sense of induction in the Michael addition step. The relative stereochemistry for **4b** and **4c** was established by an observed NOE between the protons at the 2- and 6-positions of the piperidine rings.

The 1,4-addition methodology described here complements previously reported methods for the asymmetric

SCHEME 3. Conversion of *N*-Sulfinylamino Ketones to 2,4,6-Trisubstituted Piperidines



synthesis of piperidines in several respects. Importantly, this methodology installs an alkyl group in the 4-position of the piperidine ring, which is difficult to accomplish by other routes. Furthermore, because both the 2,6-*cis*-4-*trans*- and 2,4,6-*cis*-trisubstituted piperidine isomers can be accessed depending on the configuration of the sulfinamide and selection of the appropriate reductant, four of the eight possible piperidine diastereomers can potentially be synthesized with high selectivity.

Conclusion

The first examples of the conjugate addition of *N*-sulfinyl metalloenamines to Michael acceptors are reported. High yields are observed for additions to both nitroalkene and α,β-unsaturated ketone acceptors, with the additions to α,β-unsaturated ketones proceeding with very high diastereoselectivity (97:3 to 99:1 dr). This method is general for both alkyl- and aryl-substituted α,β-unsaturated ketones and metalloenamines derived from *N*-sulfinyl ketimines with either aryl or branched alkyl substituents. The ketone addition products could then be rapidly converted to 2,4,6-trisubstituted piperidines with good yields and high selectivities. Given the abundance of natural products and biologically active compounds that contain the piperidine moiety, this method should find wide application in the asymmetric syntheses of a range of substituted derivatives.

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Supporting Information Available: Full experimental details, spectral data, characterization for all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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