ORGANIC LETTERS
2005
Vol. 7, No. 24
5393−5396

Asymmetric Conjugate Addition of Copper Reagents to α,*β*-Unsaturated *tert*-Butanesulfinyl Imines

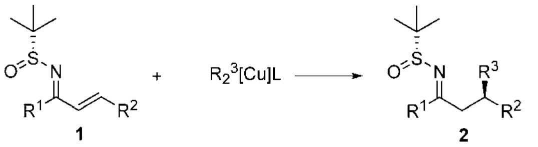
Jeffrey P. McMahon and Jonathan A. Ellman*

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

jellman@berkeley.edu

Received August 16, 2005 *(Revised Manuscript Received September 30, 2005)*

ABSTRACT



Yields up to 91%
dr's up to 96:4

Addition of organocuprates to *N*-sulfinyl α,*β*-unsaturated imines proceeds in good yields and with good diastereoselectivities. α,*β*-Unsaturated sulfinyl ketimines and aldimines have both been shown to be suitable substrates for this reaction.

N-*tert*-Butanesulfinyl imines are extremely versatile synthetic intermediates and are increasingly being used for the asymmetric synthesis of amines. *N*-*tert*-Butanesulfinyl imines are readily prepared by condensation of *tert*-butanesulfinamide with aldehydes or ketones. Subsequent diastereoselective addition of diverse nucleophiles followed by acidic removal of the sulfinyl group efficiently provides enantioenriched amine products.[1,2]

Recently we have embarked on an effort to access more complex amine products with multiple stereocenters by first performing diastereoselective transformations upon starting *N*-*tert*-butanesulfinyl imines to provide more complex imine intermediates that are subsequently converted to enantioenriched amine products. In initial efforts, we demonstrated that α-deprotonation of *N*-*tert*-butanesulfinyl imines generates metalloenamides that react with high diastereoselectivity with a number of electrophiles, including alkylating agents, aldehydes, and Michael acceptors.[3] Herein we report for the first time that *N*-*tert*-butanesulfinyl imines with *β*-stereocenters can be accessed by the diastereoselective conjugate addition of organocuprates to *N*-sulfinyl imines derived from α,*β*-unsaturated aldehydes and ketones.[4,5]

Preparation of α,*β*-unsaturated *N*-*tert*-butanesulfinyl imines **1** required slight modification of our reported protocol for the condensation of *tert*-butanesulfinamide with aldehydes and ketones, in which 2 equiv of $Ti(OEt)_4$ is used as a Lewis acid catalyst and water scavenger. Under these conditions, incomplete conversion to the imine product was observed.

---

[1] (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Weix, D.; Shi, Y. L.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092−1093. (c) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org Lett.* **2005**, *7*, 1403−1406. (d) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. *Org. Lett.* **2005**, *7*, 2599−2602. (e) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645−1647. (f) Zhong, Y.; Xu, M.; Lin, G. *Org. Lett.* **2004**, *6*, 3953−3956. (g) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org Lett.* **2005**, *7*, 1403−1406. (h) Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641−6643. (i) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303−310. (j) Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478−3488.

[2] For a recent review on the applications of arenesulfinyl imines, see: Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003−8030.

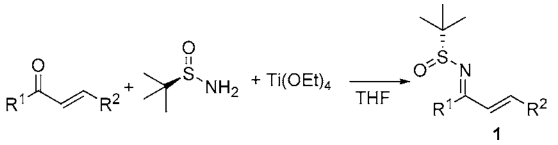
[3] (a) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276−11282. (b) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652−15653. (c) Schenkel, L.; Ellman, J. A. *Org. Lett.* **2004**, *20*, 3621−3624. (d) Pelltier, H. M.; Ellman, J. A. *J. Org. Chem.*, ASAP.

[4] For leading references and extensive literature on stereoselective additions of organocuprates to α,*β*-unsaturated ketones and esters, see: Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660−5667. (b) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363. (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (d) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. (e) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (f) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186−204.

10.1021/ol051986q CCC: $30.25

However, good conversion could be obtained by increasing the amount of $Ti(OEt)_4$ in the reaction from 2 to 4 equiv. Using this modified stoichiometry, both α,*β*-unsaturated ketimines and aldimines **1** could be prepared in yields ranging from 74% to 86% for a range of aromatic and aliphatic substitution patterns (See Table 1).

Table 1. Condensation of *tert*-Butanesulfinamide with α,*β*-Unsaturated Aldehydes and Ketones

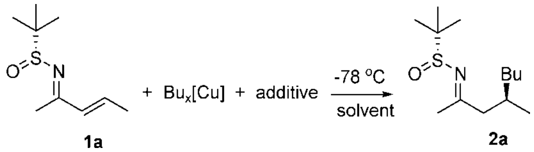


product	R¹	R²	temp	% yield
1a	Me	Me	reflux	74
1b	Ph	Me	reflux	74
1c	Me	Ph	reflux	81
1d	Ph	Ph	reflux	77
1e	-$(CH_2)_3$-		reflux	86
1f	H	Me	rt	82

Sulfinyl ketimine **1a** derived from 3-penten-2-one was first selected to optimize conditions for the conjugate addition reactions. The addition of the butyl Gilman cuprate was first evaluated and provided addition product **2a** in 71% yield, but with a low 2:1 diastereomeric ratio (entry 1, Table 2). Despite the low selectivity, this result provided an appropriate starting point for optimization efforts.

Optimization focused on copper sources, solvent, and additives to increase the diastereomeric ratio of the reaction while maintaining good yields. Diastereomer ratios were consistently higher with THF rather than Et_2O as the solvent. (Table 2). When no additives were used, CuBr was the copper source that provided the highest selectivity (entry 3). Additives that have previously been reported to improve cuprate conjugate additions were tested next. TMSCl decreased the selectivity of the reaction with each of the copper sources (entries 6−8). In contrast, the best results were seen when $BF_3{\cdot}OEt_2$ was used in combination with 2 equiv of the lithium reagent. Using CuBr as the copper source under these conditions, a 61% yield and 92:8 diastereomer ratio were obtained (entry 14). A slightly higher 68% yield and 93:7 diastereomer ratio were observed when CuCN was used as the copper source (entry 17).

Table 2. Optimization of Ketimine Additions



entry	Cu salt	equiv of BuLi	additive	solvent	% yield[a]	dr[b]
1	CuI	2	none	Et_2O	71[c]	2:1
2	CuI	2	none	THF	23	86:14
3	CuBr	2	none	THF	40	89:11
4	CuCN	2	none	THF	66	71:29
5	$CuBr{\cdot}SMe_2$	2	none	THF	68	85:15
6	CuBr	2	TMSCl	THF	41	74:26
7	CuCN	2	TMSCl	THF	33	73:27
8	$CuBr{\cdot}SMe_2$	2	TMSCl	THF	48	78:22
9	CuBr	1	$BF_3{\cdot}OEt_2$	Et_2O	51	89:11
10	CuBr	1	$BF_3{\cdot}OEt_2$	THF	17	91:9
11	CuCN	1	$BF_3{\cdot}OEt_2$	Et_2O	99	2:1
12	CuCN	1	$BF_3{\cdot}OEt_2$	THF	65	89:11
13	CuBr	2	$BF_3{\cdot}OEt_2$	Et_2O	33	3:2
14	CuBr	2	$BF_3{\cdot}OEt_2$	THF	61[c]	92:8
15	CuCN	2	$BF_3{\cdot}OEt_2$	Et_2O	33	2:1
16	$CuBr{\cdot}SMe_2$	2	$BF_3{\cdot}OEt_2$	THF	58	91:9
17	CuCN	2	$BF_3{\cdot}OEt_2$	THF	68[c]	93:7

[a] Determined by NMR analysis of the crude mixture containing 2,6-dimethoxytoluene as a standard. [b] Determined by HPLC analysis. [c] Determined by a mass balance of the purified product.

The α,*β*-unsaturated ketimine starting material **1a** existed as a 2:1 mixture of *E*/*Z* isomers as determined by NMR spectroscopy. It is notable that the diastereoselectivity of the conjugate addition greatly exceeds this modest *E*/*Z* isomer ratio, suggesting that one of the imine isomers preferentially reacts with the cuprate concomitant with rapid imine isomer equilibration. Enhanced diastereoselectivities over substrate *E*/*Z* isomer ratios have previously been observed for nucleophilic additions to *N*-sulfinyl ketimines.[6]

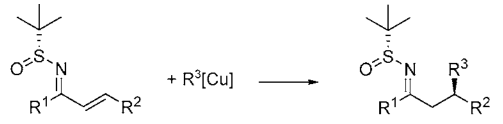
The scope of the conjugate addition reaction was next evaluated using the CuCN conditions for optimal yield and diastereoselectivity. Addition of the butyl cuprate to sulfinyl ketimine **1b** also proceeds in good yield and diastereoselectivity (entry 2, Table 3). Additions of methyl cuprates, which are documented to be the least reactive of the alkyl cuprates, were next investigated. Unfortunately, the optimal conditions for the conjugate addition of butyl cuprate were not effective for the less reactive methyl cuprate. Not only were the desired addition products obtained in modest yield, but sulfenyl ketimines were produced as major byproducts. Cuprates are documented to be more reactive in Et_2O than in THF. Indeed, successful additions of Me_2CuLi in Et_2O were observed with complete elimination of sulfenyl ketimine byproducts (entries 3−5). Good yields and diastereoselectivities were observed with a phenyl substituent present at R^2 (entry 3) and at both R^1 and R^2 (entry 4), and in initial studies, addition of the methyl cuprate to a cyclic imine also proceeded in good yield with promising selectivity (entry 5).

---

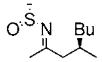
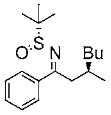
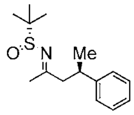
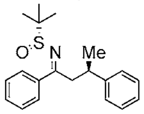
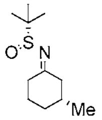
(5) Relatively few examples of asymmetric additions to α,*β*-unsaturated aldimines and ketimines have been reported. None of these methods have been utilized for the asymmetric synthesis of amines. For leading references, see: (a) Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 7451−7454. (b) Soeta, T.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 297−300. (c) Bonini, B. F.; Fochi, M.; Franchini, M. C.; Mazzanti, G.; Ricci, A.; Picard, J. P.; Dunogues, J.; Aizpurua, J. M.; Palomo, C. *Synlett* **1997**, 1321−1323. (d) Enders, D.; Heider, K. J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 598−601.

(6) (a) Cogan, D.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268−269. (b) Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709−6712.

Table 3. Substrate Scope

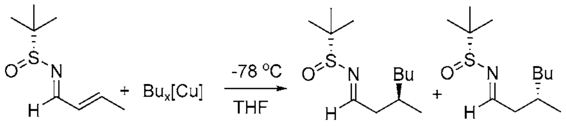


1 **2**

entry	product	method[a]	yield[b]	dr[d]
1	 **2a**	A	68%	93:7
2	 **2b**	A	76%	92:8
3	 **2c**	B	70%	85:15
4	 **2d**	B	91%[c]	96:4
5	 **2e**	B	55%	87:13

[a] Method A: 0.5 M solution of α,β-unsaturated imine in THF was added to a −78 °C 0.5 M solution of $Bu_2CuCN{\cdot}BF_3{\cdot}OEt_2$ in THF via cannula. Method B: A 0.5 M solution of α,β-unsaturated imine in Et_2O was added to a −78 °C 0.5 M solution of Me_2CuLi in Et_2O via cannula. [b] Isolated yield of purified mixture of diastereomers. [c] Isolated yield of purified major diastereomer. [d] Determined by HPLC analysis.

Table 4. Optimization of Aldimine Additions



1f additive **2f** (3*R*) **2f** (3*S*)

entry	Cu salt	equiv of BuLi	additive	% yield[a]	dr[b] (3*R*:3*S*)
1[c]	CuI	2	none	52[d]	1:1
2	CuI	2	$BF_3{\cdot}OEt_2$	78	75:25
3	CuI	1	$BF_3{\cdot}OEt_2$	15	70:30
4	CuCN	2	$BF_3{\cdot}OEt_2$	71	79:21
5	CuCN	1	$BF_3{\cdot}OEt_2$	62	80:20
6	CuBr	2	$BF_3{\cdot}OEt_2$	92	76:24
7	CuBr	1	$BF_3{\cdot}OEt_2$	48	79:21
8	$CuBr{\cdot}SMe_2$	2	$BF_3{\cdot}OEt_2$	64	77:23
9	$CuBr{\cdot}SMe_2$	1	$BF_3{\cdot}OEt_2$	4	62:38
10	CuCN	1	PBu_3	73[d]	85:15
11	CuCN	2	PBu_3	65	72:28
12	CuCN	1	PCy_3	48[d]	2:1
13	CuCN	1	PPh_3	52[d]	76:24
14	CuI	1	PBu_3	59	76:24
15	$CuBr{\cdot}SMe_2$	1	PBu_3	15	77:23
16	$(CuOTf)_2{\cdot}$benzene	1	PBu_3	nr	
17	CuOAc	1	PBu_3	55	15:85
18[e]	CuCN	1	PBu_3	57[d]	∼2:1
19[f]	CuCN	1	PBu_3	48[d]	∼2:1

[a] Determined by NMR analysis of the crude mixture containing 2,6-dimethoxytoluene as a standard. [b] Determined by HPLC analysis. [c] Reaction was run in Et_2O. [d] Determined by a mass balance of the purified product. [e] Corresponding *p*-toluenesulfinyl imine was used as starting material. [f] Corresponding 2,4,6-triisopropylbenzenesulfinyl imine was used as starting material.

The absolute configuration at the β-stereocenter was determined for the conjugate addition products in entries 1, 3, and 4 by hydrolysis to the corresponding ketones followed by correlation with the literature optical rotations for these compounds.[7] The configuration of the conjugate addition product in entry 5 was determined by comparison with the imines prepared by condensation of (*R*)-*tert*-butanesulfinamide with the commercially available (*R*)- and (*S*)-3-methyl cyclohexanones.[1e]

Conjugate additions to *tert*-butanesulfinyl aldimine **1f** were also investigated (Table 4). Initial experiments, however, gave low diastereoselectivities. Addition of Bu_2CuLi to aldimine **1f** proceeded in 52% yield and was not selective (entry 1). Using the conditions optimized for butyl cuprate addition to ketimine **1a** gave a better diastereomer ratio, but the selectivity was still low (entry 4). Reduction in the stoichiometry of BuLi to CuCN (entry 5) or use of alternative copper sources with $BF_3{\cdot}Et_2O$ as an additive did not result in any improvement in reaction diastereoselectivity (entries 6−9). Different copper(I) sources and phosphine additives, which have previously been reported to enhance diastereoselectivities, were next evaluated. Indeed, when CuCN was used as the copper source with tributylphosphine as the additive, the product was obtained in a moderate 85:15 dr and 73% yield (entry 10). Modification of the structure of the phosphine additive resulted in a slight drop in the diastereoselectivity (entries 12 and 13). Different copper sources had a pronounced effect on the diastereoselectivity observed when PBu_3 was used as an additive (entries 14−17). Most exciting was CuOAc, which gave an 85:15 dr favoring the opposite diastereomer while maintaining an acceptable 55% yield (entry 17). This allows for access of either diastereomer of the addition product using the same sulfinyl stereocenter. Conjugate additions to the α,β-unsaturated sulfinyl imines prepared from *p*-toluenesulfinamide (entry 18) and 2,4,6-triisopropylbenzenesulfinamide (entry 19) were also carried out using the optimized conditions (CuCN as the copper source and PBu_3 as an additive). However, additions to these sulfinyl imine derivatives proceeded with poor diastereoselectivities.

The facial selectivity for conjugate additions to *N*-sulfinyl α,β-unsaturated ketimines and aldimines can be rationalized by the model shown in Figure 1. The cuprate coordinates to the sulfinyl oxygen on the opposite face from the *tert*-butyl group. Coordination both activates the molecule to conjugate

---

(7) (a) For entry 1, see: Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223−11236. (b) For entries 3 and 4, see: Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97−99.

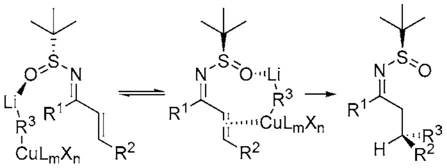


Figure 1. Model for diastereofacial selectivity.

addition and aligns the cuprate for the addition reaction.[8] Presumably, delivery of the organocuprate to the β-position is only possible through one of the imine isomers, which can be accessed through facile equilibration of the imine isomers. Sufficient information is not available to rationalize the reversal in selectivity observed for conjugate addition to aldimine **1f** under the Cu(OAc) reaction conditions (Table 4, entry 17).

In summary, we have shown that organocuprates can be added with high diastereoselectivity to α,β-unsaturated *tert*-butanesulfinyl ketimines with aliphatic and aromatic substitution patterns. Conditions were also identified for the addition of butyl cuprate to α,β-unsaturated *tert*-butanesulfinyl aldimine **2f** to provide either diastereomeric addition product with 85:15 diastereomer ratios depending on the copper source. These first examples of conjugate additions to unsaturated *N*-*tert*-butanesulfinyl imines provide β-substituted imines that should serve as useful intermediates in the asymmetric synthesis of a variety of γ-substituted amine products.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0446173). The Center for New Directions in Organic Synthesis is supported by Bristol-Myers-Squibb as a sponsoring member and Novartis as a supporting member. We would also like to thank Shaheen Shamsavari for helpful contributions.

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

OL051986Q

---

[8] Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393−401.