Asymmetric Synthesis of α,α-Dibranched Amines by the Trimethylaluminum-Mediated 1,2-Addition of Organolithiums to *tert*-Butanesulfinyl Ketimines

Derek A. Cogan and Jonathan A. Ellman*

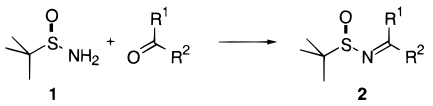
Department of Chemistry
University of California
Berkeley, California 94720

Received September 9, 1998

Asymmetric induction in the synthesis of chiral quaternary centers has been a formidable challenge in synthetic chemistry. In fact, only recently have practical and elegant routes to certain classes of quaternary centers been developed.[1] However, despite the prevalence of the amine functionality in natural products, synthetic pharmaceuticals, catalysts, and materials, no direct method has yet been reported for the asymmetric synthesis of the large class of nitrogen-substituted quaternary centers, the α,α-dibranched amines. To this end, the 1,2-addition of nucleophiles to ketimines has great potential as a general and direct approach.[2,3] Unfortunately, competitive α-deprotonation has prohibited the general use of aryl or alkyl carbanions.[2,4] Thus, the asymmetric synthesis of α,α-dibranched amines has been limited to allylation of ketimines[2] and additions to α-pyridyl-substituted ketimines.[5] Herein, we report the first direct method for the asymmetric synthesis of a broad range of α,α-dibranched amines by the unprecedented 1,2-addition of organolithium reagents to ketimines. Specifically, we report the highly diastereoselective 1,2-addition of organolithium reagents to *N*-*tert*-butanesulfinyl ketimines, which are prepared in high yield in one step from the corresponding ketones.

Although a variety of amines have been prepared by the diastereoselective addition of nucleophiles to *N*-sulfinyl aldimines,[6] far fewer transformations of *N*-sulfinyl ketimines have been reported.[7] This is likely due to the unavailability of most *N*-sulfinyl ketimine derivatives, which have traditionally been synthesized by the reaction of chiral sulfinate esters with imine anions prepared in situ by the 1,2-addition of organometallics to nitriles.[3,8] This approach is limited by the small number of readily available, nonenolizable nitriles.

We recently reported the practical two-step preparation of enantiomerically pure *tert*-butanesulfinamide (**1**) in 71−75% overall yield from *tert*-butyl disulfide. We also described the Mg(SO_4)-mediated condensation of **1** with aldehydes (eq 1 in Table 1; R^1 = H).[9] To prepare α,α-dibranched amines, the analogous condensation of **1** with ketones to provide *N*-sulfinyl ketimines would clearly be desirable. Unfortunately, attempted condensation of acetophenone and methyl isopropyl ketone with **1** employing Mg(SO_4) was not successful. By exploring a number of different dehydrating agents and catalysts, Cu(SO_4) was found to be a more effective agent for the direct condensation of aldehydes with **1**,[10] but still did not effect the ketone condensations. Titanium(IV) salts have been successfully employed in the condensations of ketones with amines[11] and ureas.[12] Therefore, a number of inexpensive Ti(IV) reagents, including Ti(O-*i*-Pr)$_4$, Ti(OEt)$_4$, and various $TiCl_n(O\text{-}i\text{-}Pr)_{4-n}$ derivatives were investigated, with Ti(OEt)$_4$ most efficiently providing *N*-sulfinyl ketimines **2a** and **2b** (84% and 87% yield) upon heating in THF (eq 1). Significantly, only the *E* isomer was detected by ^{1}H and ^{13}C NMR in $CDCl_3$.



1 **2** (1)

Table 1. Condensations of Ketones with Sulfinamide **1**

ketimine **2**	R^1	R^2	yield (%)	(*E*:*Z*)[b]
2a	Me	*i*-Pr	84	one isomer
2b	Me	Ph	87	one isomer
2c	Bu	*i*-Pr	66	one isomer
2d	Bu	Ph	77	one isomer
2e	Me	*i*-Bu	88	6:1
2f	Me	Bu	77	5:1

[a] Reactions were run with 2.0 equiv of Ti(OEt)$_4$ in THF at 60−75 °C. [b] Ratios were determined by ^{1}H NMR recorded in $CDCl_3$.

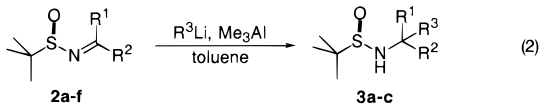
A number of ketones with varying steric and electronic demand about the carbonyl were submitted to these same conditions to investigate generality (Table 1). Although ketones with more substantial steric demand required longer reaction times and slightly higher temperatures, all ketones submitted to these conditions condensed in good yields. The ratio of *E:Z* isomers, as determined by ^{1}H NMR in $CDCl_3$, were excellent when R^1 and R^2 were dissimilarly branched (**2a**−**d**). Considering the modest steric difference between methyl and butyl substituents, the *E:Z* ratio of 5 observed for sulfinyl ketimine **2f** is remarkable. Sulfinyl ketimine **2e**, with β-substitution as the remote source of steric demand, favored the *E* isomer to an even greater degree.

The 1,2-addition of organometallic reagents to *N*-sulfinyl ketimines **2** was next explored for the preparation of α,α-dibranched amines. First, *N*-sulfinyl ketimine **2a** was added to phenylmagnesium bromide under the conditions that we had previously developed for 1,2-additions to *N*-sulfinyl aldimines (−48 °C in CH_2Cl_2).[9a] A 2:3 mixture of (R_S,*R*)-**3a** and (R_S,*S*)-**3a** was obtained in 21% yield, with the difference in mass isolated as unreacted **2a**, likely resulting from competitive deprotonation. The 1,2-addition of phenyllithium to **2a** in toluene was considerably more promising, affording **3a** in 65% yield with a 94:6 ratio of (R_S,*R*)-**3a** to (R_S,*S*)-**3a** (Table 2; entry 1). Interestingly, this highly stereoselective reaction favored the diastereomer opposite that observed for the Grignard addition. The 1,2-addition of butyllithium to **2b** was considerably less satisfying, affording (R_S,*S*)-**3b** in only 26% yield, albeit with an excellent diastereo-

(1) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388−401. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.
(2) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946.
(3) Allylmetal additions are a special case because they presumably proceed through a concerted mechanism. Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4−6.
(4) For the synthesis of racemic or achiral α,α-disubstituted amines see: (a) Barbot, F.; Miginiac, L. *Synth. Commun.* **1997**, *27*, 2601−2614. (b) Calderwood, D. J.; Davies, R. V.; Rafferty, P.; Twigger, H. L.; Whelan, H. M. *Tetrahedron Lett.* **1997**, *38*, 1241−1244. (c) Ciganek, E. *J. Org. Chem.* **1992**, *57*, 4521−4527. (d) Charette, A. B.; Gagnon, A.; Janes, M.; Mellon, C. *Tetrahedron Lett.* **1998**, *39*, 5147−5150.
(5) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537−5541.
(6) (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. (b) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Reddy, G. V.; Zhou, P. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1997**, *120, 121*, 291−303.
(7) (a) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387−6389. (b) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349−352. (c) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 341−343.
(8) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 341−343.
(9) (a) Liu, G.; Cogan, D.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914. (b) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011−8019.
(10) Guangcheng Liu, unpublished results.
(11) Selva, M.; Tundo, P.; Marques, C. A. *Synth. Commun.* **1995**, *23*, 369−378 and references therein.
(12) Armstrong, I. J. D.; Wolfe, C. N.; Keller, J. L.; Lynch, J.; Bhupathy, L. M.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 1531−1532.

10.1021/ja983217q CCC: $18.00
Published on Web 12/19/1998

Table 2. 1,2-Additions of Organolithiums to *N*-Sulfinyl Ketimines **2**



(2)

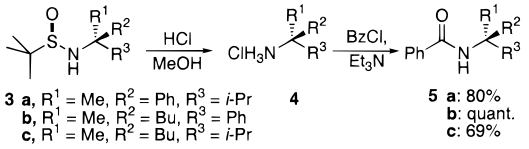
				product		
entry	**2**	R^3	Me_3Al (equiv)	(config)[a] **-3**	yield (%)	dr
1	**2a**	Ph	0	(*R*)-**3a**	65	94:6[b]
2	**2a**	Ph	1.1	(*R*)-**3a**	93	97:3[b]
3	**2b**	Bu	0	(*S*)-**3b**	26	99:1[c]
4	**2b**	Bu	1.1	(*S*)-**3b**	86	98:2[c]
5	**2f**	Ph	0	(*R*)-**3b**	67	63:37[c]
6	**2f**	Ph	1.1	(*R*)-**3b**	93	89:11[c]
7	**2d**	Me	1.1	(*R*)-**3b**	quant	99:1[c]
8	**2a**	Bu	1.1	(*S*)-**3c**[e]	61	99:1[d]
9	**2c**	Me	0	(*R*)-**3c**[e]	54	82:18[d]
10	**2c**	Me	1.1	(*R*)-**3c**[e]	82	91:9[d]

[a] Refers to the configuration at the new stereocenter. [b] Diastereoselection determined by HPLC analysis of **3a**. [c] Diastereoselection determined by chiral HPLC analysis of benzamide derivative formed after sulfinyl cleavage. [d] Diastereoselection determined by HPLC analysis of (*R*)-MTPA derivatives formed after sulfinyl cleavage. [e] Absolute configuration tentatively assigned on the basis of consistent diastereofacial selectivity for entries 1−8.

meric ratio (dr) (Table 2, entry 3). Again, the balance of the mass was isolated as unconsumed *N*-sulfinyl ketimine **2b**.

To enhance the product yield, the effect of Lewis acids, including Al(O-*i*-Pr)$_3$, trialkylaluminums, BF_3-Et_2O, and Et_2Zn, was investigated. Trialkylaluminums, such as Me_3Al and *i*-Bu_3-Al, had the most dramatic effect on the 1,2-additions. Thus, the slow addition of a toluene solution of Me_3Al and *N*-sulfinyl ketimines **2** to organolithiums consistently afforded 1,2-addition products in higher yields, and typically with higher drs than the same 1,2-additions performed in the absence of Me_3Al (Table 2). One of the most striking results was the diastereocontrol achieved for the Me_3Al-mediated 1,2-addition of butyllithium to ketimine **2f** (R^1 = Me, R^2 = Bu). Despite the similar steric size of the methyl and butyl substituents, the product was isolated in a 9:1 ratio of (R_S,*S*)-**3b** to (R_S,*R*)-**3b**, which exceeds the substrates initial *E:Z* ratio of 5.

Brief treatment of sulfinamides **3** with methanolic HCl provided the amine hydrochlorides **4**, which were isolated as the corresponding benzamides **5** in high overall yields (eq 3). Although



(3)

stereochemical assignments of the amines **4** were complicated by the inaccessibility of these amines by other sources, assignments for **4a** and **4b** could be accomplished by chemical correlation.[13] Additions to *N*-sulfinyl ketimines **2a,b,d,f** occur consistently to the same face (entries 1−7; vide infra). This provides for a reliable method for predicting the stereochemical outcome of these 1,2-additions, and allows for the tentative assignment of sulfinamide **3c**, for which straightforward chemical correlation was not possible.

The source of diastereocontrol is not yet rigorously understood, but the product stereochemistry can be predicted by a sulfinyl-directed alkyl transfer model via a cyclic six-membered transition

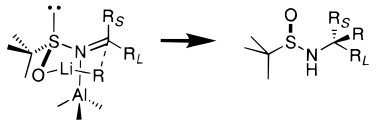


Figure 1. Model consistent with observed stereoselection for the Me_3-Al-mediated 1,2-addition of RLi to **2**.

state with the bulky *tert*-butyl group preferring the equatorial position (Figure 1). This model is supported by two pieces of experimental data. First, the treatment of sulfinyl ketimine **2a** with a mixture of Me_3Al and PhLi in toluene did not afford any 1,2-addition product, even at room temperature after 12 h. This indicates that the imine addition does not proceed via an alkyl transfer from an aluminate intermediate, but likely occurs from the organolithium species to a **2a**−Me_3Al complex. Second, the use of coordinating ethereal solvents resulted in dramatic reductions in yields and drs, consistent with both Lewis acid activation of the imine as well as organolithium coordination.

The surprising selectivity for the 1,2-addition of PhLi to sulfinyl ketimine **2f** provides further insights into the mechanism. The barriers for *E:Z* isomerization for arenesulfinyl imines have been determined to be between 13 and 17 kcal/mol.[14] Thus, due to rapid isomerization, Me_3Al-**2f** complexes may prefer one isomeric conformation to an extent more in line with the observed diastereoselection (9:1) than the parent sulfinyl ketimine (5:1). However, ^1H NMR experiments performed in toluene-d^8 indicate that the *E:Z* ratio is unaffected by the presence of Me_3Al at both +23 and −78 °C. The only observable change in the spectra upon addition of Me_3Al is a slight broadening of the α-protons of **2f**. The selectivity most likely arises from a difference in reaction rates between the two Me_3Al-**2** isomers that are in rapid equilibrium under the reaction conditions.

In summary, the first general method for the asymmetric synthesis of chiral acyclic α,α-dibranched amines is reported. The 1,2-addition substrates, *tert*-butanesulfinyl ketimines **2**, are prepared by the first direct condensation of a sulfinamide with ketones, providing straightforward access to a wide variety of sulfinyl ketimines. In the presence of Me_3Al, *tert*-butanesulfinyl ketimines react with organolithiums to provide *tert*-butanesulfinamides, **3**, in high yields and with drs >9:1, and as high as 99:1. Moreover, by the addition of Me_3Al, the diastereoselection can exceed the *E:Z* ratio of the sulfinyl ketimine substrate. Removal of the sulfinyl group is achieved with stoichiometric HCl at room temperature in less than 5 min, to afford the desired α,α-dibranched amines. As will be reported in due course, *tert*-butanesulfinyl ketimines are useful synthetic intermediates not only for the addition of organolithiums to provide α,α-dibranched amines, but also for the synthesis of other hindered amines by the 1,2-addition of other nucleophiles.

Acknowledgment. We thank Guangcheng Liu for important contributions. The support of the NSF, Abbott Laboratories, and Berlex Biosciences is gratefully acknowledged. D.A.C. thanks Pharmacia & Upjohn for a graduate fellowship.

Supporting Information Available: Experimental details for all procedures, as well as stereochemical assignments (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA983217Q

(13) As described in the Supporting Information, **3a** is converted to the benzamide, and **3b** is converted to the methyl ester of *N*-benzoyl α-methylvaline.

(14) (a) Davis, F. A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5000−5001. (b) Davis, F. A.; Kluger, E. W. *J. Am. Chem. Soc.* **1976**, *98*, 302−303.