ORGANIC LETTERS

2001
Vol. 3, No. 18
2847−2850

Asymmetric Synthesis of Trifluoromethylated Allylic Amines Using α,β-Unsaturated *N-tert*-Butanesulfinimines

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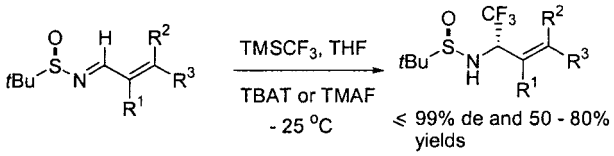
Received June 15, 2001

ABSTRACT



The trifluoromethide ion generated in situ from $TMSCF_3$ and TBAT (tetrabutylammonium triphenyldifluorosilicate), as well as TMAF (tetramethylammonium fluoride), adds to the α,β-unsaturated *N-tert*-butanesulfinimines exclusively in a 1,2 fashion with high diastereoselectivities, affording the first examples of chiral trifluoromethylated allylic amines.

Allylic amines, because of their multiple functionalities, are the focus of numerous studies. A range of useful products, such as α- and β-amino acids,[1,2] various alkaloids,[3] and carbohydrate derivatives[4] could be obtained by their double bond functionalizations. Therefore, there have been many methods available for their asymmetric preparation.[5] Despite the fact that introduction of fluorine brings profound changes in bioactive molecules,[6] no method for the asymmetric preparation of trifluoromethylated allylic amines is reported. Although addition of vinylmetallic reagents to trifluoromethylated imines is a viable approach,[7] the scope of this reaction would be limited to the availability of the vinylmetallic derivatives. Other approaches involve multiple steps involving low yields.[8] Herein, we report a straightforward method for the preparation of trifluoromethylated allylic amines using trifluoromethyl-trimethylsilane ($TMSCF_3$) as the trifluoromethide ion source.

(1) Allylic amines to amino acids: (a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc*. **1989**, *111*, 6301. (b) Jumnah, R.; Williams, J. M. J.; Williams, A. C. *Tetrahedron Lett*. **1993**, *34*, 6619. (c) Bower, J. F.; Jumnah, R.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411.

(2) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem*. **1993**, *58*, 4758.

(3) Alkaloids: (a) Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087. (b) Trost, B. M. *Angew. Chem*. **1989**, *101*, 1199.

(4) Carbohydrate derivatives: Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc*. **1993**, *115*, 444.

(5) For a recent review, see: Johannsen, M.; Jørgensen, K. A. *Chem. Rev*. **1998**, *98*, 1689. For a recent example of an enantioselective approach to allylic amines, see: Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc*. **1999**, *121*, 6761.

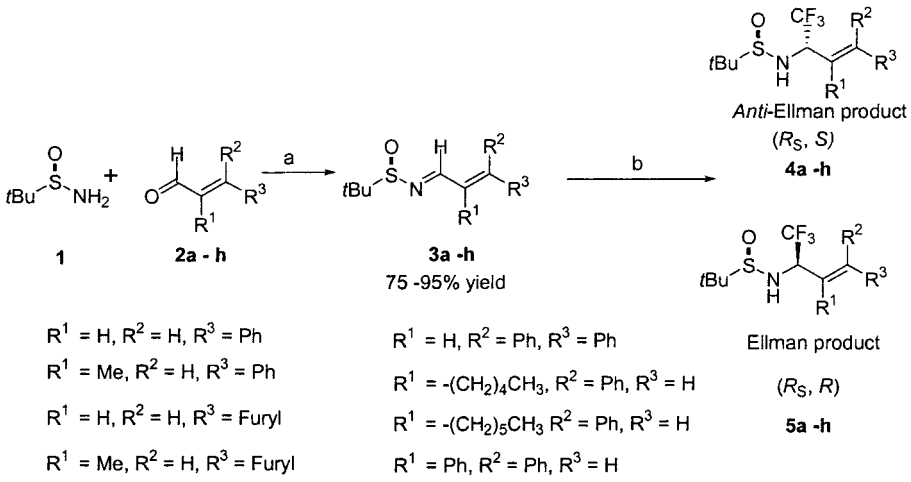
(6) Importance of fluorine in medicinal chemistry: (a) McCarthy, J. *Utility of Fluorine In Biologically Active Molecules*; Division of Fluorine Chemistry Tutorial, 219th National Meeting of the American Chemical Society, San Francisco, March 26, 2000. (b) Filler, R.; Kobayashi, Y.; Yagulpolskii, Y. L. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993. (c) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (d) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*. A Critical Review; ACS Monograph 187; American Chemical Society: Washington, DC, 1995. (e) Welch, J. T., Ed. *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991.

(7) There is no report on the addition of vinylmetallic derivatives to the trifluoromethylated imines. For the addition of allylmetal to trifluoromethylated ketimines: see, Felix, C.; Laurent, A.; Lesniak, S.; Mison, P. *J. Chem. Res., Synop*. **1991**, 32.

(8) (a) Xu, Y.; Dolbier, W. R., Jr. *J. Org. Chem*. **2000**, *65*, 2134. (b) Kumadaki, I.; Jonoshita, S.; Harada, A.; Omote, M.; Ando, A. *J. Fluorine Chem*. **1999**, *97*, 61.

10.1021/ol010134x CCC: $20.00
Published on Web 08/09/2001

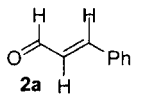
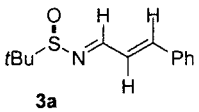
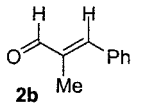
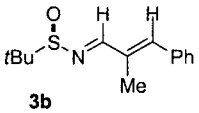
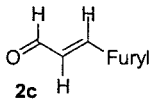
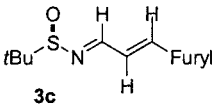
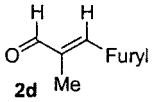
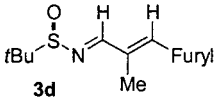
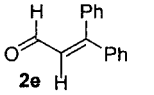
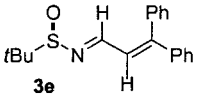
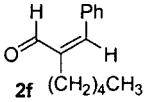
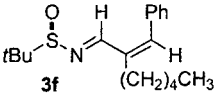
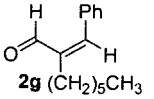
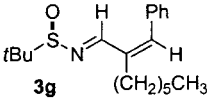
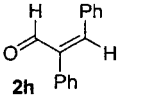
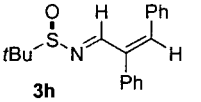
Scheme 1[a]



[a] Reagents and conditions: (a) $Ti(OEt)_4$, THF, 2−6 h, rt; (b) $TMSCF_3$, THF, TBAT or TMAF, −25 °C.

Following our recent success with stereocontrolled trifluoromethide transfer to the *N*-*tert*-butanesulfinimines[9] we envisioned that under the similar reaction conditions α,β-unsaturated imines would undergo similar trifluoromethylation. To test the feasibility of this process we have developed a method for the preparation of chiral α,β-unsaturated imines from corresponding α,β-unsaturated aldehydes (with known stereochemistry) and (*R*)-*N*-*tert*-butanesulfinamide in the presence of 3 equiv of $Ti(OEt)_4$.[10] This condensation strategy is very general. The reaction is tolerant to all kind of substitutions at α- and β-positions and provides the *tert*-butanesulfimines in good to excellent yields (Table 1).

Table 1. Condensation of α,β-Unsaturated Aldehydes with (*R*)-*N*-*tert*-Butanesulfinamide

aldehydes	sulfinimines	yields (%)
 **2a**	 **3a**	90
 **2b**	 **3b**	87
 **2c**	 **3c**	85
 **2d**	 **3d**	83
 **2e**	 **3e**	80
 **2f**	 **3f**	75
 **2g**	 **3g**	70
 **2h**	 **3h**	86

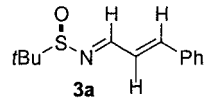
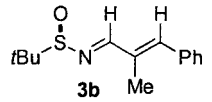
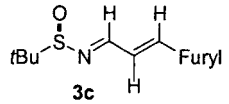
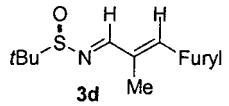
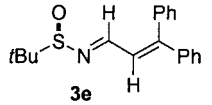
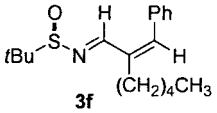
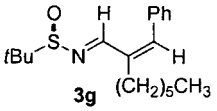
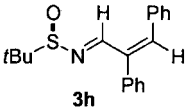
Because α,β-unsaturated imines are less reactive toward nucleophilic addition reactions compared to nonconjugated imines, we initially carried out a temperature/yield/diastereoselectivity study with the representative imine **3a**. The optimum yield/diastereoselectivity were observed at −25 °C to afford the corresponding adduct in 90:10 (R_S,*S*:R_S,*R*)

(9) (a) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77. (b) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589. For our other nucleophilic trifluoromethylation reactions, see: (c) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc*. **1989**, *111*, 393. (d) Krishnamurti, R.; Bellew, A. D. R.; Prakash, G. K. S. *J. Org. Chem*. **1991**, *56*, 984. (e) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev*. **1997**, *97*, 757. (f) Prakash, G. K. S.; Ramaiah, R. *Synlett* **1991**, 643. (g) Wiedemann, J.; Heiner, T.; Mloston, G.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed*. **1998**, *37*, 820.

(10) Addition of organometallic reagents to *tert*-butanesulfinimines is known in the literature. (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc*. **1997**, *119*, 9913. (b) Tang, T. P. Ellman, J. A. *J. Org. Chem*. **1999**, *64*, 12. However, no report exists on the preparation and reactions of the α,β-unsaturated *N*-*tert*-butanesulfinimes. We have found that $Ti(OEt)_4$ is most effective among other Lewis-acidic dehydrating agents. **General procedure** for the preparation of the α,β-unsaturated *N*-*tert*-butanesulfinimes is as follows: Into a 25-mL round-bottomed flame-dried flask fitted with a magnetic stirring bar, a rubber septum, and an argon-filled balloon were placed 1 mmol of α,β-unsaturated aledyde and 1 mmol of (*R*)-*N*-*tert*-butanesulfinamide in 5 mL of THF. The reaction flask was cooled to 0 °C, and 3 equiv of $Ti(OEt)_4$ was added slowly via a syringe. After 0.5 h of stirring at 0 °C, the reaction mixture was warmed to room temperature and stirred until TLC indicated the reaction was complete (4−6 h). At this time, the reaction mixture was added to an ice-cooled solution of brine (5 mL). The resulting suspension was filtered through a plug of Celite. The Celite was washed three times with ethyl acetate. The resulting biphasic mixture was transferred to a separating funnel, the aqueous layer was separated, and the organic layer was washed with water (10 mL), dried, and concentrated to afford pure sulfinimines (as analyzed by NMR).

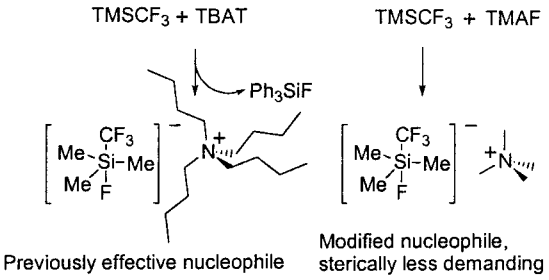
diastereomeric ratio and 65% overall yield.[11] It is important to note that no 1,4-addition product was obtained. The scope of this reaction was investigated with the imines **3b**−**h** (Table 2). As is evident with the imines **3b** and **3d**, substitution at the α-position by a methyl group increases the diastereoselectivity without major loss in yields. High branching (imine **3e**) at the β-position has no influence on the reaction yield. The reaction is also tolerant to heterocycle substitutions (**3c** and **3d)** at β-positions. However, under the reaction conditions imines **3f** and **3g** with a long alkyl chain substitution in the α-position gave lower yields of addition products as a single diastereomer. We have overcome these problems by considering the steric aspect of the reaction. Nucleophilic addition reactions depend on not only the electrophilicity of the substrates but also the steric volume of the nucleophiles. Substitution with a long alkyl chain at the α-position does not change the electrophilicity of the imines in a significant manner. The lower yields of the addition products with the imines **3f** and **3g** could be due to steric congestion, and thus reducing the steric volume (Scheme 2) of the effective nucleophile would increase the yields of the products. In fact, when TMAF (tetramethylammonium fluoride) was used as a fluoride source, the addition products for the imines **3f** and **3g** were obtained in good yields.[10] Under these conditions even the sterically bulky 2,3-disubstituted imine **3h** gave the corresponding addition product in good yield. The rationale for the high *anti*-Ellman products in our trifluoromethylation reactions could be explained by Cram-Davis' open transition state model (Scheme 3).[12] Thus the pentavalent intermediate with its large tetra-alkylammonium counterion delivers the trifluoromethide ion preferably from the *re* face of the α,β-unsaturated imines and affords the Cram products **4a**−**h** (Scheme 1). The stereochemistry of the (−)-**4a** (R_S,*S*) was determined by single-crystal X-ray analysis.[13] As a demon-

Table 2. Nucleophilic Trifluoromethylation of **3a**−**h**

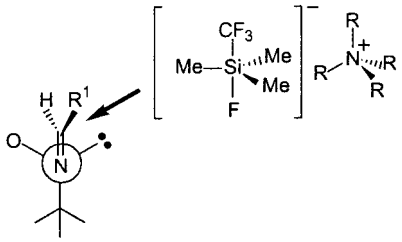
sulfinimines	sulfinamides	
	(R_S,*S*) : (R_S,*R*)[a]	yields (%)[b]
 **3a**	90 : 10	55
 **3b**	>99	73
 **3c**	92 : 08	76
 **3d**	98 : 02	50
 **3e**	>99	62
 **3f**	>99 (90 : 10)[c]	25 (82)[c]
 **3g**	>99 (92 : 08)[c]	20 (75)[c]
 **3h**	(93 : 07)[c]	(62)[c]

[a] Diastereomeric ratios were determined by ^{19}F NMR from the crude product. Unless otherwise mentioned, yields and diastereomeric ratios are for TBAT as the fluoride source. [b] Isolated yields of the major diastereomer. [c] Diastereomeric ratios and yields when TMAF (tetramethylammonium fluoride) was used as a fluoride source.

Scheme 2



Scheme 3

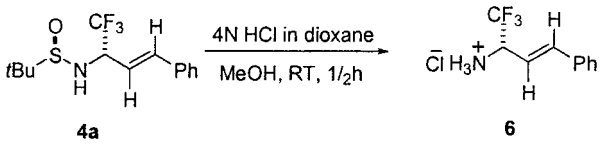


(11) **General procedure** for the addition of $TMSCF_3$ to the sulfinimines: Into a 25-mL round-bottomed flame-dried flask fitted with a magnetic stirring bar, a rubber septum, and an argon-filled balloon were placed 0.453 mmol of **3a** and TBAT (tetrabutylammonium triphenyldifluorosilicate; Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc*. **1995**, *117*, 5166) (0.498 mmol, 0.267 g) in 6 mL of THF. The reaction flask was cooled to −25 °C, and $TMSCF_3$ (0.083 g, 0.588 mmol) in 3 mL of THF was added slowly down the side of the flask. The resulting solution was stirred at −25 °C until the white slurry of the TBAT was disappeared (0.5−1 h). The reaction mixture was quenched with 2 mL of saturated NH_4Cl, extracted with ethyl acetate, dried with Na_2SO_4, and concentrated to give the crude **4a** in 90:10 diastereomeric ratio. Reaction with TMAF (tetramethylammonium fluoride) was also carried out under similar conditions.

(12) Davis, F. A.; McCoull, W. *J. Org. Chem*. **1999**, *64*, 3396.

stration, sulfinamide **4a** was hydrolyzed to amine hydrochloride **6** without any stereochemical loss (Scheme 4) in quantitative yield.

Scheme 4



4a **6**

In summary, the first asymmetric synthesis of trifluoromethylated allylic amines was accomplished by highly diastereoselective addition of trifluoromethide ion using $TMSCF_3$ and TBAT, as well as TMAF, as fluoride sources to yield α,β-unsaturated *N-tert*-butanesulfinamides.

Acknowledgment. The support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

Supporting Information Available: ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010134X

(13) We thank Prof. Robert Bau and Mr. Kavin Jin for their help in obtaining the crystal structure of **4a**.