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Asymmetric Synthesis of Homoallylic Amines Bearing Adjacent Stereogenic Centers by Addition of Substituted Allylic Zinc Reagents to N-*tert*-Butanesulfinylimines†

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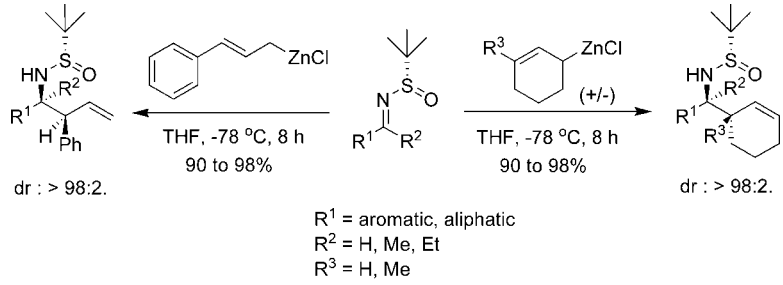
ABSTRACT



A highly diastereoselective addition of substituted racemic allylic zinc reagents to chiral N-*tert*-butanesulfinylimines resulting in the formation of homoallylic amines is reported. This method is quite general and also efficient for the preparation of enantiomerically pure homoallylic amines bearing quaternary centers and also adjacent quaternary centers.

The stereoselective formation of a carbon−carbon bond is of greatest importance in asymmetric synthesis. Especially challenging is the generation of adjacent stereogenic centers including quaternary centers.[1] In simple systems, this has been achieved by the face-selective addition of carbon nucleophiles to carbon−heteroatom double bonds. Addition of unsubstituted allylic organometallic reagents to Ellman's imine (**1**)[2] leading to the formation of chiral homoallylic amines bearing a single stereogenic center is an excellent example in the present context.[3] To our knowledge, there is no report on asymmetric addition of highly substituted racemic allylic organometallic reagents to **1** since they are not readily accessible.[4,5] During the total synthesis of salinosporamide A, Corey provided an elegant method for

† This paper is dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

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(3) (a) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979. (b) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4. (c) Cogan, D. A.; Liu, G.-C.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883. (d) Maji, M. S.; Fröhlich, R.; Studer, A. *Org. Lett.* **2008**, *10*, 1847. (e) Kolodney, G.; Sklute, G.; Perrone, S.; Knochel, P.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 9291. (f) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823.

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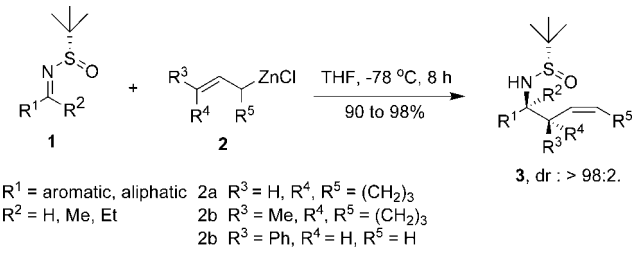
preparing highly substituted racemic allylic zinc reagents in high purity and excellent yields.[6] With this method in hand, we investigated the asymmetric addition of substituted racemic allylic zinc reagents to **1** (Scheme 1) and results

Scheme 1. Reaction of Substituted Allylic Zinc Reagents with Various *N*-*tert*-Butanesulfinylimines



leading to the formation of a variety of homoallylic amines bearing adjacent stereogenic centers in high enantiopurity are reported herein. Chiral homoallylic amines reported herein are amenable to further modifications, hence opening an access for novel compounds of pharmaceutical and biological interest.[7]

Treatment of (*S*)-*N*-*tert*-butanesulfinylaldimine[2,8] **1a** (1 equiv) with racemic cyclohexenylzinc chloride[5] (**2a**, 1.2 equiv) in THF at −78 °C for 8 h afforded *anti*-homoallylic amine **3a** in high yield (98%) and with a high diastereomeric ratio (dr ≥ 98:2). *Anti*-homoallylic amine **3a** was obtained as a colorless crystalline solid (mp = 126−128 °C). The structure and absolute stereochemistry of **3a** were confirmed by single-crystal X-ray diffraction analysis (Figure 1). The

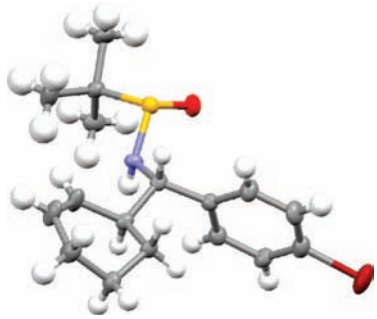


Figure 1. X-ray crystal structure of **3a**.

diastereoselectivity of the reaction was determined to be >98:2 by ^{1}H NMR analysis of the crude product. Encouraged by these results, we turned our attention to other substituted aromatic *N*-*tert*-butanesulfinyl aldimines. Interestingly, a large number of substituted aromatic *N*-*tert*-butanesulfinyl aldimines, such as *p*-fluoro, *p*-fluoro-*o*-bromo, *p*-methyl, and *p*-methoxy derivatives, reacted cleanly with cyclohexenylzinc chloride (**2a)** leading to corresponding *anti*-homoallylic amines **3b**−**e** (Table 1, entries 2−5) in excellent yields (93−96%) and high diastereomeric ratios (dr >98:2). In the same way, aliphatic *N*-*tert*-butanesulfinylaldimines such as cyclohexyl aldimine **1f** and ethyl aldimine **1g** smoothly reacted with **2a** affording the corresponding *anti*-homo allylic amines **3f** and **3g** in 92% and 97% yield (dr 97:3 and 98:2), respectively. The heterocyclic *N*-*tert*-butanesulfinyl aldimine **1h** also reacted with **2a** to form *anti*-homoallylic amine **3h** in 95% yield with dr ≥98:2.

Similarly, reaction of organometallic reagent **2a** with *N*-*tert*-butylsulfinyl methyl ketimines **1i** and **1j** in THF at −78 to −30 °C for 8 h afforded **3i** and **3j**, respectively, bearing a quaternary center in high yields (92−96%) and with high diastereomeric ratios (dr ≥98:2). Likewise, reaction of **2a** with *N*-*tert*-butylsulfinyl ethyl ketimine **1k** also proceeded to *anti*-homoallylic amine **3k** containing a quaternary center in 94% yield with dr >98:2. Addition of 3-methyl-2-cyclohexenylzinc chloride (**1b**) to *N*-*tert*-butylsulfinyl methyl ketimine **1l** resulted in a regiospecific and diastereospecific addition yielding **3l**. Noticeably, the new carbon−carbon bond is formed exclusively from the most substituted end of allylic system, leading to the *anti*-homoallylic amine **3l** bearing two adjacent quaternary centers in good yield (90%) with dr >98:2.

Interestingly, the cinnamylzinc chloride (**2c**) also displayed high diastereoselectivity (Table 1, entries 13−19). Thus, the addition of various substituted aromatic *N*-*tert*-butanesulfinyl aldimines, such as *p*-bromo, *p*-fluoro, *p*-fluoro-*o*-bromo, *p*-methyl, and *p*- methoxy derivatives, led to the corresponding *syn*-homoallylic amines (Table 1, entries 13−17) in excellent yields with dr ≥98:2. Similarly, heterocyclic *N*-*tert*-butanesulfinyl aldimine **1s** and aliphatic *N*-*tert*-butanesulfinyl aldimines **1r** also reacted with **2c** giving corresponding *syn*-homoallylic amines (Table 1, entries 18 and 19) in good yields (93−95%) and excellent diastereoselectivity (dr >98:2). Unfortunately, this method is not suitable for crotylation as it gives a mixture of diastereomers. The structure and stereochemistry of the *syn*-homoallylic amine **3m** (mp = 82−83 °C) resulting from addition of cinnamylzinc

(4) Substituted allylic lithium and magnesium reagents display a high reactivity, and they are unstable. Their synthesis is rather difficult. Direct zinc insertion to substituted allyl bromides is less satisfactory and gives homocoupling products. (a) Schlosser, M.; Desponds, O.; Lehmann, R.; Moret, E.; Raucheschwalbe, G. *Tetrahedron* **1993**, *49*, 10175. (b) Bellassoued, M.; Frangin, Y.; Gaudemar, M. *Synthesis* **1977**, 205.

(5) Recently, Knochel reported the LiCl-mediated preparation of substituted allylic zinc reagents with a moderate formation of homocoupled products. (a) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376.

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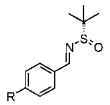
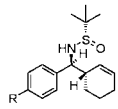
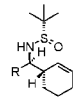
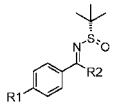
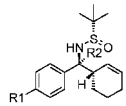
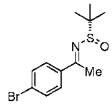
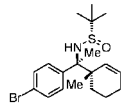
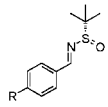
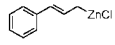
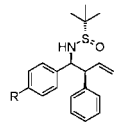
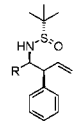
Table 1. Asymmetric Addition of Substituted Allylic Organometallic Reagent to *N-tert*-Butanesulfinylimines

entry	substrate (**1**)	zinc reagent (**2**)	product (**3**)	yield (%)[a]	dr[b]
					
1	**1a**: R = Br	**2a**	**3a**	98	≥98:2
2	**1b**: R = F	**2a**	**3b**	95	≥98 2
3	**1c**: R = CH_3	**2a**	**3c**	96	≥98:2
4	**1d**: R = OCH_3	**2a**	**3d**	93	≥98:2
					
5	**1e**: R = *p*-F-*o*-Br-Ph	**2a**	**3e**	96	≥98:2
6	**1f**: R = Cy	**2a**	**3f**	92	97:3
7	**1g**: R = Et	**2a**	**3g**	97	≥98:2
8	**1h**: R = Furl	**2a**	**3h**	95	≥98:2
					
9[c]	**1i**: R^1 = H, R^2 = Me	**2a**	**3i**	92	≥98:2
10[c]	**1j**: R^1 = Br, R^2 = Me	**2a**	**3j**	96	≥98:2
11[c]	**1k**: R^1 = H, R^2 = Et	**2a**	**3k**	94	≥98:2
					
12[c]	**1l**	**2b**	**3l**	90	≥98:2
					
13	**1m**: R = Br	**2c**	**3m**	95	≥98:2
14	**1n**: R = F	**2c**	**3n**	94	≥98:2
15	**1o**: R = CH_3	**2c**	**3o**	95	≥98:2
16	**1p**: R = OCH_3	**2c**	**3p**	94	≥98:2
					
17	**1q**: R = *p*-F-*o*-Br-Ph	**2c**	**3q**	94	≥98:2
18	**1r**: R = Et	**2c**	**3r**	93	≥98:2
19	**1s**: R = Furyl	**2c**	**3s**	95	≥98:2

[a] Isolated yield of analytically pure products. [b] The diastereoselectivity was determined by ^{1}H NMR analysis. The "≥98:2" denotes that signals for only one diastereomer were observed. dr relative to sulfur. [c] Reaction conditions: −78 to −30 °C, 8 h.

chloride (**2c**) to *N-tert*-butanesulfinyl aldimine **1m** was confirmed by the single-crystal X-ray diffraction analysis (Figure 2). A possible mechanistic model to explain the

(8) (a) Liu, G.; Cogan, D. A.; Owenst, D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

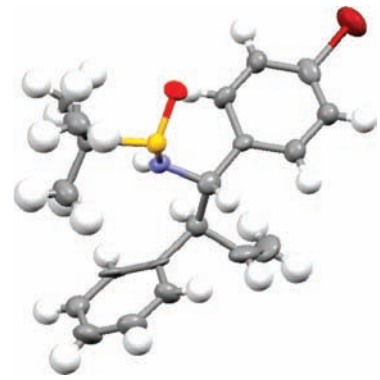
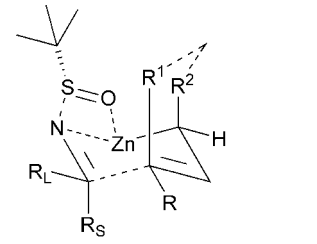


Figure 2. X-ray crystal structure of **3m**.

achieved stereoselectivity is depicted in Figure 3, which involves a chairlike transition state (TS-1).

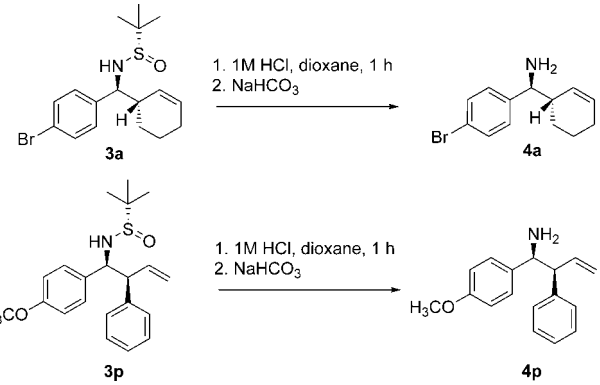


For **2a**: R = H, R^1, R^2 = $(CH_2)_3$
2b: R = CH_3, R^1, R^2 = $(CH_2)_3$
2c: R = Ph, R^1, R^2 = H

Figure 3. Possible transition state (TS-1).

Finally, the sulfinyl group can be cleaved readily under mild acidic conditions to provide free amine **4** in quantitative yield.

Scheme 2. Deprotection of Sulfinyl Group



In summary, we have described an efficient, highly diastereoselective addition of substituted racemic allyliczinc

chloride reagents to various chiral *N*-*tert*-butanesulfinyl aldimines and ketimines affording homoallylic amines. This method is found to be very efficient for the preparation of enantiomerically and diastereomerically pure homoallylic amines bearing quaternary centers and also adjacent quaternary centers. Extension of this work is currently underway in our laboratory.

Supporting Information Available: Complete experimental procedures, characterization data, copies of NMR spectra, and single X-ray crystallographic data for compounds **3a** and **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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