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Room-Temperature Highly Diastereoselective Zn-Mediated Allylation of Chiral *N-tert*-Butanesulfinyl Imines: Remarkable Reaction Condition Controlled Stereoselectivity Reversal

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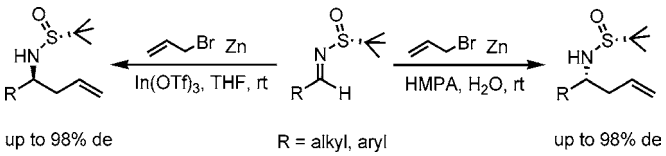
ABSTRACT



An efficient method for the highly diastereoselective synthesis of chiral homoallylic amines by Zn-mediated allylation of chiral *N-tert*-butanesulfinyl imines at room temperature was developed. By simply tuning the reaction conditions, the method allows the achievement of a highly remarkable opposite stereocontrol, affording the desired stereochemical outcome in good yield and with excellent diastereoselectivity (up to 98% dr). With *N*-sulfinyl ketimines, the corresponding quaternary carbon-containing chiral homoallylic amines could also be produced.

The asymmetric addition of allylic nucleophiles to the carbonyl imino derivatives has been established as a powerful method for the synthesis of chiral homoallylic amines[1] which are important precursors to numerous organic compounds. Among the strategies developed, diastereoselective allyl addition to chiral auxiliary derived imines has received major attention.[1b,2] With appropriate chiral auxiliaries, the reaction can be carried out stereoselectively and provides enantiopure amines effectively. Examples involving chiral α-amino acid derivatives,[2a−d] sulfinyl imines,[2e−g] and hydrazones[2h−j] have shown some success. In many cases, however, the diastereoselectivity and the efficiency of these reactions are not predictable, and vary upon the change of the reaction substrates as well as the allylic nucleophiles. With the same auxiliary, the dramatic reversal of the stereoselectivity has been observed, but often gave low diastereoselectivity.[3] The exploration of new approaches for readily preparing both of the enantiomers of homoallylic amines using one chiral auxiliary has been a subject of interest. Herein, we[4] report an efficient and practical synthesis of each of chiral homoallylic amines based on Zn-mediated allylation to chiral (*R*)-*N-tert*-butanesulfinyl imines. By simply varying the reaction

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(1) For reviews: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.

(2) For examples, see: (a) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766. (b) Ken Lee, C.-L.; Ling, H. Y.; Loh, T.-P. *J. Org. Chem.* **2004**, *69*, 7787. (c) van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 3943. (d) Loh, T.-P.; Ho, D. S.-C.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865. (e) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4. (f) Cogan, D. A.; Liu, G.-C.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. (g) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823. (h) Enders, D.; Chelain, E.; Raabe, G. *Bull. Soc. Chim. Fr.* **1997**, *134*, 299. (i) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491. (j) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741. (k) Yanada, R.; Negoro, N.; Okaniwa, M.; Ibuka, T. *Tetrahedron* **1999**, *55*, 13947. (l) Hunt, J. C. A.; Lloyd, C.; Moody, C. J.; Slawin, A. M. Z.; Takle, A. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3443. (m) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464.

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conditions, the method allows the achievement of a highly remarkable opposite stereocontrol.

Previously, the diastereoselective allylmagnesium[2f] and allylindium[2g] addition to chiral *N*-*tert*-butanesulfinyl imines have been reported by Ellman and Foubelo, respectively. In their studies, a six-membered chair transition-state model was proposed (Figure 1, TS-1), in which the allylmetal (M = Mg, In) was coordinated to the sulfinyl oxygen. For example, when (*R*)-*N*-*tert*-butanesulfinyl imine is employed, the *si*-face addition will be favored, thus leading to the majority of (*S*)-amine product. With this framework in mind, we assumed that an acyclic transition state (TS-2) might be engaged if a rather strong Lewis acid was presented in the reaction system. As a result, the chelation of Lewis acid with both nitrogen and sulfinyl oxygen of imine would direct allyl attack selectively from the sterically unblocked *si*-face to give (*S*)-amine. On the other hand, we can assume another type of acyclic transition state model TS-3, in which the allylmetal is coordinated to additional Lewis bases rather than the sufinyl oxygen. As depicted, the uncoordinated *N*-sulfinyl group adopts an approximate synperiplanar configuration.[5] The allyl addition to the less hindered *re*-face of imine would be preferred, thereby facilitating (*R*)-amine formation. Thus, with the unique nature of chiral *N*-*tert*-butanesulfinyl imine, we rationalized that the opposite stereocontrol of the allylation might be achieved using coordination protocol.[6]

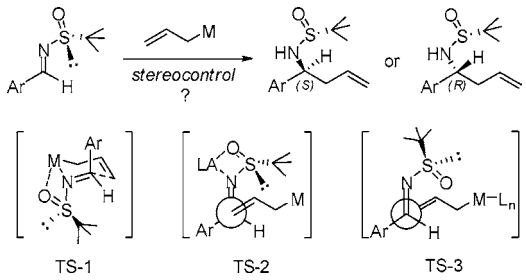
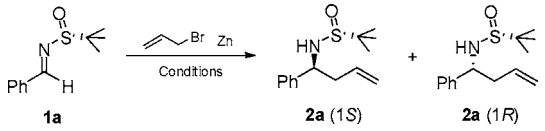


Figure 1. Mechanistic proposals on stereocontrol.

Our studies to develop the above proposed reactions were initiated by using (*R*)-*N*-sulfinyl imine **1a** as a substrate and in situ generated allylzinc bromide as the allylation reagent in THF. Unlike the allylindium addition[2g] that needs to be carried out at 60 °C for completion (4 h), the reaction proceeded very smoothly at room temperature to afford the product **2a** in 99% yield and 90:10 (1*S*:1*R*)[7] dr in 30 min (Table 1, entry 1). Not surprisingly, the observed stereocontrol is consistent with the cyclic chelation model TS-1. Taking into account the proposed acyclic transition state model TS-2, we investigated the addition of Lewis acids. Ideally, those Lewis acidic activities stronger than Zn(II) will work. Under similar reaction conditions, various Lewis acids were examined as additives. Among them, $In(OTf)_3$ was found to be the best, a significant improvement in diastereoselectivity up to 99:1 could be obtained (entries 2−4). Notably, the use of 2 equiv of Zn (entry 3) or more (entry 4) was found useful to provide a higher yield than 1.5 equiv (entry 2).

Table 1. Screening and Optimization of the Reaction Conditions[a]



entry	solvent[b]	Zn (equiv)	additive	time (h)	yield[c] (%)	dr[d] (1*S*:1*R*)
1	THF	1.5	none	0.5	99	90:10
2	THF	1.5	$In(OTf)_3$ (1.1 equiv)	12	73	99:1
3	THF	2.0	$In(OTf)_3$ (1.1 equiv)	10	**93**	**98:2**[e]
4	THF	3.0	$In(OTf)_3$ (1.3 equiv)	10	**97**	**99:1**[e]
5	THF	2.0	TMEDA (2.0 equiv)	12	99	81:19
6	THF	2.0	HMPA (2.0 equiv)	1	99	53:47
7	DMF	2.0	none	1	99	38:62
8	DMF	2.0	TMEDA (2.0 equiv)	12	98	16:84
9	DMSO	2.0	none	4	98	32:68
10	HMPA	2.0	none	1	99	26:74
11	HMPA	2.0	H_2O (10 μL)	12	**97**	**1:99**[e]
12	THF	2.0	H_2O (10 μL)	12	81	72:28

[a] Reaction was performed with 0.25 mmol of imine **1a** in 5 mL of solvent at rt. [b] Dry solvent. [c] Isolated yield. [d] Determined by ^1H NMR of the crude materials. [e] Enantiomeric ratio by HPLC, see ref 7.

Encouraged by the above success, we next attempted to test the possibility of stereoselectivity reversal as hypothesized in TS-3. Lewis base TMEDA was initially examined as additive, despite a moderate diastereoselectivity (1*S*/1*R* 81:19), it shows the potential of opposite stereocontrol (entry

(3) For selected examples, see: (a) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Itoh, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778. (b) Ukaji, Y.; Kume, K.; Watai, T.; Fujisawa, T. *Chem. Lett.* **1991**, 173. (c) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766. (d) Alvaro, G.; Savoia, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2083. (e) Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. *Eur. J. Org. Chem.* **2002**, 3153. (f) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Diez, R.; Galvez, J. A. *Eur. J. Org. Chem.* **2002**, 3763. (g) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651.

(4) For our recent work involving chiral *N*-*tert*-butanesulfinyl imines, see: (a) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953. (b) Zhong, Y.-W.; Isumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747. (c) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Isumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956.

(5) For related crystal structures and theoretical calculations support, see: (a) Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539. (b) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3. (c) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 545. (d) Tietze, L. F.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1998**, 1629. (e) Bharatam, P. V.; Uppal, P.; Kaur, A.; Kaur, D. *J. Chem. Soc., Perkin Trans. 2* **2000**, 43.

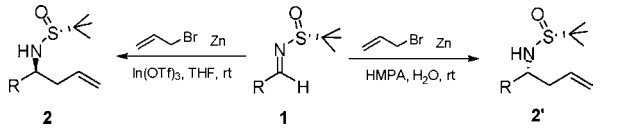
(6) Examples of stereoselectivity reversal using *N*-*tert*-butanesulfinyl imines have been reported for organomagnesium or organolithium reagents addition, Strecker reaction and very recently hydride reduction; see: (a) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303. (b) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. *Org. Lett.* **2005**, *7*, 2599. (c) Wang, H.; Zhao, X.; Li, Y.; Lu, L. *Org. Lett.* **2006**, *8*, 1379. (d) Colyer, J. T.; Andersen, N. G.; Tedrow, J. S.; Soukup, T. S.; Faul, M. M. *J. Org. Chem.* **2006**, *71*, 6859.

(7) The configuration was assigned by comparison with literature data for the free homoallylic amine; see the Supporting Information for details.

5 vs 1). With HMPA, a diastereomeric ratio of 53:47 (1*S*/1*R*) was observed (entry 6). When DMF, DMSO or HMPA was directly used as solvent instead of THF, a clear reversal of the diastereofacial selectivity was attained (entries 7, 9, and 10). More excitingly, performing the reaction with TMEDA in DMF resulted in a much better **2a** (1*R*) selectivity (1*S*/1*R* 16:84, entry 8). These results suggests that the zinc-(II) ion is coordinated to the solvent molecules or TMEDA. To further improve this opposite stereocontrol, the reaction conditions were carefully screened. Eventually, we were very pleased to find that the desired **2a** (1*R*) product could be isolated in 97% yield and with 98% de (1:99 dr) in HMPA in the presence of proper amount of H_2O[8] (entry 11). The critical role of H_2O in the reaction system is not clear at this time, it seems that H_2O disrupts the chelation of Zn(II) with sufinyl imine (entry 12).

With two optimized conditions established, we began to evaluate the reaction scope. A wide variety of *N*-sulfinyl aldimines (**1**) were investigated using the reaction conditions of entry 3 and 11 in Table 1, respectively (Table 2).

Table 2. Diastereoselective Allylation to (*R*)-*N*-*tert*-Butanesulfinyl Aldimines with Two Different Reaction Systems[a]



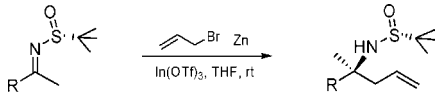
			THF system[b]		HMPA system[c]	
entry	**1**	R	yield[d] (%)	dr[e]	yield[d] (%)	dr[e]
1	**1a**	C_6H_5	93	98:2	97	1:99
2	**1b**	4-FC_6H_4	98	98:2	97	1:99
3	**1c**	4-ClC_6H_4	98	98:2	96	3:97
4	**1d**	4-BrC_6H_4	93	97:3	99	2:98
5	**1e**	4-MeC_6H_4	95	96:4	88	3:97
6	**1f**	4-$MeOC_6H_4$	91	95:5	81	2:98
7	**1g**	2-ClC_6H_4	91	97:3	73	2:98
8	**1h**	2-MeC_6H_4	95	98:2	89	3:97
9	**1i**	3-BrC_6H_4	98	98:2	99	2:98
10	**1j**	β-naphthyl	81	95:5	86	3:97
11	**1k**	cyclopropyl	98	86:14	97	4:96
12	**1l**	cyclohexyl	99	97:3	94	3:97
13	**1m**	ethyl	93	88:12	92	5:95
14	**1n**	isopropyl	96	94:6	94	2:98
15	**1o**	phenethyl	92	90:10	93	4:96
16	**1p**	phenetheneyl	83	91:9	87	6:94

[a] Reactions were carried out with 0.25 mmol of imine **1**, 0.5 mmol of Zn/allyl bromide, and additive in 5 mL of dry solvent at rt. [b] 0.275 mmol of $In(OTf)_3$ was used as additive. [c] 10 μL of H_2O was used as additive. [d] Isolated yield. [e] Determined by ^1H NMR of the crude materials.

Gratifyingly, all the reactions went smoothly and afforded the allylation products in good yields as well as high diastereoselectivities. *N*-sulfinyl imines of aromatic aldehyde proved to be excellent substrates in both systems, giving 90−98% de in allylation. For aliphatic imines (entries 11−14), the HMPA system gave even better diastereoselectivities. Thus, with two different reaction systems, the opposite stereocontrol could be easily achieved.

We also examined *N*-sulfinyl ketimines **3** as substrates to produce the corresponding quaternary carbon-containing chiral homoallylic amines. The asymmetric allylation of ketoimines is a very challenging topic in organic synthesis, to our knowledge, only a limited number of examples have been reported to date.[9] Ketimines are relatively less reactive than aldimines, in our case, **3a** did not even react with allylzinc bromide in THF when no additive was used. To our delight, using the conditions of entry 4 in Table 1 for THF system, the reactions proceeded well to a series of ketimine substrates and afforded the desired products in moderate yields and excellent distereomeric ratios (Table 3).

Table 3. Diastereoselective Allylation to (*R*)-*N*-*tert*-Butanesulfinyl Ketimines with THF System[a]



entry	**3**	R	**4**	yield[b] (%)	dr[c]
1	**3a**	C_6H_5	**4a**	69	97:3
2	**3b**	4-MeC_6H_4	**4b**	67	96:4
3	**3c**	4-$CF_3C_6H_4$	**4c**	89	96:4
4	**3d**	4-$MeOC_6H_4$	**4d**	76	95:5
5	**3e**	4-ClC_6H_4	**4e**	83	97:3
6	**3f**	4-BrC_6H_4	**4f**	85	97:3
7	**3g**	4-FC_6H_4	**4g**	79	97:3
8	**3h**	3-MeC_6H_4	**4h**	66	95:5
9	**3i**	3-ClC_6H_4	**4i**	81	98:2

[a] Reactions were carried out with 0.25 mmol of imine **3**, 0.75 mmol of Zn/allyl bromide, and 0.325 mmol of $In(OTf)_3$ in 5 mL of dry THF at rt. [b] Isolated yield. [c] Determined by 1H NMR of the crude materials.

In most cases, 90−96% de's were observed. These results are among the best in asymmetric allylation of aromatic ketoimines. Presumably, the added Lewis acid $In(OTf)_3$ increases the reactivity of ketimines. With the optimized HMPA system, however, ketimines are not activated; thus, the reactions did not take place.

In summary, we have developed a highly diastereoselective Zn-mediated allylation of chiral *N*-*tert*-butanesulfinyl imines. The method enables efficient and general synthesis of enantiomerically enriched homoallylic amines including quaternary ones at room temperature in high yields. By simply tuning the reaction solvent and additive, a remarkable reversal of diastereofacial selectivity can be achieved to afford the desired stereochemical outcome. Further studies

(8) The amount of H_2O has a substantial influence on the reaction yield and diastereoselectivity; see the Supporting Information for details. Also, a similar water effect was found for additions to imines, see refs 2a and 6c.

(9) For recent advances on asymmetric allylation of ketimines, see: (a) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (b) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. For examples of allylmagnesium bromide addition to *N*-sulfinyl ketoimines, see ref 2e,f.

are being conducted to better understand the mechanistic details of the chelation control.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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