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Asymmetric Radical Addition of Ethers to Enantiopure *N*-*p*-Toluenesulfinyl Aldimines, Mediated by Dimethylzinc–Air

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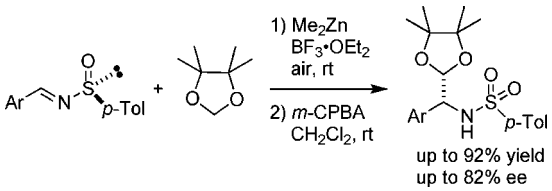
ABSTRACT



Asymmetric radical addition of ethers to enantiopure aromatic *N*-*p*-toluenesulfinyl aldimines has been achieved. The requisite radicals were generated by dimethylzinc–air. Lewis acid activation of the *N*-*p*-toluenesulfinyl aldimines followed by radical addition gives a mixture of sulfinamide and sulfonamide products. Subsequent treatment of the mixture with dry *m*-CPBA affords the sulfonamide product in enantiomerically enriched form.

The prevalence of chiral amine moieties in natural products, biologically active compounds, chiral building blocks, auxiliaries, and catalysts necessitates the development of novel methods for their syntheses.[1]

Our recent reports[2] indicated that carbon-centered radicals generated from ether,[3] unfunctionalized cycloalkanes,[4] and primary alkyl iodides,[5] in the presence of dimethylzinc and air, all add to imines to give the adducts in good to excellent yields. We have also reported the reaction of carbon-centered radicals generated from ethers, with aldehydes,[6] arylamines, alkoxyamines, and dialkylhydrazines.[7] Among the imines that were investigated, *N*-sulfonyl imines were most efficient. The potential application of the radical reaction to the synthesis of nonracemic oxygenated amine derivatives prompted us to investigate carbon-centered radical addition of ethers to enantiopure *N*-sulfinyl imines.[8,9]

Although there are numerous examples of asymmetric anionic additions to *N*-sulfinyl imines,[10,11] to our knowledge,

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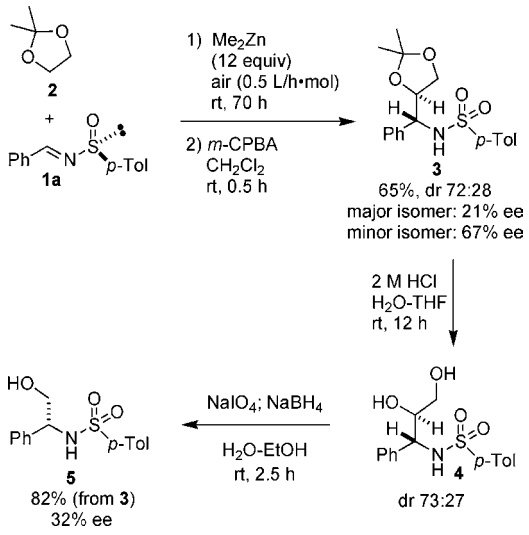
there has been only one report[12] which likely describes asymmetric addition of radicals to *N*-sulfinyl imines. This report by Lin, Xu, and co-workers describes a SmI_2-mediated reductive cross-coupling reaction between aldehydes and chiral *N*-*tert*-butanesulfinyl imines. The reaction may involve the addition of radical anion intermeditates.

We report herein a stereoselective addition of α-alkoxyalkyl radicals to chiral *N*-sulfinyl imines.

The requisite *N*-sulfinyl imines were synthesized in enantiomerically pure forms using Davis' procedure.[13] With the enantiomerically pure *N*-sulfinyl imines in hand, we commenced our investigation by treating a solution of (*S*)-*N*-*p*-toluenesulfinyl benzaldehyde imine (**1a**) in 2,2-dimethyl-1,3-dioxolane (**2**) with dimethylzinc (1 M in hexane) and air at ambient temperature.[3a] However, complete consumption of **1a** required 12 equiv of dimethylzinc and 70 h, giving a mixture of sulfonamide **3** and its sulfinamide analogue. Subsequent treatment of the mixture with dry *m*-CPBA[14,15] produced **3** in 65% yield as a 72:28 mixture of diastereoisomers[3a] (Scheme 1).

The sense of asymmetric induction of the radical addition reaction was determined by converting adduct **3** into known

Scheme 1. Me_2Zn−Air-Initiated Asymmetric Radical Addition of **2** to Imine **1a**[a] and the Conversion of Adduct **3** to Alcohol **5**



[a] The reaction was carried out using **1a** (1 mmol) and **2** (250 equiv). Diastereomeric ratios (dr) were determined by ^1H NMR of crude product. Enantiomeric excess was determined by HPLC analysis (see the Supporting Information).

alcohol **5**[16] via diol **4**. The prolonged reaction time and requirement of large amounts of dimethylzinc were initially attributed to the unexpected poor ability of *N*-sulfinyl imine **1a** as an α-alkoxyalkyl radical acceptor. However, the radical addition step required 4 h, and 3 equiv of Me_2Zn when THF (**6**) was used to give adduct **7** in high yield (Table 1, entry 1), thus suggesting that the steric bulk due to the methyl groups of dioxolane **2** was the reason for the slow reaction.

Ethers that would generate more nucleophilic carbon-centered radicals as a result of an extra adjacent oxygen atom were also investigated. With 1,3-benzodioxole (**8**), adduct **9** was obtained in 43% yield with 51% ee (entry 2). The best results were obtained when 4,4,5,5-tetramethyl-1,3-dioxolane (**10**) was used, giving adduct **11a** in 67% yield with 83% ee (entry 3).[17] The higher enantiocontrol observed in the case of dioxolane **10** relative to that observed when planar dioxole **8** was used was presumably due to the steric hindrance caused by the methyl groups. The use of *tert*-butyl methyl ether (**12**) required a large amount of dimethylzinc (30 equiv) and over 3 days to produce adduct **13** in poor yield and ee (entry 4).

Having identified an ether that produced the adduct in good yield and ee, we sought to optimize the reaction conditions. To this end, activation of the *N*-sulfinyl imine **1a** with boron trifluoride etherate (1 equiv) led to significant acceleration of the reaction with increased yield of 86% and comparable enantioselectivity of 80% after 2.5 h using 3 equiv of

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(11) For latest examples of nucleophilic addition to chiral *N*-sulfinyl imines: (a) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979−4982. (b) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129−3132. (c) Kościołowicz, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1444−1448. (d) Kawęcki, R. *Tetrahedron: Asymmetry* **2006**, *17*, 1420−1423. (e) Beenen, M. A.; Wiex, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304−6305. (f) Ding, C.-H.; Chen, D.-D.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. *Synlett* **2006**, 1272−1274. (g) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Chem. Commun.* **2006**, 1833−1835. (h) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693−1696. (i) Davis, F. A.; Ramachandar, T.; Chai, J.; Skucas, E. *Tetrahedron Lett.* **2006**, *47*, 2743−2746. (j) Velázquez, F.; Arasappan, A.; Chen, K.; Sannigrahi, M.; Venkatraman, S.; McPhail, A. T.; Chan, T.-M.; Shih, N.-Y.; Njoroje, F. G. *Org. Lett.* **2006**, *8*, 789−792. (k) Wang, Y.; He, Q.-F.; Wang, H.-W.; Zhou, X.; Huang, Z.-Y.; Qin, Y. *J. Org. Chem.* **2006**, *71*, 1588−1591. (l) Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* **2006**, *8*, 139−142. (m) Hansen, D. B.; Starr, M. L.; Tolstoy, N.; Joullié, M. M. *Tetrahedron: Asymmetry* **2005**, *16*, 3623−3627. (n) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2005**, *7*, 5393−5396. (o) Rajapakse, H. A.; Young, M. B.; Zhu, H.; Charlton, S.; Tsou, N. N. *Tetrahedron Lett.* **2005**, *46*, 8909−8912. (p) García Ruano, J. L.; Topp, M.; López-Cantarero, J.; Alemán, J.; Remuiñán, M. J.; Cid, M. B. *Org. Lett.* **2005**, *7*, 4407−4410. (q) Li, Y; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882−5886. (r) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269−11276. (s) Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J.* **2005**, *11*, 5269−5278. (t) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045−3047. (u) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. *Org. Lett.* **2005**, *7*, 2599−2602. (v) Chelucci, G.; Baldino, S.; Solinas, R.; Baratta, W. *Tetrahedron Lett.* **2005**, *46*, 5555−5558. (w) Xu, W.; Dolbier, W. R., Jr. *J. Org. Chem.* **2005**, *70*, 4741−4745.

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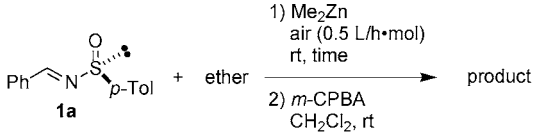
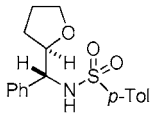
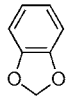
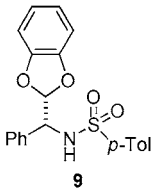
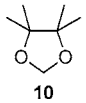
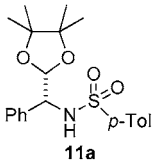
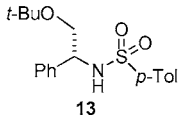
(15) García Ruano, J. L.; Alemán, J.; Cid, M. B.; Parra, A. *Org. Lett.* **2005**, *7*, 179−182.

(16) Pelter, A.; Ward, R. S.; Sirit, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1745−1762.

(17) The use of (*R*)-*N*-*tert*-butanesulfinyl benzaldehyde imine resulted in a complex mixture of products.

Table 1. Asymmetric Radical Addition of Other Ethers to **1a**[a]



entry	ether	time (h)	product	yield, ee
1[b]	 **6**	4	 **7**	88%, dr 75:25[c] major isomer: 16% ee minor isomer: 59% ee
2[d]	 **8**	46	 **9**	43%, 51% ee
3[d]	 **10**	45	 **11a**	67%, 83% ee
4[e]	MeO*t*-Bu **12**	91	 **13**	27%, 41% ee

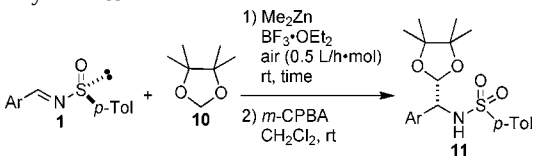
[a] The reaction was carried out using **1a** (1 mmol) and ether (250 equiv). Enantiomeric excess was determined by HPLC analysis (see the Supporting Information). [b] Me_2Zn (3 equiv). [c] Determined by ^1H NMR of crude product. [d] Me_2Zn (6 equiv). [e] Me_2Zn (30 equiv). $TsNH_2$ was obtained in 61% yield.

dimethylzinc.[5] A further increase in yield to 92% was observed when the amount of ether was reduced to 125 equiv (Table 2, entry 1).[18] With the optimized conditions established, the scope of the reaction was found to cover a range of aromatic *N*-sulfinyl imines subtrates (Table 2). Modest to high yields with good enantioselectivities of the adducts were obtained using aromatic *N*-sulfinyl imines with different substitition patterns (entries 2 to 5). Having a methyl group in the *ortho*-position close to the imine carbon led to longer reaction time and use of more dimethylzinc and boron trifluoride etherate (entry 2) relative to having a methyl group in the *para*-position (entry 3). The presence of an electron-withdrawing group in the *para*-position resulted in the use of lesser amount of dimethylzinc and shorter reaction time (entry 4) relative to that of an electron-donating group in the same position (entry 5). Both polyaromatic and heteroaromatic substrates required excess reagents and prolong reaction time to produce the adducts in moderate yields and ees (entries 6 and 7).

The utility of the adduct was demonstrated by conversion of an enantiomerically enriched sample of **11a** into known alcohol **5**[16] without epimerization, using a Lewis acid mediated reductive acetal cleavage strategy (Scheme 2).[19]

(18) Adduct **11a** was obtained in 73% yield with 73% ee when 60 equiv of dioxolane **10** was used.

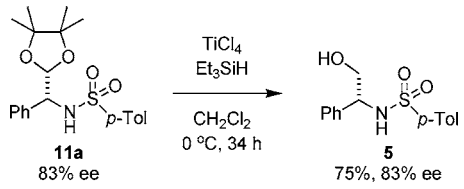
Table 2. Asymmetric Radical Addition of Ether **10** to *N*-Sulfinyl Imines **1**[a]



entry	**1**	Ar	Me_2Zn (equiv)	time (h)	**11**	yield (%)	ee[b] (%)
1	**1a**	Ph	3	2	**11a**	92	80
2[c]	**1b**	2-MeC_6H_4	9	45	**11b**	61	75
3	**1c**	4-MeC_6H_4	3	5	**11c**	77	81
4	**1d**	4-ClC_6H_4	3	5	**11d**	87	82
5[d]	**1e**	4-$MeOC_6H_4$	12	72	**11e**	69	74
6[e]	**1f**	2-naphthyl	12	49	**11f**	71	79
7[f]	**1g**	2-furyl	18	180	**11g**	50	70

[a] Unless otherwise mentioned, **1** (1 mmol), **10** (125 equiv), and $BF_3{\cdot}OEt_2$ (1 equiv) were used [b] Determined by HPLC analysis (see the Supporting Information). [c] $BF_3{\cdot}OEt_2$ (3 equiv) was used. [d] **10** (200 equiv) was used. [e] $BF_3{\cdot}OEt_2$ (4 equiv) was used. [f] $BF_3{\cdot}OEt_2$ (6 equiv) was used.

Scheme 2. Conversion to Alcohol **5** and Determination of Absolute Configuration of **11a**



Hence, the absolute configuration of adduct **11a** was established as (*R*).

The observed stereoselectivity stems from preferential attack of the radical from the less sterically hindered *si*-face of the imino group of the *N*-sulfinyl imine (Figure 1).[20] Tentatively, the absolute configurations of the other adducts are assigned as (*R*) by analogy.

In summary, α-alkoxyalkyl radicals generated from ethers by dimethylzinc-air, have been stereoselectively added to enantiomerically pure *N*-sulfinyl imines. Lewis acid activation of the *N*-sulfinyl imine substrates facilitates radical addition. Studies on the improvement of enantiocontrol,

(19) Both Brönsted acid mediated and oxidative cleavage strategies led to either decomposition or recovery of starting material along with minimal product formation.

(20) *N*-Sulfinyl aldimines preferentially adopt a conformation in which the oxygen atom and imino group are synperiplanar: (a) Dobrowolski, J. Cz.; Kawęcki, R. *J. Mol. Struct.* **2005**, *734*, 235−239. (b) Bharatam, P. V.; Uppal, P.; Kaur, A.; Kaur, D. *J. Chem. Soc., Perkin Trans. 2* **2000**, 43−50. (c) Tietze, L. F.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1998**, 1629−1637. (d) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555−2563.

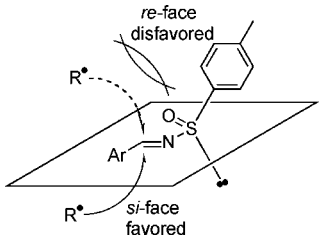


Figure 1. Rationale of stereochemical outcome.

substrate range, as well as addition of non-oxygenated carbon-centered radicals will be reported in due course.

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

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