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Radical Addition of Ethers to Imines Initiated by Dimethylzinc

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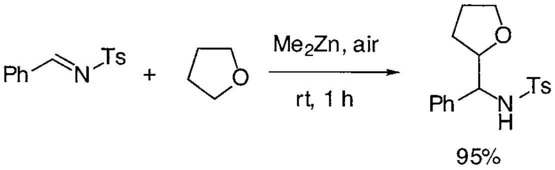
ABSTRACT



Ethers undergo addition to imines in the presence of dimethylzinc and air through a radical process.

Very recently, we described an amidophosphine-copper-catalyzed asymmetric addition of diethylzinc to imines.[1,2] In the presence of the copper catalyst, diethylzinc undergoes a highly enantioselective addition reaction with a variety of *N*-sulfonylimines to give the ethyl adducts in high yields. During further investigation of the reaction using dimethylzinc as a carbonucleophile, we unexpectedly encountered an addition reaction of ether to imine in high yield by the action of dimethylzinc and air. The reaction provides the first example of α-alkoxy radical generation through hydrogen abstraction of an ether using dialkylzincs.[3] Alkyl radicals are often generated through homolytic cleavage of carbon−heteroatom bonds, and their direct generation through C−H hydrogen abstraction has scarcely been reported. It is also noteworthy that radicals hardly undergo intermolecular addition to imines, while intramolecular addition to imines and intermolecular addition to oxime ethers are synthetically useful reactions.[4,5] Although nucleophilic addition of α-alkoxy radicals has been reported,[6,7] there has been no general and efficient entry for the addition to imines.

In the first stage of our studies, we attempted the methylation of benzaldehyde *N*-tosylimine **1a** with dimethylzinc in the presence of the chiral amidophosphine-copper catalyst.[2] The reaction in toluene failed to proceed, and **1a** was recovered unchanged. When THF was used as a solvent, we were pleased to find by TLC monitoring that **1a** disappeared after 18 h at room temperature and a new spot appeared. The product, however, was not **3a** but THF adduct **2a** in nearly quantitative yield. The addition of solvent THF

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[1] (a) Hasegawa, M.; Taniyama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153−10158. (b) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533−5536. (c) Kambara, T.; Tomioka, K. *J. Org. Chem.* **1999**, *64*, 9282−9285. (d) Tomioka, K. *Synthesis* **1990**, 541−549.

[2] (a) Nagai, K.; Fujihara, H.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Chem. Lett.* **2002**, 8−9. (b) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056.

[3] Radical generation with diethylzinc involving halogen abstraction has been reported: (a) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951−3961. (b) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189−9193. (c) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148−1150. (d) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335−6336.

[4] For reviews of radical addition to C═N bonds, see: (a) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695−713. (b) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496. (c) Naito, T. *Heterocycles* **1999**, *50*, 505−541. (d) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594. For other excellent reviews of radical reactions, see: (e) Yet, L. *Tetrahedron* **1999**, *55*, 9349−9403. (f) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069. (g) Giese B. In *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds, Organic Chemistry Series*; Baldwin, J. E., Ed.; Pergamon Press: Elmsford, NY, 1986; Vol. 5.

[5] For selected recent examples of alkyl radical addition to C═N bonds, see: (a) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131−134. (b) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922−9923. (c) Halland, N.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290−1295. (d) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190−12191. See also ref 3a−c.

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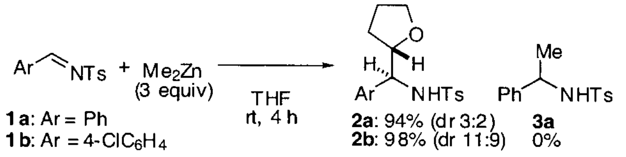
occurred even in the absence of the phosphine and copper(II) to give **2a** as a 3:2 mixture of two diastereomers in 94% yield (Scheme 1).

Scheme 1. Addition of THF to **1a** and **1b**



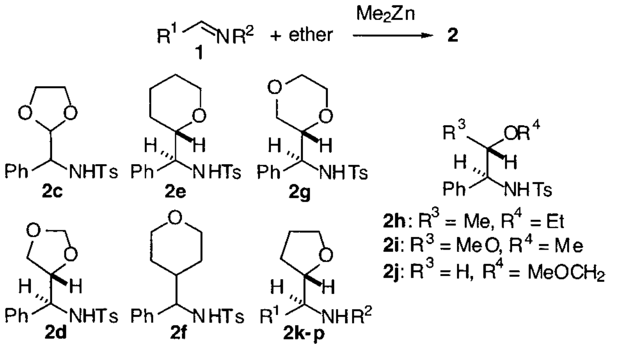
The reaction of 1 mmol of 4-chlorobenzaldehyde *N*-tosylimine **1b** with 3 molar equiv of dimethylzinc in 22 mL of THF under argon atmosphere at room temperature (Method A)[8] for 4 h gave **2b** in 98% yield with a diastereomeric ratio (dr) of 11:9. The structure including the relative configuration was confirmed by the X-ray crystallographic analysis of the major isomer of **2b**.[9] The CAChe MM3 calculation of **2a** gave the coupling constants between the adjacent methine protons of 6.2 and 4.2 Hz for major and minor isomers, respectively, showing good agreement with those observed, 5.8 and 4.6 Hz, respectively. The major diastereomers show a larger coupling constant of the methine protons (5.2−6.8 Hz) than the minor diastereomers (4.0−5.8 Hz).

Cyclic ethers other than THF are also applicable. 1,3-Dioxolane reacted with **1a** stereo- and regioselectively to afford **2c** in 77% yield together with **2d** (dr 9:2) in 22% yield (Table 1, entry 1). Six-membered THP reacted with **1a** giving **2e** (dr 13:7) in 76% along with **2f** in 7% yield (entry 2). 1,4-Dioxane was also a good nucleophile and provided **2g** (dr 10:3) in 84% yield (entry 3).

Linear ethers are also applicable as nucleophiles. Diethyl ether reacted with **1a** to afford **2h** (dr 11:9) in 77% yield (entry 4). The reaction with dimethoxymethane gave two regioisomers **2i** and **2j** in 40 and 30% yield, respectively (entry 5).

The reaction also proceeded whether an imine had an electron-withdrawing or -donating group. In addition to **1b**, which has an electron-withdrawing group, imines **1c**, **1d**, and **1e** having an electron-donating 4- or 2-substituted phenyl group were applicable as reaction partners, producing the corresponding THF adducts **2k** (80%, dr 3:2), **2l** (92%, dr 13:7), and **2m** (91%, dr 7:3), respectively (entries 6−8).

Table 1. Addition of Ethers to Imines Initiated by Dimethylzinc Using Method A



entry	imine			ether	*t* (h)	product[a] **2**	yield (%)
	1	R¹	R²				
1	**1a**	Ph	Ts	1,3-dioxolane	18	**2c**	77
						2d	22
2	**1a**	Ph	Ts	THP	24	**2e**	76
						2f	7
3	**1a**	Ph	Ts	1,4-dioxane	24	**2g**	84
4[b,c]	**1a**	Ph	Ts	Et_2O	42	**2h**	77
5[b,c]	**1a**	Ph	Ts	$(MeO)_2CH_2$	144	**2i**	40
						2j	30
6	**1c**	PMP	Ts	THF	16	**2k**	80
7	**1d**	4-tol	Ts	THF	7	**2l**	92
8	**1e**	2-tol	Ts	THF	16	**2m**	91
9	**1f**	Ph	Moc	THF	5	**2n**	76
10[b]	**1g**	Ph	PMP	THF	18	**2o**	80
11[d]	**1h**	$Ph(CH_2)_2$	PMP	THF	42	**2p**	75

[a] The dr was from 9:2 to 11:9 (see text). [b] Me_2Zn (6 equiv). [c] Conducted at 0 °C. [d] Me_2Zn (10 equiv).

Imines bearing an N-substituent other than a tosyl group are sufficiently reactive to give ether adducts. *N*-Methoxycarbonyl (Moc) imine **1f** reacted with THF to give **2n** (dr 7:3) in 76% yield (entry 9). Electron-donating *N*-4-methoxyphenyl (PMP) imine **1g** was converted to **2o** (dr 13:7) in 80% yield (entry 10). It is noteworthy that 3-phenylpropanal *N*-PMPimine **1h** reacted with THF, giving **2p** (dr 3:2) in 75% yield (entry 11).

The reaction seems to be initiated by a trace amount of oxygen to generate methyl radical from dimethylzinc.[3,10] Under an argon atmosphere, with silicon grease applied to the connections of the apparatuses (Method B),[8] the conversion of **1a** to **2a** in THF was only 4% after 48 h, and most

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(6) (a) Mosca, R.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron* **2001**, *57*, 10319−10328. (b) Kim. S.; Kim, N.; Chung, W.-j.; Cho, C. H. *Synlett* **2001**, 937−940. (c) Hirano, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 2457−2458. (d) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 613−615. (e) Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H. *Chem. Commun.* **1999**, 1745. (f) Alves, M. J.; Gilchrist, T. L.; Sousa, J. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1305−1310. (g) Clark, A. J.; Rooke, S.; Sparey, T. J.; Taylor, P. C. *Tetrahedron Lett.* **1996**, *37*, 909−912. (h) Ishida, A.; Sugita, D.; Itoh, Y.; Takamuku, S. *J. Am. Chem. Soc.* **1995**, *117*, 11687−11694. (i) Citterio, A.; Filippini, L. *Synthesis* **1986**, *6*, 473. (j) Fraser-Reid, B.; Anderson, R. C.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977**, *55*, 3986−3995. (k) Jacobs, R. L.; Ecke, G. G. *J. Org. Chem.* **1963**, *28*, 3036−3038.

(7) Intramolecular nucleophilic addition of ether radical was nicely applied to the G ring formation of ciguatoxin by Hirama et al.: Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904−1907 and references therein.

(8) Three methods, A−C, are described in this paper. A trace amount of air-oxygen seemed to enter the reaction flask through the connections of the apparatuses in Method A. Silicon grease on the connections prevented air invasion in Method B.

(9) The structure of the major isomer was presented.

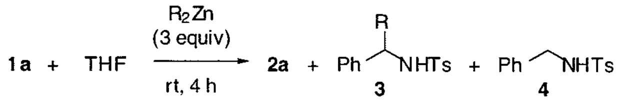
(10) Generation of an alkyl radical by the autoxidation of trialkylborane is well-known and has been widely studied since Brown's report: (a) Brown, H. C.; Kabalka, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 714−716. For recent examples for use of triethylborane−air as a radical initiator, see: (b) Guindon, Y.; Prévest, M.; Mochirian, P.; Guérin B. *Org. Lett.* **2002**, *4*, 1019−1022. (c) Kitagawa, O.; Yamada Y.; Sugawara, A.; Taguchi, T. *Org. Lett.* **2002**, *4*, 1011−1013. (d) Williams, A. L.; Grillo, T. A.; Comins, D. L. *J. Org. Chem.* **2002**, *67*, 1972−1973. (e) Mima, K.; Ishihara, T.; Kuwahata, S.; Konno, T.; Yamanaka, H. *Chem. Lett.* **2002**, 192−193. (f) Mancheño, M. J.; Ramírez-López, P.; Gómez-Gallego, M.; Sierra, M. A. *Organometallics* **2002**, *21*, 989−992.

of **1a** was recovered. With an airstream of constant bubbling (10 mL/h) (Method C), the reaction was markedly accelerated to give **2a** in 95% yield after 1 h.[8] The photochemical process[6h] is ruled out because the reaction proceeded smoothly under the dark conditions, giving **2a** in 95% yield.

Interestingly, established and standard radical generation conditions were not operative in this reaction. Triethylborane−air conditions[6e] gave rise to the production of only ethyl adduct **3b** in 29% yield after 48 h. Dibenzoyl peroxide in refluxing THF[6g,k] resulted in the production of a trace amount of **2a** and the nearly quantitative recovery of **1a** after 24 h.

Three other organozinc reagents were evaluated for their radical-generating behavior in the reaction of **1a** with THF by the Method A (Table 2). Diethylzinc produced **2a** in 48% yield along with ethyl adduct **3b** (33%) and reduction product **4** (2%) (Table 2, entry 2). Diisopropylzinc gave **2a** (6%), isopropyl adduct **3c** (34%), and **4** (27%) (entry 3). Diphenylzinc produced phenyl adduct **3d** in 7% yield, and most of **1a** was recovered (entry 4). Production of **2a** and the bond dissociation energy (bde) of R−H bond seem related.

Table 2. Bond Dissociation Energy and Addition of THF to **1a** Initiated by Zinc Reagents using Method A[a]

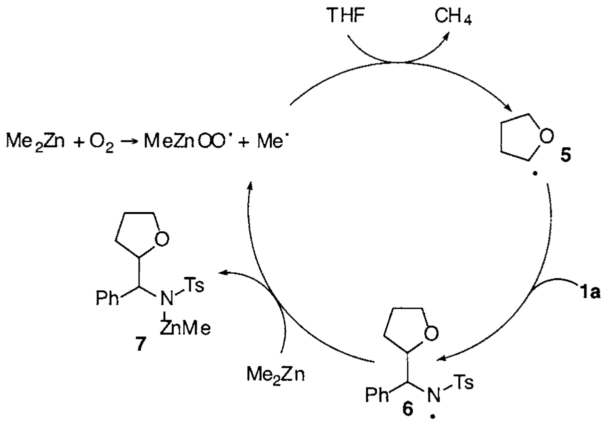


entry	R	bde[b] (kJ/mol)	**2a** yield (%)	**3**	yield of **3** produced (%)	**4** yield (%)
1[c]	Me	440	94	**3a**	0	0
2	Et	411	48	**3b**	33	2
3	*i*-Pr	398	6	**3c**	34	27
4	Ph	464	0	**3d**	7	0

[a] No products other than **2a**, **3**, and **4** were obtained. [b] Data from ref 11. [c] Data from Scheme 1 for comparison.

Due to its unstability, the methyl radical, once generated, would abstract an α-hydrogen of an ether rapidly enough,[11] and the resulting ether radical reacts with an imine. The hydrogen abstraction with more stable ethyl and isopropyl radicals would be slower and the direct reaction of an alkyl radical with an imine competes to give the alkyl adducts.

Scheme 2. Plausible Mechanism for the THF Addition to **1a**



We envision the mechanism of the reaction as follows (Scheme 2). Dimethylzinc and oxygen would initiate the reaction by releasing a methyl radical,[3] which then abstracts an α-hydrogen from THF to generate THF radical **5**. Aminyl radical **6** formed by the addition of **5** to imine **1a** reacts with dimethylzinc to produce zinc amide **7**, which gives adduct **2a** after aqueous workup, and a methyl radical, which is involved in the further reaction.[3a−c] The direct production of **2a** and **5** through the α-hydrogen abstraction from THF by **6** might be, if any, a minor pathway because the reaction requires a superstoichiometric amount of dimethylzinc.

In conclusion, a new methodology for the generation and the reaction of an ether radical with an imine was developed by employing dimethylzinc as a radical source. The reaction failed to proceed with other radical sources such as triethylborane or dibenzoyl peroxide. Although organozinc reagents are versatile and established sources of carbonucleophiles,[12] the dimethylzinc-based radical generation from an ether would become a quite unique and promising methodology.

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Supporting Information Available: Experimental procedures for Methods A−C, characterization data of the products, MM3 calculation data of **2a**, and X-ray data of major **2b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The α-C−H bde of THF has been reported to be 385 kJ/mol. McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532.

(12) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757−824.