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Initiator-Dependent Chemoselective Addition of THF Radical to Aldehyde and Aldimine and Its Application to a Three-Component Reaction

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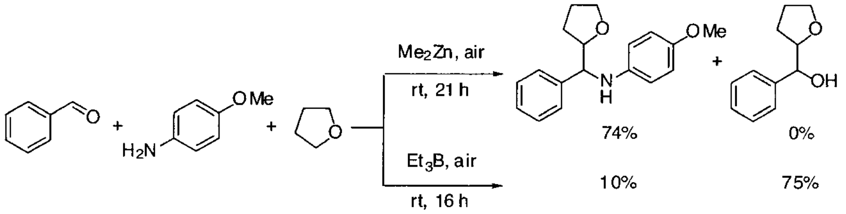
ABSTRACT



The product distribution of the three-component reaction of aldehydes, arylamines, and THF was dependent on a radical initiator, preferentially giving the corresponding THF adducts of imines with dimethylzinc and adducts of aldehyde with triethylborane.

Chemoselectivity has been one of the goals of organic chemistry. Especially differentiation of C═O and C═N double bonds as nucleophilic targets has been the topic of recent allylation[1] and Mannich-type reactions.[2] However, to the best of our knowledge, there has been no report on such differentiation for radical reactions.[3] We describe herein that a THF radical[4] undergoes chemoselective addition to aldehydes and aldimines depending on the choice of radical-generating agents, dimethylzinc and triethylborane. The chemoselectivity was well demonstrated in the three-component reaction of aldehydes, amines, and THF.

We have recently reported radical addition reaction of ethers with aldimines, in which methyl radicals, generated from dimethylzinc as an initiator and molecular oxygen, abstract an α-hydrogen of ethers to generate ether radicals,

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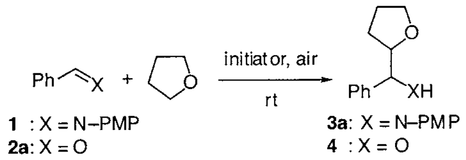
consequently giving the ether adducts of aldimines in high yields.[5−7] For example, the reaction of benzaldehyde *N*-4-methoxyphenylimine (*N*-PMP-imine) **1** with THF was conducted in the presence of 6 equiv of dimethylzinc under constant air bubbling (10 mL/h), producing THF adduct **3a** in 83% yield after 5 h at room temperature (Table 1, entry 1).[8] As a logical extension of our approach, we then examined the reaction of benzaldehyde **2a** as a radical acceptor, instead of aldimine **1**. However, the addition reaction of a THF radical with **2a** was sluggish under the dimethylzinc−air conditions, producing THF adduct **4** in less than 8% yield even after 5 days (entry 3). This poor efficiency is in dramatic contrast to the reaction of **2a** with the use of triethylborane−air as a radical initiator (a modified Nagaoka procedure),[4a,g] giving **4** in 81% yield after 6 h (entry 4).[9,10] It is also important to note that the reaction of **1** under the triethylborane (12 equiv)−air conditions gave **3a** in 63% yield after prolonged reaction time of 18 h (entry 2).[11]

Table 1. Initiator-Dependent Chemoselective Addition of THF Radical to Benzaldehyde PMP-imine **1** and Benzaldehyde **2a**

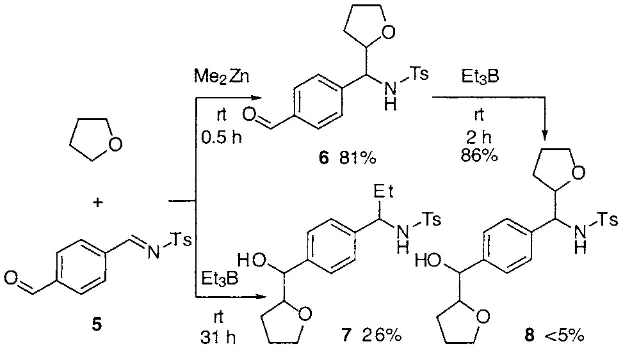


entry	**1**/**2a**	initiator (equiv)	*t* (h)	product	yield (%)
1	**1**	Me_2Zn (6)	5	**3a**	83
2	**1**	Et_3B (12)	18	**3a**[a]	63
3	**2a**	Me_2Zn (12)	120	**4**	<8
4	**2a**	Et_3B (12)	6	**4**	81

[a] An ethyl adduct of **1** was obtained in 26% yield.

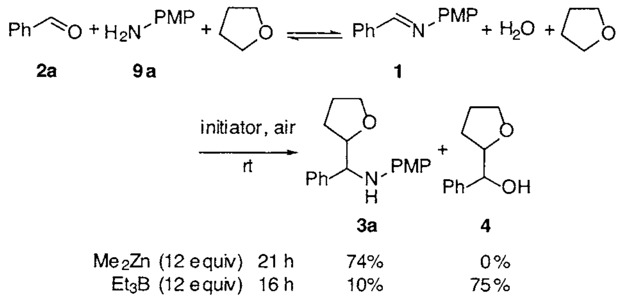
The initiator-dependent chemoselectivity was more highlighted by the reaction of imino-aldehyde **5** having both carbonyl and imino groups (Scheme 1). Under the dimethylzinc−air conditions, the THF radical preferentially reacted with the imino group to provide mono-THF adduct **6** in 81% yield, and no other products resulting from the reaction of THF with the aldehyde moiety were observed. In contrast, under the triethylborane conditions, the addition of THF occurred mainly to the carbonyl group, giving **7** as a major product in 26% yield and di-THF adduct **8** in less than 5% yield. Mono-THF adduct **6** further underwent the addition reaction with THF under the triethylborane−air conditions, giving **8** in 86% yield.

Scheme 1. Reaction of THF with Imino-aldehyde **5**



The chemoselectivity was more clearly demonstrated by the reaction of a THF solution of a mixture of **2a** and *p*-anisidine **9a**, those establishing equilibrium with an imine and water (Scheme 2). A solution of 1 mmol each of **2a** and **9a** in 22 mL of THF was treated with 12 mmol of an initiator (1.0 M solution in hexane) under a continuous air stream (0.5 mL/h) at room temperature. By the dimethylzinc

Scheme 2. Chemoselective THF Radical Addition Reaction of an Equilibrium Mixture of **2a** and **9a**



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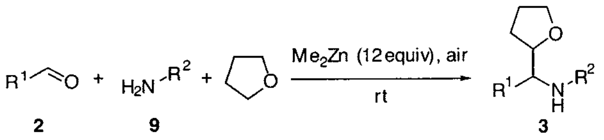
initiation, THF-imine adduct **3a** was preferentially isolated in 74% yield after 21 h, whereas THF-aldehyde adduct **4** was obtained in 75% yield along with **3a** (10%) and **9a** (65%) after 16 h under the triethylborane initiation. It is also interesting to note that the reaction of the equilibrium mixture in the presence of both initiators was not clean and gave a mixture of **3a** (13%), **4** (12%), ethyl adduct of aldimine (7%), and aldimine **1** (56% recovery) after 12 days.

The utility of the imine-selective reaction with the use of dimethylzinc initiator was further demonstrated by the following three-component reaction of various aldehydes, arylamines, and THF (Table 2).[12] A mixture of benzaldehyde **2a** with aniline **9b** and 4-trifluoromethylaniline **9c** in THF provided THF adduct **3b** in 66% yield and THF adduct **3c** in 47% yield (entries 2 and 3). The reaction also proceeded smoothly whether aldehydes had an electron-withdrawing or -donating group, giving **3d** in 64% yield from 4-chlorobenzaldehyde **2b** and **9a** and **3e** in 57% yield from *p*-anisaldehyde **2c** and **9a** (entries 4 and 5). Acyclic and cyclic aliphatic aldehydes **2d** and **2e** were also applicable, giving **3f** and **3g** in 50 and 44% yields, respectively (entries 6 and 7). Thus, the three-component reaction can be generalized.

Table 2. Chemoselective Three-Component Reaction with the Use of Dimethylzinc as an Initiator



entry	2	R¹	9	R²	*t* (h)	3	yield (%)
1	**2a**	Ph	**9a**	PMP	22	**3a**	74
2	**2a**	Ph	**9b**	Ph	16	**3b**	66
3	**2a**	Ph	**9c**	4-CF$_3$C$_6$H$_4$	22	**3c**	47
4	**2b**	4-ClC$_6$H$_4$	**9a**	PMP	22	**3d**	64
5	**2c**	PMP	**9a**	PMP	45	**3e**	57
6	**2d**	PhCH$_2$CH$_2$	**9a**	PMP	46	**3f**	50
7	**2e**	*c*-C$_6$H$_{11}$	**9a**	PMP	138	**3g**	44

The initiator-dependent chemoselective addition reaction can be generalized and is interesting. Initiation by dimethylzinc favors THF-imine addition, and triethylborane initiation provides a THF-aldehyde addition product. Mechanistic details for the origin of the chemoselectivity are the focus of our ongoing study.

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

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