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### Radical Addition of Ethers to Terminal Alkynes with High E-Selectivity

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Direct radical additions of ethers to terminal alkynes were investigated by using Me<sub>2</sub>Zn/O<sub>2</sub> as radical initiator to afford 2-vinyl ether derivatives with high E-selectivity, while reversed E/Z selectivity is obtained with  $Et_3B/O_2$ . Two competitive pathways are suggested for the formation of vinyl radical B: zinc-radical exchange (route a) followed by protonation

#### Introduction

Direct C-H functionalization via different synthetic methods has been fruitfully developed in the past decades. In this regard, radical approach has some significant advantages in terms of its efficiency to transform saturated C-H bonds and the mildness of the reaction conditions, and therefore, is of particular importance in organic synthesis.<sup>[1]</sup> α-Alkoxyalkyl radicals, generated through direct hydrogen abstraction from ethers by a radical source, have been reported to react with aldehydes, imines, amines, and electron-deficient alkenes to give heteroatom-containing compounds of various structural characteristics and functionalities.<sup>[2-4]</sup> In the light of these achievements, we were interested to investigate the radical addition of ethers onto electron-deficient terminal alkynes, and to explore a potential one-pot route leading to 2-vinyl ether derivatives.<sup>[3b,5]</sup>

To our delight, direct radical addition of ether onto terminal alkynes afforded 2-vinyl ether derivatives with a high degree of *E*-selectivity in Me<sub>2</sub>Zn/O<sub>2</sub> condition.<sup>[6]</sup> When Et<sub>3</sub>B/O<sub>2</sub> was used as radical source, the corresponding products were obtained with the reversed E/Z selectivities.

A series of deuteration experiments was then performed to elucidate the reaction mechanism. Two competitive reaction pathways, including routes a and b, ensued on the formation of vinyl radical intermediate **B**. In the major pathway (Me<sub>2</sub>Zn/O<sub>2</sub> condition), vinylzinc intermediates, in-situgenerated from vinyl radicals, gave exclusively E configura-

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provides *E*-configuration products exclusively through Zn(II) complexation. Hydrogen abstraction by vinyl radicals (route b) yields mainly Z isomers.

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tion products after protonation, in which, Me<sub>2</sub>Zn plays both as the mild radical initiator and as a Lewis acid complexing ligand.<sup>[7]</sup> In the competitive minor pathway thereof, the vinyl radical abstracts the ether  $\alpha$ -hydrogen atom to produce a mixture of low E/Z ratio products, which therefore, blemished otherwise perfect stereocontrol. To date, reports upon intermolecular radical hydrogen abstraction from sp<sup>3</sup>-hybrized C atoms by vinyl radical under the mild conditions are very scarce to the best of our knowledge.<sup>[8]</sup>

Vinyl radical intermediates have been reported to react with metallic reagents to give various metallic vinylides.<sup>[9]</sup> However, only one recent result described of trapping vinyl radicals with Me2Zn to provide vinylzinc derivatives for further transformation.<sup>[4a]</sup> In this paper, we also demonstrate that the in-situ generated vinylzinc intermediates can be transformed into iodo-substituted analogs and Negishi coupling products.

#### **Results and Discussion**

In preliminary studies, the reaction of THF and (3-chlorophenyl)acetylene was chosen as model system to examine various radical sources.<sup>[10]</sup> The optimal ratio of O<sub>2</sub> to N<sub>2</sub>  $(O_2/N_2 = 1:1000)$  was first identified. A series of experiments was then performed,<sup>[11]</sup> and the results are shown in Table 1.

It was found that 3 equiv. of dimethylzinc give mainly E-**3b** in 24% yield (Table 1, entry 1) with a high E selectivity  $(E/Z \approx 13.5:1)$ . 3 equiv. of diethylzinc provide E-3b in 18% yield (Table 1, entry 2), along with small amounts of ethyl adduct; 3 equiv. of triethylborane produce a mixture of E/ Z-3b (E/Z = 1:2.3) in 33% of yield (Table 1, entry 3). When the amount of Me<sub>2</sub>Zn was increased to 5 equiv., the reaction yield was improved to 41% (Table 1, entry 5). Pro-

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Entry

Table 1. Radical addition of THF onto (m-chlorophenyl)acetyl-ene.<sup>[a]</sup>



Linti	maater (equili)	remp# unie [ii]	Tieres [/ o]	B/B futto
1	$Me_2Zn$ (3)	r.t./5	24	13.5:1 <sup>[f]</sup>
2	$Et_2Zn$ (3)	r.t./5	18	5.6:1
3	Et <sub>3</sub> B (3)	r.t./5	33	1:2.3
4	$Et_3B(5)$	r.t./5	60	1:2.3
5	$Me_2Zn$ (5)	r.t./5	41	Nd <sup>[e]</sup>
6 <sup>[d]</sup>	$Me_2Zn$ (8)	r.t./8	53	20:1

[a] Unless noted, all reactions were carried out at 0.2 mmol scale in 4 mL of THF under a mixture of  $O_2/N_2$  atmosphere at room temp. [b] E/Z ratio was determined by <sup>1</sup>H NMR spectrum of the crude product. [c] Me<sub>2</sub>Zn was added in two batches. [d] Me<sub>2</sub>Zn was added in three batches. [e] Nd = not determined. [f] E/Z ratio in Me<sub>2</sub>Zn condition ranged from 25% to 10%.

longing the reaction time and lowering the reaction temperature turned out to be disadvantageous. Further studies then identified the optimal condition to be 0.2 mmol of (3-

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The scope and limitations of this reaction were then explored. As shown in Table 2, a series of aromatic alkynes readily reacts with several cyclic and acyclic ethers to provide the corresponding 2-vinyl ether derivatives. The reaction of phenylacetylene with THF gives (E)-tetrahydro-2styrylfuran (3a) in 28% yield with E selectivity of 8.5:1 (Table 2, entries 1). The presence of electron-withdrawing groups, such as chloro, bromo and fluoro attached to the aromatic alkynes enhances the reactivity and improves the yields somewhat (Table 2, entries 2–12). The products' E/Zselectivity varies with different substitution patterns on the aryl groups.<sup>[12]</sup> For example: the E/Z selectivity for the reaction of (p-bromophenyl)acetylene with THF is about 7:1 (Table 2, entries 6), while the reaction of THF with (*m*-chlorophenyl)- and (p-fluorophenyl)acetylene gives products with a selectivity of 20:1 and 29:1, respectively (Table 2, entries 2, 10). However, the E/Z selectivity for the reaction of (3,4-dichlorophenyl)acetylene and (2,4-difluorophenyl)-

Table 2. Addition of cyclic and acyclic ethers onto the terminal aromatic alkynes initiated by Me<sub>2</sub>Zn.<sup>[a]</sup>

		۲ 1	her $\frac{Me_2Zn}{R^{1}}$ R <sup>1.7</sup>	D R <sup>2</sup> 3-7		
		1a: R = H 1b: R = 3-chloro 1c: R = 4-bromo 1d: R = 4-fluoro 1e: R = 2,4-difluoro 1f: R = 3,4-dichloro				
		<b>5b</b> : R = 3-chloro <b>5c</b> : R = 4-bromo	<b>6b</b> : R = 3-chloro <b>6c</b> : R = 4-bromo	<b>7b</b> : R = 3-chloro <b>7c</b> : R = 4-bromo		
ry	1	Ether 2	Product	Yield [%]	$E/Z^{[b]}$	
	1a	THF	3a	28	8.5:1	
	1b	THF	3b	53	20:1	
		THP	4b	39	13:1	
		1,3-dioxolane	5b	63 (3.7:1)	13.5:1	
			6b		9.5:1	
		diethyl ether	7b	41	>99:1	
	1c	THF	3c	51	7:1	
		THP	4c	40	16.5:1	
		1,3-dioxolane	5c	56 (4:1)	3:1	
			60		3.5:1	
		diethyl ether	7c	47	>99:1	
	1d	THF	3d	43	29:1	
	1e	THF	3e	37	14:1	
	1f	THF	3f	35	8.5:1	

[a] Unless noted, all reactions were carried out at 0.2 mmol scale with 8 molar equiv. of dimethylzinc (added in three batches) in 4 mL of THF under a mixture of  $O_2/N_2$  atmosphere at room temperature (summer) for 8 h. [b] The *E*/*Z* ratio was determined by <sup>1</sup>H NMR spectrum of the crude products.

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acetylene is only 8.5:1 and 14:1 (Table 2, entries 11, 12). It was also found that the reaction of THF with (*p*-ni-trophenyl)acetylene does not lead to desired products.<sup>[13]</sup>

Cyclic ethers other than THF and acyclic ether are also applicable in the reaction. 1,3-Dioxolane reacts with **1b** to afford **5b/6b** (**5b/6b** = 3.7:1, Table 2, entries 4)<sup>[14]</sup> in a total yield of 63%, and with a *E/Z* selectivity of 13.5:1 and 9.5:1, and with **1c** to afford **5c/6c** (**5c/6c** = 4:1, Table 2, entries 8) in 56% yield with a *E/Z* selectivity of 3:1 and 3.5:1. THP reacts with **1b** to give **4b** in 39% yield (*E/Z* = 13:1, Table 2, entries 3), and with **1c** to give **4c** in 40% yield (*E/Z* = 16.5:1, Table 2, entries 7). Linear ethers were also investigated. For example, diethyl ether reacts with **1b** and **1c** to afford **7b** in 41% yield and **7c** in 47% yield with *E* selectivity up to 99:1 (no *Z*-isomer was detected in the reaction mixture, Table 2, entries 5, 9).

Deuteration experiments were performed to probe the reaction mechanism. As shown in Scheme 1, when the reaction of (*m*-chlorophenyl)acetylene (**1b**) in THF was quenched with 99% D<sub>2</sub>O, deuterated E/Z-**3b** was readily obtained in 50% yield (E/Z = 15:1). It was found that 87% deuterium atom was incorporated into E-**3b** at C<sup>2</sup> position, with less than 1% D into Z-3b (Scheme 1). In the reaction of (3,4-dichlorophenyl)acetylene with THF, the deuterium atom ratio in *E*-3f was only 41%, and with 0% D incorporated in *Z*-3f (E/Z = 8:1).

The following plausible mechanism is proposed: as shown in Scheme 2, a methyl radical, generated in-situ from dimethylzinc by a trace amount of oxygen, abstracts the 2-H of the ether reactant **2** to provide an  $\alpha$ -alkoxy radical intermediate **A**, which then undergoes a direct radical addition onto terminal alkyne **1** to form a new C–C bond and a vinyl radical intermediate **B**. In the major reaction pathway, trapping of the intermediate **B** with Me<sub>2</sub>Zn produces an alkenylzinc intermediate **C** (route a)<sup>[4a,15]</sup> and a methyl radical for further reaction. Quenching the reaction with water or possible zinc-proton exchange with terminal alkyne **1** provides the desired 2-vinyl-substituted ether derivative **3**. The complexation of Zn<sup>II</sup> with the oxygen atom of the ether in the intermediate **C**, as illustrated in Scheme 2, leads to the formation of the *E*-alkenyl ether products.

The existence of the alkenylzinc intermediate C was partly proved by deuteration experiments (Scheme 1), in which, intermediate C was eventually caught by  $D_2O$  to af-

D/H







Scheme 2. A plausible mechanism to afford E/Z configuration 2-vinyl ether derivatives.

ford *E* configuration products with high deuterium content. Interestingly, some of the C<sup>2</sup>-H remained in deuterated *E*-**3b** and *E*-**3f**, maybe as a result of zinc-proton exchange of intermediate C with terminal alkyne 1, or with trace amounts of water in the reaction mixture.<sup>[16]</sup>

The results in Scheme 1 show that no deuterium atoms are incorporated into *Z* configuration isomers, which implies that route b affords *E*-configuration products exclusively. We speculate that *Z*-isomers might be generated from the alternative route b. As shown in Scheme 2, abstraction of a hydrogen atom of the ether reactant **2** by the vinyl radical intermediate **B** regenerates the  $\alpha$ -alkoxy radical **A**, and provides the product **4** in low *E*/*Z* selectivity.<sup>[17]</sup> The tendency of the reaction to take the minor pathway (route b) would be enhanced by the high reactivity of the 2-position hydrogen atom of the ether reactants **2**. The existence of route b was partly proved by deuterium experiments and by the relative low *E*/*Z* selectivity in the reaction of dioxolane, THF and the high *E*/*Z* selectivity in the reaction of ethyl ether.<sup>[18]</sup>

To evaluate the extent of the zinc-proton exchange between intermediate **C** and terminal alkyne **1**, the reaction of deuterated (3,4-dichlorophenyl)acetylene (over 99% deuterium atom attached to the terminal alkyne **C** atom) in THF was carried out by using Me<sub>2</sub>Zn as radical source. The reaction was quenched by deuterated water. As shown in Scheme 3, about 79% deuterium was incorporated into C<sup>2</sup> position of *E*-**3f**-*d*, while no deuterium was detected in C<sup>2</sup> position of compound *Z*-**3f**-*d*. If the reaction was quenched by H<sub>2</sub>O, 20% deuterium was attached to C<sup>2</sup> position of *E*-**3f**-*d*. These results suggest that the reaction of intermediate **C** with terminal alkyne **1** produces unreacted zinc alkynylide in the reaction mixture and thus reduces the yield.



Experiments to trap intermediate **C** with other electrophiles were also performed. When the reaction mixture of THF radical with (*m*-chlorophenyl)acetylene was treated with iodine, an iodo-substituted analog **8** was obtained in 45% yield (Scheme 4).<sup>[19]</sup> Negishi coupling of intermediate **C** with iodobenzene affords the corresponding product **9** in 30% yield.<sup>[19,20]</sup>



Scheme 4. Experiments of trapping intermediate C with different electrophiles.

We then turn to investigate the reaction details of the route b by using Et<sub>3</sub>B/O<sub>2</sub> Radical source. The reaction of (*m*-chlorophenyl)acetylene with THF in the condition of 5 equiv. Et<sub>3</sub>B afforded **3b** in 60% yield with a reversed E/Z selectivity (E/Z = 1:2.3, Scheme 5). Quenching the reaction with I<sub>2</sub> enhanced the Z/E ratio (E/Z = 1:3.8).<sup>[21]</sup> The reaction of (*p*-bromophenyl)acetylene in THF gave similar results. The major products – (Z) configuration vinyl ethers in this case, were primarily resulted from hydrogen-abstracting route b. Addition of I<sub>2</sub> quenched the *E* configuration vinyl-borane intermediates generated in route a, and then improved the Z isomer ratio. The reaction of diethyl ether with **1b**, which gave no Z-isomer in Me<sub>2</sub>Zn/O<sub>2</sub> condition, because of low reactivity of its 2-position hydrogen, yielded a mixture of products in a low E/Z ratio with a reduced yield.

The reaction of (*m*-chlorophenyl)acetylene with a mixture of 90% [D<sub>8</sub>]THF and 10% THF was performed by employing Et<sub>3</sub>B/O<sub>2</sub> in order to determine the source of the



Scheme 3. The reaction of deuterated (3,4-dichlorophenyl)acetylene with THF.

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Scheme 5. Experiments with  $Et_3B/O_2$  as radical initiator. <sup>[a]</sup>  $Et_3B$  was added in two batches; <sup>[b]</sup> quenching the reaction with NH4Cl (aq.); <sup>[c]</sup> quenching the reaction with 12; <sup>[d]</sup> The E/Z ratio was determined by <sup>1</sup>H NMR spectrum of the crude products.

hydrogen atom abstracted by intermediate **C** in route b (Scheme 2).<sup>[22,23]</sup> It was found that 25% deuterium atom was incorporated into C<sup>2</sup> position of *E*-**3b**-*d*, while about 27% percent deuterium into C<sup>2</sup> position of compound *Z*-**3b**-*d* (Scheme 6). These results indicate that the ether reactants can act as source for hydrogen atoms abstracted by



Scheme 6. The reaction of (*m*-chlorophenyl)acetylene with 90% deuterated  $[D_8]$ THF and 10% THF. <sup>[a]</sup> 10% THF solvent come from Et<sub>3</sub>B (THF solution).



Scheme 7. Possible explanation for the observed Z-selectivity in route b.

vinyl radicals in route b. Route b competes with route a, as a minor pathway for the  $Me_2Zn/O_2$  system and as a major one for  $Et_3B/O_2$  conditions.

We assume that ether reactants, as indicated in Scheme 7, readily approach the vinyl radical intermediate **B** from the opposite direction of the ether functionality in route b.<sup>[24,25]</sup> This might explain why mainly Z configuration products are observed for  $Et_3B/O_2$  reaction conditions.

#### Conclusions

We have investigated the direct radical addition of a variety of cyclic and acyclic ethers onto terminal alkynes, which, by using Me<sub>2</sub>Zn/O<sub>2</sub> as radical initiator, afford a series of 2-vinyl ether derivatives with a high degree of *E*selectivity. With Et<sub>3</sub>B/O<sub>2</sub> as radical source the corresponding products are obtained with reversed *E/Z* selectivity. Two competitive reaction pathways ensue over the formation of vinyl radical intermediate **B**. Zinc-radical exchange (route a) produces the alkenylzinc intermediate **C**, in which Zn<sup>II</sup> acts as a Lewis acid ligand, chelating with the ether oxygen atom to control the alkene's configuration, and to provide *E*-configuration products exclusively after protonation. However, hydrogen abstraction from the ether by the vinyl radical (route b) would instead give mainly the *Z* configuration isomers.

#### **Experimental Section**

General Procedure for the Radical Addition of Ethers Onto Terminal Alkynes: A 1.0 M solution of dimethylzinc in hexane (0.6 mL, 0.6 mmol, 3.0 equiv.) was added to a solution of (*m*-chlorophenyl) acetylene (1b) (27 mg, 0.20 mmol) in THF (4 mL, 50 mmol, 250 equiv.) under a mixture of  $O_2/N_2$  atmosphere ( $O_2/N_2 = 1:1000$ ) at room temperature. 3 h later, another batch of dimethylzinc solution (0.6 mL, 0.6 mmol) was added. 6 h later, the third batch of dimethylzinc solution (0.4 mL, 0.4 mmol) was added. After stirred at room temp. for 8 h, the reaction mixture was quenched by the addition of saturated NH<sub>4</sub>Cl solution, and then was extracted with dichloromethane (3 × 5 mL). Combined organic layer was washed with saturated aqueous sodium hydrogen carbonate, brine, and dried with sodium sulfate. After removal of the solvent, purification of the resulting crude material by column chromatography (petroleum ether/ethyl acetate = 80:1) afforded the desired product *E*-**3b** (22 mg, 53%).

**Supporting Information** (see also the footnote on the first page of this article): All reaction procedures and spectroscopic data for the products.

### Acknowledgments

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- [11] Prolonged reaction time resulted in low yields of products, so small amounts of  $O_2$  was added to the system in order to accelerate the reaction.
- [12] Although intermediate **B** can be stabilized by the electron-withdrawing groups, the effect of different substitution on E/Z selectivity is still unclear.
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- [22] It was found that  $[D_8]$ THF radical can not be generated directly by ethyl radical. However, this can be obtained by addition of a small amount of THF to the solvent  $[D_8]$ THF.
- [23] Me<sub>2</sub>Zn/O<sub>2</sub> system was also tested, but no Z-isomer was obtained; see Supporting Information.

# SHORT COMMUNICATION

[25] It was suggested by a referee of this article that the preferential formation of the Z adduct might as well involve two sp<sup>2</sup>-isomeric radicals (going through an sp intermediate). For some examples of highly Z-selective radical additions, see: a) B. A. Trofimov, N. K. Gusarova, S. N. Arbuzova, N. I. Ivanova, A. V. Artem'ev, P. A. Volkov, I. A. Ushakov, S. F. Malysheva, V. A. Kuimov, J. Organomet. Chem. 2009, 694, 677; b) B. A. Trofimov, S. F. Malysheva, N. K. Gusarova, N. A. Belogorlova, S. F. Vasilevsky, V. B. Kobychev, B. G. Sukhov, I. A. Ushakov, Mendeleev Commun. 2007, 17, 181; c) K. Miura, K. Oshima, K. Utimoto, Bull. Chem. Soc. Jpn. 1993, 66, 2356; d) M. B. Faraoni, V. I. Dodero, J. C. Podesta, ARKIVOC 2005, 88.

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