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Radical α-C−H Hydroxyalkylation of Ethers and Acetal

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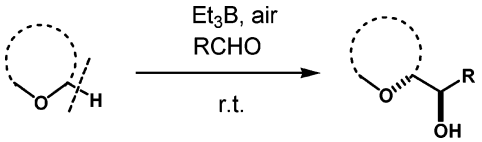

Ethers and an acetal were found to undergo direct intermolecular addition to aldehydes under the Et_3B/air conditions. This study presents a very unique and simple means for the radical α-C−H hydroxyalkylation of oxygen-containing compounds.

Carbon−carbon (C−C) bond formation via the C−H functionalization of organic molecules is a current topic of interest in synthetic organic chemistry.[1−3] Ethers and the derivatives thereof are among the most attractive substrates in C−H chemistry because of their ubiquity in molecular architecture. Radical C−H functionalization is particularly useful for this purpose due to the susceptibility to hydrogen abstraction of C−H bonds α to ethereal oxygen, which makes possible the selective chemical transformation.[4−6] Several notable means for direct C−C bond formation via the radical-mediated α-hydrogen abstraction of ethers involve the use of triflon derivatives,[7] dimethylzinc/air,[8] phthalimide-*N*-oxyl (PINO) radical,[9] 2-chloroethylsulfonyl oxime ethers,[10] and *N*-acyl aldohydrazones.[11]

We have previously reported a novel means for the radical C−H transformation of THF with aldehydes using Et_3B/air[12,13] and Et_3B/*tert*-butyl hydroperoxide (TBHP)[14,15] (Scheme 1). The ease of operation and relatively mild conditions are the merits of the former, whereas a short reaction time makes the latter highly efficient. We have also demonstrated that the direct transformation of ethereal α-C−H bonds into C−C bonds leads to greater flexibility in the synthetic design of oxygenated molecular frameworks (Scheme 2). For instance, the C−H functionalization of THF enabled the unprecedented chemical transformation of the common cyclic ether into a γ-(hydroxyalkyl)-γ-butyrolactone that serves as a bioactive

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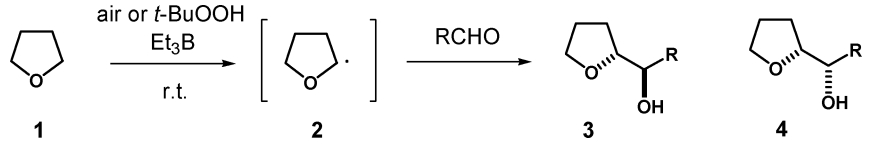
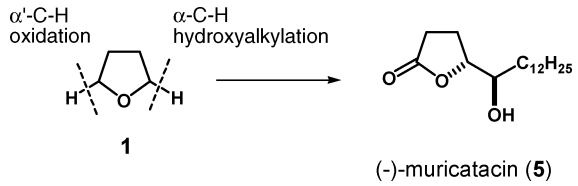
SCHEME 1. α-C−H Hydroxyalkylation of THF with Aldehydes under Et_3B/Air or Et_3B/TBHP Conditions



SCHEME 2. α- and α′-C−H Functionalization of THF



SCHEME 3. Radical Transformation of the C−H Bond Adjacent to Ethereal Oxygen

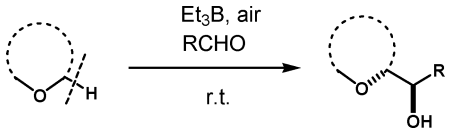


TABLE 1. α-C−H Hydroxyalkylation of THF (1) with Aldehydes under Et_3B/Air Conditions[a]

entry	aldehyde	time (h)	yield (%)[b]	**3**:**4**[c]
1	4-$MeOC_6H_4CHO$ **a**	13	83	89:11
2	PhCHO **b**	11	76	86:14
3	Piperonal **c**	8	80	88:12
4	2-BrC_6H_4CHO **d**	5	82	71:29
5	$C_{12}H_{25}CHO$ **e**	11	61[d]	64:36
6	4-$MeOC_6H_4CHO$ **a**	33[e]	78	88:12

[a] The reaction was carried out with a slight modification of the original protocol (ref 12); 120 equiv of THF, 6 equiv of Et_3B with continuous admission of air (ca. 30 mL·h^{-1}·mmol aldehyde^{-1}). [b] Isolated yields based on aldehydes. [c] Ratio determined by ^1H NMR measurement of the threo/erythro mixture. [d] Two-step yields of diastereomeric acetates derived from **3e**/**4e**. [e] Air was introduced at a rate of 20 mL·h^{-1}·mmol aldehyde^{-1}.

compound as well as a useful building block in organic synthesis.[16]

In the present study, various ethers and an acetal are shown to undergo the α-C−H hydroxyalkylation under the Et_3B/air conditions, thereby demonstrating the wide applicability of this novel chemistry that provides a unique methodology for the radical C−H functionalization of oxygen-containing molecules (Scheme 3).

We initially set about the optimization of the originally reported Et_3B/air[12] conditions for the C−H transformation of THF. It was found that under the Et_3B/TBHP conditions, higher yields of the α-C−H hydroxyalkylation products were obtained by increasing the amounts of the ether substrate and Et_3B. This is also the case for the Et_3B/air system (Table 1). Thus, aromatic and aliphatic aldehydes were completely consumed within the time shown in Table 1 by using excess THF and Et_3B. A representative procedure is as follows: to a solution of aldehyde in THF was added Et_3B at room temperature under argon atmosphere. After removal of the argon balloon, the mixture was stirred at the same temperature

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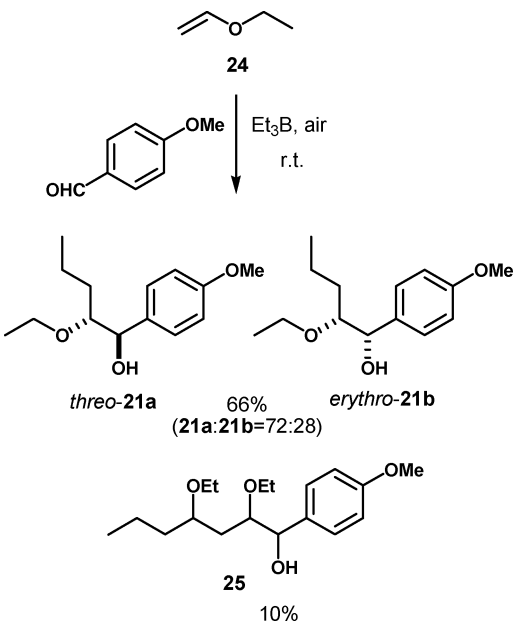
SCHEME 4. Radical Hydroxyalkylation of Ethyl Vinyl Ether (24)

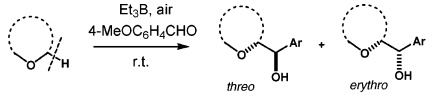


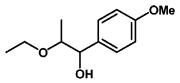
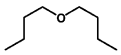
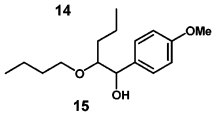
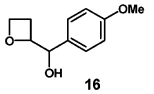
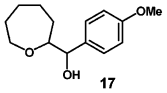
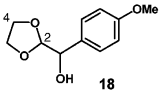
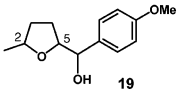
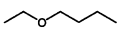
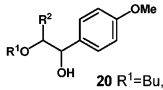
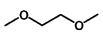
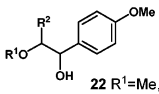
with continuous bubbling of air through a syringe needle with a balloon (flow rate: ca. 30 mL·h^{-1}·mmol aldehyde^{-1}). It should be emphasized that the flow rate of air strongly influenced the reaction rate: the reaction was considerably accelerated by the increased admission of air to the reaction mixture; e.g., ca. 30 mL·h^{-1} ·mmol^{-1} for 13 h vs ca. 20 mL·h^{-1}·mmol^{-1} for 33 h was required for the completion of the α-hydroxyalkylation of THF with 4-methoxybenzaldehyde (Table 1, entries 1 and 6).

Under the optimized conditions, the C−H hydroxyalkylation of several ethers and an acetal with 4-methoxybenzaldehyde was carried out. Table 2 shows that in addition to THF (**1**), such ethers and an acetal as diethyl ether (**6**), oxetane (**8**), 2-methyltetrahydrofuran (**11**), and 1,3-dioxolane (**10**) undergo α-C−H hydroxyalkylation to provide adducts in good yields. Dibutyl ether (**7**) (64% yield; dr 71:29), oxepane (**9**) (63% yield; dr 88:12), butyl ethyl ether (**12**) (50% yield; **20**:**21** = 58:42; dr 71:29 for **20**, dr 72:28 for **21**), and ethylene glycol dimethyl ether (**13**) (55% yield; **22**:**23** = 62:38; dr 51:49 for **22**) were also found to afford α-hydroxyalkylated ethers under the same conditions in moderate yields.[17] It is interesting to note that the threo selectivity was generally observed in this hydroxyalkylation reaction (entries 1−4 and 7). Unsymmetrical cyclic ether **11** underwent the hydroxyalkylation in moderate regioselectivity (C5:C2 = 54:46). As there are two hydrogens at C5 and one hydrogen at C2, the relative reactivity for abstraction per hydrogen was

(17) In the case of THP, however, the yield of the adduct was found to be low (ca. 20% yield; dr 80:20). This result seems to be related to the previous observation of the low susceptibility to hydrogen abstraction of THP.[4e,f]

TABLE 2. α-C−H Hydroxyalkylation of Ethers and Acetal with 4-Methoxybenzaldehyde under Et_3B/Air Conditions



entry	ether	product	concn,[a] time[b]	yield[c] (*threo*:*erythro*)
1	 **6**	 **14**	50 mM 22 h	72% (dr 74:26)[d,e]
2	 **7**	 **15**	30 mM 20 h	64% (dr 71:29)[d,f]
3	 **8**	 **16**	130 mM 15 h	77% (dr 78:22)[g]
4	 **9**	 **17**	75 mM[h] 20 h	63% (dr 88:12)[g]
5	 **10**	 **18**	120 mM 9 h	79%[i]
6	 **11**	 **19**	100 mM 12 h	84%[j]
7	 **12**	 **20** R^1=Bu, R^2=Me **21** R^1=Et, R^2=Pr	30 mM 48 h	50%[k] (dr 71:29 for **20**) (dr 72:28 for **21**)
8	 **13**	 **22** R^1=Me, R^2=CH_2OMe **23** R^1=CH_2CH_2OMe, R^2=H	60 mM 52 h	55%[l] (dr 51:49 for **22**)

[a] Aldehyde concentration in ethers or an acetal; all reactions except entry 4 were carried out with 6 equiv of Et_3B (relative to aldehyde). [b] Air was introduced at a rate of ca. 30 mL·h^{-1}·mmol aldehyde^{-1}. [c] Isolated yields based on aldehyde. [d] Ratios determined by ^{1}H NMR measurement of the threo/erythro mixture. [e] 1-(4-Methoxyphenyl)propan-1-ol (3%) and 4-methoxybenzyl alcohol (6%) were also produced. [f] Unreacted aldehyde (7%) and 1-(4-methoxyphenyl)propan-1-ol (7%) were obtained. [g] Ratio determined based on separated diastereomers. [h] 10 equiv of Et_3B was used. [i] Combined yield of regioisomeric C2/C4 hydroxyalkylation products (C2:C4 = 68:11). [j] Combined yield of regioisomeric C5/C2 hydroxyalkylation products (C5:C2 = 54:46). The stereochemistry of the adducts has yet to be determined. [k] Combined yield of regioisomeric products (**20**:**21** = 58:42). Unreacted aldehyde (30%), 1-(4-methoxyphenyl)propan-1-ol (2%), and 4-methoxybenzyl alcohol (2%) were obtained. [l] Combined yield of regioisomeric products (**22**:**23** = 62:38). Unreacted aldehyde (17%), 1-(4-methoxyphenyl-)propan-1-ol (8%), and 4-methoxybenzyl alcohol (13%) were obtained.

roughly estimated to be C2:C5 = 46/1:54/2 = ca. 1.7:1.[18] In the case of butyl ethyl ether (**12**), both α positions adjacent to ethereal oxygen exhibited similar susceptibility to hydrogen abstraction (**20**:**21** = 58:42) slightly favoring 1-butoxyethyl radical formation. The relative reactivity of the methylene and the methyl hydrogen of **13** on a per-hydrogen basis was calculated to be 62/4:38/6 = ca. 2.5:1. Although the degree of preference in the reaction of ethers **11** and **13** was low, the relative rates of abstraction of different hydrogens with an ethyl radical seemed to reflect thermodynamic factors that preferentially produced more stable carbon-centered radicals. In some cases, ethyl adducts and/or 4-methoxybenzyl alcohol was produced, but the amounts of the byproducts were generally negligible (2−7%). The hydroxyalkylation of ether **13**, which showed moderate reactivity toward hydrogen abstraction, however, was found to provide somewhat increased amounts of ethyl adduct (8%) and a reduced product (13%).

When ethyl vinyl ether (**24**) was subjected to the Et_3B/air-mediated α-C−H hydroxyalkylation, alcohols **21a** and **21b** favoring the threo isomer (**21a**:**21b** = 72:28) were obtained in 66% yield along with telomeric adduct **25** (10%) (Scheme 4). This indicates that the addition of ethyl radical to the vinyl group, which is a more exothermic process than the abstraction of hydrogen α to oxygen, is predominant due to the small dissociation energy of the π bond.[19] Although the polarity of a nucleophilic ethyl radical seems to be mismatched with that of electron-rich olefin **24**, ethyl radical addition takes place efficiently in a relatively short reaction time (ca. 5 h) as the enthalpic factors may be important in determining the reaction rate of weak nucleophilic radicals.[20,21] Thus, an ethyl radical generated from Et_3B/air rapidly underwent addition to **24** to give stable but highly nucleophilic alkoxyalkyl radical **26**, which was captured by 4-methoxybenzaldehyde in the presence of an oxophilic and Lewis acidic Et_3B to afford hydroxyalkylation products **21a** and **21b** (Scheme 5).[22] Alcohol **25** was also produced via the assembly of 4-methoxybenzaldehyde with alkoxyalkyl radical **27** generated from the addition of radical **26** to vinyl ether **24**.

In conclusion, we have demonstrated that the α-C−H hydroxyalkylation of oxygen-containing molecules such as ethers and an acetal can be carried out by the use of Et_3B/air as the radical reagents. The ease of operation makes the present method a superior means for the synthesis of α-substituted ethers and related compounds. As the intermolecular coupling of ether radicals with aldehydes is rarely recognized as a strategic means for C−C bond formation in organic synthesis, the radical

(18) The ratio was calculated without taking into consideration the geometrical effects of the two diastereomeric hydrogens at C5 on the rate of hydrogen abstraction.

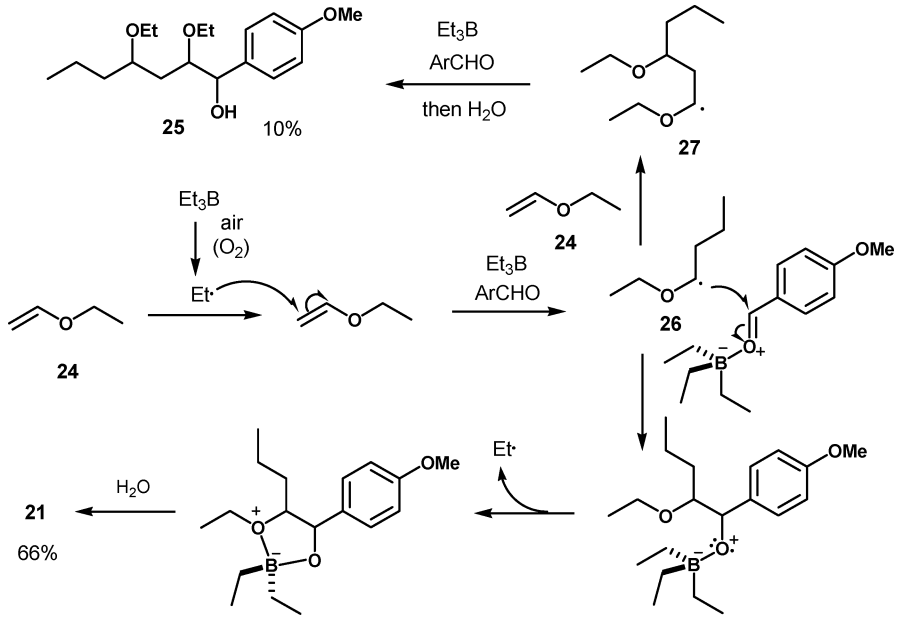
(19) Comprehensive reviews of the addition of carbon-centered radicals to alkenes: (a) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340−1371. (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753−764. (c) Reference 4h. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.: Pergamon: Oxford, UK, 1991; Vol. 4.

(20) Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* **1996**, *118*, 437−439.

(21) The formation of ethyl radical adducts in this particular case also indicates that under the Et_3B/air conditions, an ethyl radical serves as the principal radical source whereas an ethoxyl radical, which is postulated to exist in the reaction mixture, does not. Ethoxyl radical generation in the Et_3B/air system: Sato, T.; Hibino, K.; Otsu, T. *Nippon Kagakukai Shi* **1975**, 1080−1084. Also, see: Chung, T. C.; Janvikul, W.; Lu, H. L. *J. Am. Chem. Soc.* **1996**, *118*, 705−706.

(22) Possible precoordination of triethylborane with carbonyl compounds, see: Beraud, V.; Gnanou, Y.; Walton, J. C.; Maillard, B. *Tetrahedron Lett.* **2000**, *41*, 1195−1198.

SCHEME 5. Plausible Mechanism of Hydroxyalkylation of Ethyl Vinyl Ether (24)



C−H transformation of ethers presented in this study will provide a basis for new C−H transformation chemistry.

Experimental Section

General. For details, see the Supporting Information.

Typical Procedure for α-C−H Hydroxyalkylation of Ethers and an Acetal with 4-meThoxybenzaldehyde under Et_3B/air Conditions. 2-Ethoxy-1-(4-methoxyphenyl)propan-1-ol (14): To a solution of 4-methoxybenzaldehyde (408 mg, 3.0 mmol) in Et_2O (6) (60 mL, 570 mmol) was added Et_3B (2.6 mL, 18 mmol) at room temperature under argon atmosphere. After removal of the argon balloon, the mixture was stirred at the same temperature with continuous bubbling of air through a syringe needle with a balloon (flow rate: ca. 30 mL·h^{-1}·mmol aldehyde^{-1}) for 22 h. [**Caution**: Triethylborane, a liquid, pyrophoric toward oxygen, should be handled with care to avoid direct exposure to air.] The reaction mixture was treated with 28% NH_4OH and extracted with CH_2Cl_2. [A 28% NH_4OH solution and CH_2Cl_2 used in combination allow for the removal of an unidentified polar byproduct that may have originated in Et_3B. The removal of the polar byproduct in the crude mixture, which is detectable on an iodine−silica gel TLC plate, may otherwise be difficult. The crude mixture must be washed with 28% NH_4OH solution for adequate purification.] The organic extract was dried over $MgSO_4$. Following solvent evaporation in vacuo, the residue was purified by silica gel column chromatography (AcOEt/Hex 1:4) to give an inseparable mixture of alcohol **14** (456 mg, 72%; dr 74:26) and 1-(4-methoxyphenyl)-propan-1-ol (13 mg, 3%) as a colorless oil, and 4-methoxybenzyl alcohol (25 mg, 6%) as a colorless oil. Alcohols *threo*-**14a** and *erythro*-**14b** were obtained by the following sequence: namely, acetylation of a mixture of **14** and 1-(4-methoxyphenyl)propan-1-ol (Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; 83% yield), the separation of the acetates by flash chromatography (Et_2O/toluene 1:18), and the reductive removal of the acetyl group with LAH (quant.). *threo*-Alcohol **14a**: IR (neat) ν 3458, 2931 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 2H), 6.92−6.86 (m, 2H), 4.33 (d, 1H, J = 8.2 Hz), 3.80 (s, 3H), 3.71 (dq, 1H, J = 9.3, 7.0 Hz), 3.50−3.40 (m, 2H), 1.26 (t, 3H, J = 7.0 Hz), 0.97 (d, 3H, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.6, 128.3, 113.6, 80.1, 77.8, 64.4, 55.2, 15.6, 15.5; MS *m/z* 210 (M$^+$), 137 (100%); HRMS (EI) calcd for $C_{12}H_{18}O_3$ (M$^+$) 210.1256, found 210.1255. *erythro*-Alcohol **14b**: IR (neat) ν 3446, 2979 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.24 (m, 2H), 6.91−6.85 (m, 2H), 4.80 (d, 1H, J = 3.8 Hz), 3.8 (s, 3H), 3.64−3.48 (m, 3H), 2.70−1.90 (br s, 1H), 1.2 (t, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 132.8, 127.4, 113.4, 79.0, 74.6, 64.3, 55.2, 15.6, 13.5; MS *m/z* 210 (M$^+$), 137 (100%); HRMS (EI) calcd for $C_{12}H_{18}O_3$ 210.1256 (M$^+$), found 210.1250. The NMR spectra of the ethyl adduct and the reduction product were identical with those of commercially available 1-(4-methoxyphenyl)propan-1-ol and 4-methoxybenzyl alcohol.

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Supporting Information Available: Experimental procedures for the α-C−H hydroxyalkylation of ethers **7**, **8**, **9**, **11**, **12**, **13**, and **24** and acetal **10** and determination of the stereochemistry of the hydroxyalkylation products, characterization data, and ^{1}H/^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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