

Hydroxyalkylation of α -C–H Bonds of Tetrahydrofuran with Aldehydes in the Presence of Triethylborane and *tert*-Butyl Hydroperoxide

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Abstract: The α -hydroxyalkylation of tetrahydrofuran with aldehydes via radical C–H abstraction was conducted using triethylborane in the presence of *tert*-butyl hydroperoxide. This study presents a rare instance of *direct intermolecular radical addition of unactivated cyclic ether to aldehydes*.

C–H functionalization of organic molecules is presently a focal point of intensive research.^{1–3} Carbon–carbon bond formation at the otherwise unreactive α -C–H position of cyclic ethers is generally carried out by free-radical^{4,5} and carbenoid C–H insertion reactions.^{6,7} These methods have a significant potential for providing rapid access to α -substituted cyclic ethers, ubiquitous structural motifs of bioactive molecules.⁸ However, direct assembly between unactivated cyclic ethers and aldehydes through α -C–H functionalization remains unexploited despite its significant synthetic challenge.

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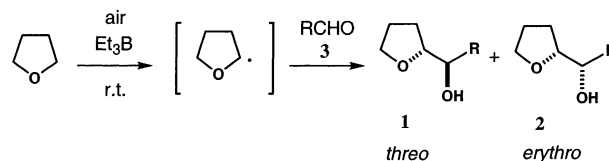
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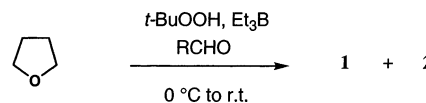
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SCHEME 1



SCHEME 2



We recently reported an α -hydroxyalkylation of tetrahydrofuran (THF) with aldehydes that occurred via the α -C–H abstraction of THF by ethyl radicals from triethylborane in the presence of air (Scheme 1).^{9,10} The use of air as a safe, inexpensive ethyl-radical generator¹¹ is generally time-consuming, even with continuous application to the reaction mixture. Various new reagent systems were thus devised and evaluated for the promotion of the above reactions.¹² This study shows triethylborane and *tert*-butyl hydroperoxide (TBHP) used in combination to be quite effective for promoting the α -C–H hydroxyalkylation of THF with aldehydes, and, accordingly, this combination may be used to replace the triethylborane/air system (Scheme 2).^{13,14}

The oxidation of organoboranes with neutral hydrogen peroxides proceeds via a free-radical process.¹⁵ It should follow then that certain hydroperoxides under neutral conditions may initiate alkyl-radical generation from trialkylboranes, thus facilitating the radical α -C–H abstraction of THF (Table 1).

As a trialkylborane/peroxide combination for the α -hydroxyalkylation of THF with 4-methoxybenzaldehyde, triethylborane/TBHP was found to most efficiently provide alcohols **1a/2a** (Table 1, entry 1). Both tri-*sec*-

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TABLE 1. α -Hydroxyalkylation of THF with 4-Methoxybenzaldehyde (**3a**) Mediated by Various Trialkylboranes and Hydroperoxides

		$\begin{array}{c} \text{R}_3\text{B} \\ \text{Hydroperoxides} \\ \text{THF} \\ 0^\circ\text{C to r.t.} \end{array}$		$\begin{array}{c} \text{4-MeOC}_6\text{H}_4\text{CHO} \\ \text{3a} \end{array} \longrightarrow \text{1a/2a}$	
entry	reagents (equiv)	reaction time (min)	yield (%) ^a	1a/2a ^b ratio	
1	Et ₃ B (10), THF (106), TBHP (6)	5	80	90:10	
2	Bu ₃ B (10), THF (90), TBHP (6)	15	79	92:8	
3	<i>s</i> -Bu ₃ B (10), THF (86), TBHP (6)	70	6	87:13	
4	Ph ₃ B (10), THF (106), TBHP (6)	70	28	86:14	
5	Et ₃ B (10), THF (106), H ₂ O ₂ (6)	70	9	89:11	
6	Et ₃ B (10), THF (106), CHP ^c (6)	70	82	90:10	

^a Isolated yields referred to aldehydes. ^b Ratios determined by ¹H NMR of the threo/erythro mixture. ^c Cumene hydroperoxide.

TABLE 2. α -Hydroxyalkylation of THF with 4-Methoxybenzaldehyde (**3a**): Effects of Reagent Amounts

		$\begin{array}{c} \text{Et}_3\text{B} \\ t\text{-BuOOH} \\ \text{THF} \\ 0^\circ\text{C to r.t.} \end{array}$		$\begin{array}{c} \text{4-MeOC}_6\text{H}_4\text{CHO} \\ \text{3a} \end{array} \longrightarrow \text{1a/2a}$	
entry	reagents (equiv)	reaction time (min)	yield (%) ^a	1a/2a ^b ratio	
1	Et ₃ B (10), THF (13), TBHP (6)	70	36	92:8	
2	Et ₃ B (1), THF (106), TBHP (6)	70	22	90:10	
3	Et ₃ B (5), THF (106), TBHP (6)	70	66	90:10	
4	Et ₃ B (10), THF (106), TBHP (6)	5	80	90:10	

^a Isolated yields referred to aldehydes. ^b Ratios determined by ¹H NMR of the threo/erythro mixture.

butylborane and triphenylborane in the presence of TBHP failed to give alcohols **1a/2a** in significant yield (Table 1, entries 3 and 4). The yields obtained on using tributylborane/TBHP or triethylborane/cumene hydroperoxide were comparable to those obtained with triethylborane/TBHP, but the separation of unidentified byproducts from the reaction mixture was difficult in either reagent system (Table 1, entries 2 and 6). Hydrogen peroxide as an ethyl-radical generator caused a marked decrease in the yields of **1a/2a** (Table 1, entry 5). The threo selectivity of the α -hydroxyalkylated products under the above conditions was essentially the same in all cases. Table 2 indicates a notable increase in the alcohol yield and an enhanced reaction rate when using excess triethylborane and THF (Table 2, entry 4). Table 3 shows the best yield in the presence of 6 equiv TBHP. The TBHP content was found to have no significant effect on the ratio of **1a/2a** but did so on the reaction rate (Table 3). Under the optimized conditions using 10 equiv of triethylborane, 6 equiv of TBHP, and 106 equiv of THF, α -C–H hydroxyalkylation of THF with various aldehydes was carried out (Table 4). The aromatic aldehydes were consumed within 5 min, while the aliphatic aldehydes required longer reaction times. The yield and threo selectivity of products **1** and **2** were generally high for all the aromatic aldehydes except the ortho-substituted benzaldehyde **3d** and moderate to low for the aliphatic

TABLE 3. α -Hydroxyalkylation of THF with 4-Methoxybenzaldehyde (**3a**) Mediated by Triethylborane/TBHP: Effects of the TBHP Amount

		$\begin{array}{c} 10 \text{ eq. Et}_3\text{B} \\ t\text{-BuOOH} \\ 106 \text{ eq. THF} \\ 0^\circ\text{C to r.t.} \end{array}$		$\begin{array}{c} \text{4-MeOC}_6\text{H}_4\text{CHO} \\ \text{3a} \end{array} \longrightarrow \text{1a/2a}$	
entry	TBHP (equiv)	reaction time (min)	yield (%) ^a	1a/2a ^b ratio	
1	0.2	70	12	94:6	
2	1.0	70	27	91:9	
3	2.0	70	55	93:7	
4	3.0	35	66	92:8	
5	4.0	15	76	91:9	
6	5.0	15	77	90:10	
7	6.0	5	80	90:10	
8	7.0	5	72	90:10	

^a Isolated yields referred to aldehydes. ^b Ratios determined by ¹H NMR of the threo/erythro mixture.

TABLE 4. α -Hydroxyalkylation of THF with Aldehydes Mediated by Triethylborane/TBHP

		$\begin{array}{c} 10 \text{ eq. Et}_3\text{B} \\ 6 \text{ eq. } t\text{-BuOOH} \\ 106 \text{ eq. THF} \\ 0^\circ\text{C to r.t.} \end{array}$		$\begin{array}{c} \text{RCHO} \\ \text{3} \end{array} \longrightarrow \text{1/2}$	
entry	3	R	reaction time (min)	yield (%) ^a	1/2 ^b ratio
1	3a	4-MeOC ₆ H ₄	5	80	90:10
2	3b	Ph	5	82	86:14
3	3c	3,4-methylenedioxyphenyl	5	79	89:11
4	3d	2-BrC ₆ H ₄	5	78	69:31
5	3e	C ₁₂ H ₂₅	70	65 ^{c,d}	64:36 ^e
6	3f	C ₆ H ₁₁	70	43 ^{c,d}	45:55 ^e

^a Isolated yields referred to aldehydes. ^b Ratios determined by ¹H NMR of the threo/erythro mixture. ^c Two-step yields of the diastereomeric acetates derived from **1/2**. ^d Isolated yields are based on recovered aldehydes. ^e Ratios determined by ¹H NMR of acetates.

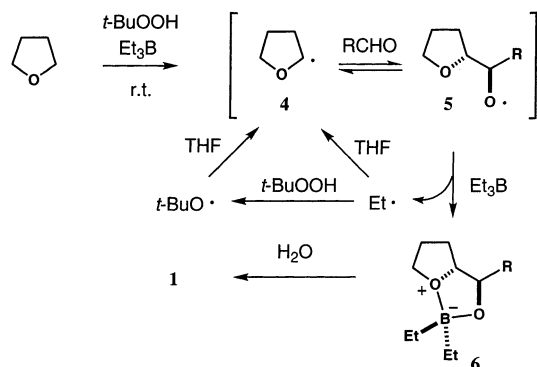
substrates. Interestingly, in the case of **3f**, the *erythro*-alcohol **2f** (see the Supporting Information) was preferentially formed, albeit in a small degree of selectivity.

A plausible mechanism for this reaction is shown in Scheme 3.¹⁶ Possibly, the alkoxy-radical intermediate **5** arising from the addition of THF radical **4** to aldehydes may be trapped by triethylborane. When alcohols **1e** and **2e** were treated with PhI(OAc)₂ in the presence of iodine to form the alkoxy radical **5e**,¹⁷ rapid fragmentation of the alcohols occurred to give tridecanal (**3e**) in a 72% isolated yield (Scheme 4). The alkoxy radical **5** is thus clearly shown to readily produce the more stable THF radical **4** and carbonyl compounds. The reversion of **5** to **4** in Scheme 3 may thus be favored unless the alkoxy radical **5** is immediately captured by the triethylboranes. Malacria et al.^{13a–c} and Clive and Postema^{13d} noted that triethylborane functions as an alkoxy-radical scavenger in the intramolecular radical cyclization of iodo- and selenocarbonyl compounds.

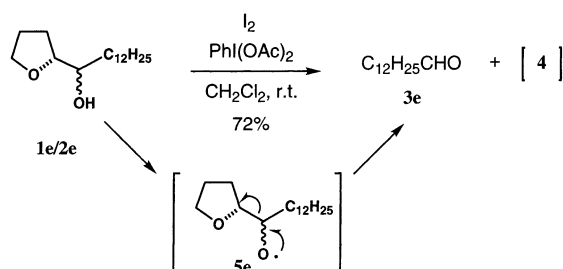
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SCHEME 3



SCHEME 4



In conclusion, a new effective means for the direct α -C–H hydroxyalkylation of THF with aldehydes has been established through the use of triethylborane/TBHP to generate THF radicals via the α -C–H abstraction. The present study provides important insight into the C–H functionalization of cyclic ethers via radical reaction.

Experimental Section

General Procedures. For details, see the Supporting Information.

Representative Procedure for the α -Hydroxyalkylation of THF with Aldehydes Using Triethylborane and TBHP. To aldehydes (1.0 mmol) was added 1.0 M Et_3B in THF (10 mL,

10 mmol) at 0 °C. After 15 min, 5.78 M TBHP in nonane (1.0 mL, 6.0 mmol) was added dropwise to the mixture at the same temperature. After being stirred for 10 min, the mixture was allowed to warm to room temperature and stirred for an additional period during which the reaction proceeded to completion. **Caution:** The addition of peroxides to trialkylboranes may lead to highly exothermic reactions. We encountered no violent reaction with the present procedures, but special care is advised. The reaction mixture was treated with 28% NH_4OH and extracted with CH_2Cl_2 . (A 28% NH_4OH solution allows the removal of unidentified polar materials possibly from Et_3B . Removal of polar byproducts in the crude mixture, detectable on an iodine/silica gel TLC plate, may otherwise be difficult. The crude mixture must thus be washed with 28% NH_4OH for adequate purification.) The organic extracts were dried over MgSO_4 . Following the solvent evaporation in vacuo, the residue was purified by column chromatography on silica gel to give alcohols **1/2** (AcOEt/Hex as the eluent). **1e/2e** and **1f/2f** were further acetylated to the corresponding acetates. The diastereomeric ratio of **1/2** was determined by the comparison of ^1H NMR signals of a *threo*/*erythro* mixture of alcohols or acetates (see the Supporting Information).

Alkoxy-Radical Fragmentation of 1e/2e. To a solution of alcohols **1e/2e** (165 mg, 0.61 mmol) in CH_2Cl_2 (3.0 mL) at rt were added diacetoxyiodobenzene (296 mg, 0.92 mmol) and iodine (171 mg, 0.67 mmol). After being stirred for 50 min, the mixture was treated with saturated $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with Et_2O . The organics were dried over MgSO_4 , and solvent evaporation gave crude products whose purification by silica gel column chromatography (1:12 AcOEt/Hex as an eluent) afforded tridecanal (87 mg, 72%) as a colorless solid. Spectra of the product were identical with those of authentic tridecanal in all respects.

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Supporting Information Available: Analytical and spectroscopic data for all new compounds. ^1H and ^{13}C NMR spectra of *threo*-alcohols **1a–f** and *erythro*-alcohols **2a–f**. ^1H NMR spectra of the *threo*/*erythro*-alcohols **1a–d/2a–d** and *threo*/*erythro*-acetates derived from **1e/2e** and **1f/2f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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