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Aerobic Hydroxylation of *N*-Borylenamine: Triethylborane-Mediated Hydroxyalkylation of α,β-Unsaturated Oxime Ether

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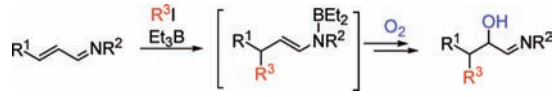
ABSTRACT



Intermolecular hydroxyalkylation of α,β-unsaturated imines involving Et_3B-mediated regioselective alkyl radical addition and subsequent hydroxylation with molecular oxygen has been developed, in which *N*-borylenamine generated by trapping of the enaminyl radical with Et_3B was a key intermediate in the proposed aerobic hydroxylation mechanism.

Free-radical-mediated hydroxyalkylation reactions involving both carbon−carbon bond formation and oxygenation processes provide an attractive approach for preparing complex molecules.[1] Therefore, some investigations have focused on oxygenation of carbon radicals, generated by radical addition to alkenes. Intramolecular hydroxyalkylation studies of stannyl radical-mediated or cobalt-catalyzed oxygenative cyclization of olefinic halides have been conducted by Nakamura,[2] Prandi,[3] and other groups.[4] The challenging intermolecular hydroxyalkylation has recently been achieved by use of a Grignard reagent,[5] cobalt(II),[6] photochemical irradiation,[7] electrolysis,[8] cerium(IV),[9] manganese(III),[10] and aluminum(III).[11,12] However, these reported methods have some unavoidable drawbacks, which are generation of ketone

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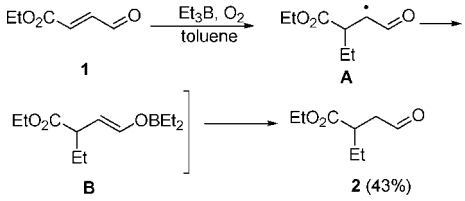
as an overoxidation product or low reaction efficiency. Nothing is known about intermolecular hydroxyalkylation using a conventional radical initiator such as Et_3B[13] or AIBN. Herein, we report the Et_3B-induced hydroxyalkylation reaction of α,β-unsaturated imines in connection with our recent study on hydroxysulfenylation.[14] In hydroxysulfenylation reaction, the stabilization of intermediate radical, generated by the thiyl radical addition to carbon−carbon double bond, by homoconjugative interaction between the carbon-centered radical and the sulfur atom was key factor. On the other hand, the hydroxyalkylation without such a stabilizing functional group might be difficult and therefore challenging.

In an initial attempt, we treated α,β-unsaturated aldehyde **1** with Et_3B in the presence of molecular oxygen in toluene (Scheme 1).[15]

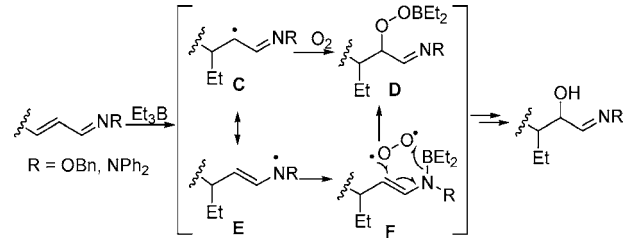
Scheme 1. Ethyl Radical Addition to α,β-Unsaturated Aldehyde



Although the substrate **1** was consumed within 10 min, instead of the desired hydroxyalkylation product only the simple Michael-type adduct **2** was isolated in 43% yield. This indicates that oxygenation of radical intermediate **A** by molecular oxygen would be difficult due to rapid transformation of **A** into the corresponding borylenolate **B**.[16]

We then directed our attention to the potential of α,β-unsaturated imines as substrates. Since α-imino radical **C** would be more stable than α-carbonyl radical **A**, this should allow trapping by molecular oxygen (Scheme 2). Borylenamine **F** should also undergo an ene-type reaction with molecular oxygen via homolytic cleavage of the B−N bond

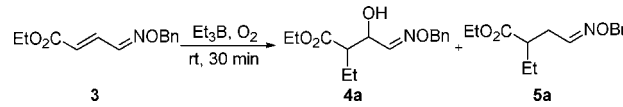
Scheme 2. Hydroxyalkylation of α,β-Unsaturated Imines



to produce α-oxygenated **D**,[17] facilitated by the lower bond dissociation energy of B−N compared with B−O.[18]

Promising results were obtained using α,β-unsaturated oxime ether **3** (Table 1).[19] We conducted investigations to

Table 1. Hydroxyalkylation of α,β-Unsaturated Oxime Ether **3**



			yield[a] (%)	
entry	solvent	additive	**4a**[b]	**5a**
1[c]	**toluene**		**78**	
2[d]	toluene		26 (64)[e]	
3[f]	toluene		n.d.	
4[c]	benzene		61	10
5[c]	Et_2O		76	
6[c]	THF		44	10
7[c]	CH_2Cl_2		4	92
8[g]	**CH_2Cl_2**	**Me_3Al**	**69**	**7**
9[g]	toluene	Me_3Al	53	

[a] Isolated yield. [b] **4a** was obtained as an *E*/*Z* mixture with *anti*/*syn* = 3:2−2:1. [c] The reaction was carried out with Et_3B (3.0 equiv) and bubbling of O_2 gas (3.6 equiv). [d] The reaction was carried out with Et_3B (1.0 equiv) and bubbling of O_2 gas (3.6 equiv). [e] Yield in parentheses is for recovered starting substrate **3**. [f] The reaction was carried out with Et_3B (3.0 equiv) under O_2 atmosphere. [g] The reaction was carried out with Et_3B (3.0 equiv), Me_3Al (2.2 equiv), and bubbling of O_2 gas (3.6 equiv).

determine optimal conditions for the hydroxyalkylation of **3**, which showed high reactivity in our recent studies.[14,20] First, O_2 gas (3.6 equiv) was bubbled into a mixture of **3** and Et_3B (3.0 equiv) in toluene (entry 1). As expected, the hydroxyalkylation reaction proceeded regioselectively to give the desired product **4a** in 78% yield as an *E*/*Z* mixture with

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(18) The formation of the B−OR bond is thermodynamically favored over the B−NR_2 bond according to the following bond energies: BDE (B−O) for $(EtO)_3B$ = 519 kJmol^{-1}; BDE (B−N) for $(Me_2N)_3B$ = 422 kJmol^{-1}; for reviews on alkylboranes, see: (a) Reference 13. (b) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674.
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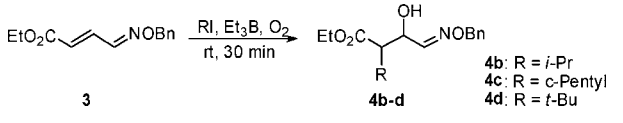
anti/*syn* = 2:1.[21] The reaction proceeded effectively without a reducing agent such as Bu_3SnH, because Et_3B played an important role in reduction of the hydroperoxy radical or hydroperoxide to the corresponding alcohol. Therefore, a significant decrease in the chemical yield was observed when the amount of Et_3B was reduced to 1.0 equiv (entry 2). An excess of O_2 prevented hydroxyalkylation due to decomposition of Et_3B (entry 3). This hydroxyalkylation was strongly influenced by the reaction solvent, with the use of benzene or THF leading to a decrease in chemical yield of **4a** (entries 4 and 6). Under similar reaction conditions, the reaction of **3** in CH_2Cl_2 produced simple Michael-type **5a** in 92% yield (entry 7). Interestingly, the use of trimethylaluminum as an additive-promoted hydroxyalkylation even in CH_2Cl_2, producing **4a** in 69% yield (entry 8).[22]

Using the optimized reaction conditions, a range of alkyl iodides were examined as carbon radical precursors in the iodine atom-transfer reaction (Table 2).[23]

Table 2. Hydroxyalkylation of **3** with Alkyl Iodide

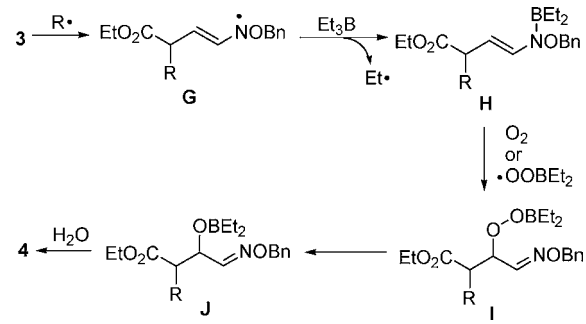


entry	RI	conditions[a]	yield (%)[b] (*anti*/*syn*)
1	*i*-PrI	A	61 (2:1)
2	*i*-PrI	B	41 (2:1)
3	c-pentyl I	A	51 (3:1)
4	c-pentyl I	B	50 (2:1)
5	*t*-BuI	A	60 (3:1)
6	*t*-BuI	B	64 (3:1)

[a] Conditions A: RI (20 equiv), Et_3B (3.0 equiv), Me_3Al (2.2 equiv) O_2 bubbling (3.6 equiv) in CH_2Cl_2. Conditions B: RI (20 equiv), Et_3B (3.0 equiv), O_2 bubbling (3.6 equiv) in toluene. [b] Isolated yield.

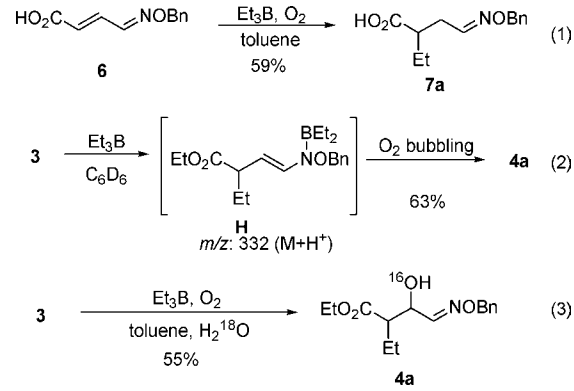
Hydroxyalkylation of **3** was run either with alkyl iodide and Et_3B in the presence of Me_3Al in CH_2Cl_2 (conditions A: entry 8 in Table 1) or in the absence of Me_3Al in toluene (conditions B: entry 1 in Table 1). Both secondary and bulky tertiary alkyl radicals worked well to afford the desired products **4b**−**d** in moderate to good yields. We propose a possible reaction pathway for this hydroxyalkylation reaction (Scheme 3). The first step involves regioselective alkyl radical addition to **3** followed by trapping of aminyl radical **G** with Et_3B to generate borylenamine **H**. The borylenamine **H** undergoes either an ene-type reaction with molecular oxygen or an addition reaction of the borylperoxy radical to form borylperoxide **I**. The reduction of **I** with Et_3B, followed by the hydrolysis of the resulting borinate **J** produced alcohol

Scheme 3. Possible Reaction Pathway



4. In this reaction, Et_3B acted as a multirole reagent inducing radical initiation, radical termination, and reduction.[24]

Our proposed reaction pathway was supported by the following experiments. In marked contrast to ester **3**, the reaction of carboxylic acid **6** exclusively gave Michael-type adduct **7a** under the optimized hydroxyalkylation conditions. This was because the intermediate borylenamine would be immediately protonated by free carboxylic acid (eq 1).



This supports the presence of borylenamine **H** as a key intermediate in the proposed aerobic hydroxylation mechanism. In addition, ^1H NMR and APCI mass spectra of a mixture of **3**, Et_3B, and a catalytic amount of O_2 in C_6D_6 supported complete conversion of **3** into *N*-borylenamine **H** (eq 2). After spectral confirmation of borylenamine formation, treatment of **H** with oxygen gas afforded the desired product **4a** in 63% yield. An alternative mechanistic hypothesis that the hydroxyl group originates from H_2O can be excluded based on a $H_2{}^{18}O$-labeled experiment, where hydroxyalkylation in the presence of $H_2{}^{18}O$ exclusively gave unlabeled **4a** (eq 3).[25]

Further investigations using various α,β-unsaturated imines as substrates were performed (Table 3). The reaction of acrolein derivative **8** produced secondary alcohol **9** in 60% yield (entry 1). The hydroxyalkylation reaction of conjugated hydrazone **10** also proceeded, albeit with relatively lower yield (entry 2). Oxazolidinone **12** was converted into alcohol

(21) The relative configurations of *anti*-**4a** and *syn*-**4a** were deduced by NOESY experiments of γ-lactam derivatives which were prepared from a mixture of diastereomers **4a**; for details see the Supporting Imformation.

(22) Kunz's group reported hydroxylation of aluminum enolate with molecular oxygen. However, our hydroxyalkylation with Me_3Al did not proceed in the absence of Et_3B; see ref 11.

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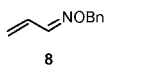
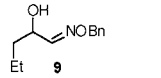
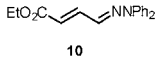
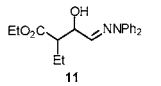
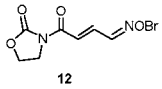
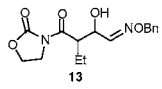
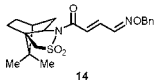
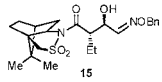
(25) Yajima, T.; Saito, C.; Nagano, H. *Tetrahedron* **2005**, *61*, 10203.

Table 3. Hydroxyalkylation of Various α,β-Unsaturated Imines

entry	substrate	conditions[a]	product	yield (%)[b] (*anti*/*syn*)
1	 **8**	C	 **9**	60
2	 **10**	D	 **11**	34 (3:2)
3	 **12**	D	 **13**	79 (17:1)
4	 **14**	C	 **15**	72 (3:1)
5		D		62 (3:1)

[a] Conditions C: Et_3B (3.0 equiv), Me_3Al (2.2 equiv) O_2 bubbling (3.6 equiv) in CH_2Cl_2. Conditions D: Et_3B (3.0 equiv), O_2 bubbling (3.6 equiv) in toluene. [b] Isolated yield.

13 with good yield and stereoselectivity. Finally, we extended our hydroxyalkylation to a diastereoselective reaction using chiral α,β-unsaturated oxime ether **14** which bears Oppolzer's camphorsultam.[26,27] The stereoselectivity on ethyl radical addition was completely controlled by the chiral auxiliary. The hydroxyalkylated product **15** was obtained in good yield but with moderate *anti*/*syn* selectivity.

In conclusion, we have developed for the first time an Et_3B-mediated aerobic hydroxyalkylation reaction of α,β-unsaturated imines. The reaction is characterized by mild conditions, is straightforward, and allows for the efficient and concomitant construction of a carbon−carbon bond and a carbon−oxygen bond. In the proposed reaction pathway, the borylenamine was characterized and confirmed as a key intermediate of the proposed hydroxylation mechanism.

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Supporting Information Available: Experimental procedure and characterization data and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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