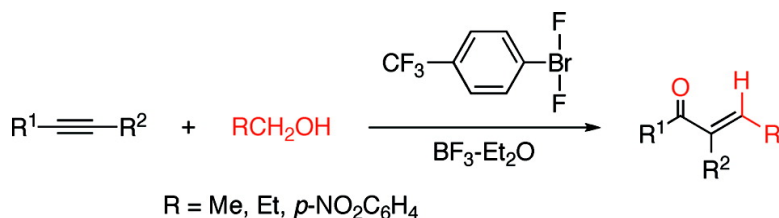## Communication

Difluoro-□-Bromane-Induced Oxidative Carbon−Carbon Bond-Forming Reactions: Ethanol as an Electrophilic Partner and Alkynes as Nucleophiles

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Difluoro-λ^3-Bromane-Induced Oxidative Carbon−Carbon Bond-Forming Reactions: Ethanol as an Electrophilic Partner and Alkynes as Nucleophiles

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To increase the complexity of a simple organic molecule using efficient, selective, and high-yielding methods under metal-free conditions is one of the paramount challenges in modern organic synthesis.[1] Development of oxidative carbon−carbon bond-forming reactions of alcohols with alkynes yielding α,β-unsaturated ketones with defined stereochemistry is an interesting example of achieving this goal but has never been reported. We report herein the first example for one-pot synthesis of conjugated enones **3** via oxidative coupling of alkynes **1** and primary alcohols using *p*-trifluoromethylphenyl(difluoro)-λ^3-bromane (**2**)[2] under transition-metal-free conditions, in which very high levels of stereo- and regiocontrol were attained (Scheme 1).

Recently, we reported the stereoselective synthesis and characterization of (*E*)-β-fluorovinyl-λ^3-bromanes.[3] The reaction involves BF$_3$-catalyzed fluoro-λ^3-bromanation of terminal alkynes with difluoro-λ^3-bromane **2** and proceeds in a Markovnikov fashion yielding (*E*)-β-fluorovinyl-λ^3-bromanes stereoselectively. Use of an alcohol as an additive in the reaction, however, dramatically changed the reaction course: for instance, reaction of 1-decyne (**1b**) with difluorobromane **2** in the presence of EtOH (2−4 equiv) and BF$_3$−Et$_2$O in dichloromethane afforded *trans*-2-dodecen-4-one (**3b**), instead of the β-fluoro-1-decenylbromane, in moderate yields (22−48%). After extensive studies on reaction conditions, we found an efficient procedure for the oxidative carbon−carbon bond forming reaction, which involves initial exposure of EtOH (5 equiv) to difluorobromane **2** (3 equiv) in the presence of BF$_3$−Et$_2$O (2 equiv) at −30 °C for 30 min, followed by the addition of **1b**. The reaction (at −30 °C for 24 h) afforded a 77% yield of the *trans*-enone **3b** stereoselectively with no evidence for formation of the *Z*-isomer (Table 1, entry 2). Use of chloroform or 1,2-dichloroethane gave comparable results, while more polar solvents (MeCN, AcOEt, Et$_2$O, DME, etc.) afforded low yields (less than 15%) of **3b**. It should be noted that no formation of the enone **3b** was detected, when difluoro-λ^3-iodane *p*-CF$_3$C$_6$H$_4$IF$_2$ was used instead of bromane **2**, and a large amount of **1b** was recovered unchanged (entry 3).

A wide range of terminal alkynes efficiently undergo the λ^3-bromane-mediated oxidative coupling with ethanol under metal-free conditions and afforded moderate to good yields of *trans*-enones **3a**−**s** in a exclusively stereo- and regioselective manner: no formation of the regioisomeric enals was detected. Yields of the conjugated enones **3j**−**m** gradually increase with the increasing electron-withdrawing nature of the terminal acyloxy groups of 10-undecynyl esters (entries 11−14), while in the reaction with phenylacetylenes the presence of more electron-donating *para* substituents increase the reaction efficiency (entries 17−20). To our delight, the coupling reactions of internal alkynes such as 2-decyne and 1-phenyl-1-propyne were found to be exclusively regioselective: thus, an ethylidene group derived from EtOH combined with the acetylenic carbon atom attached to a methyl group, while an oxo group attached to the other acetylenic carbon, yielding (*E*)-enones **3t** and **3u** stereoselectively (entries 21, 22).
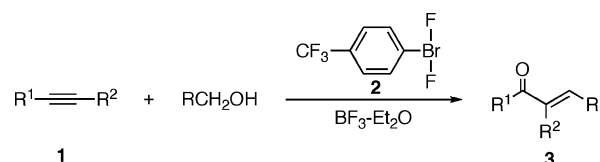
Scheme 1

**Table 1.** λ^3-Bromane-Induced Oxidative Coupling of Alcohols and Alkynes **1**[a]

entry	alkyne **1** R^1	R^2	RCH$_2$OH (R)	3 yield (%)[b]
1	*n*-C$_6$H$_{13}$	H	Me	**3a** 76
2	*n*-C$_8$H$_{17}$	H	Me	**3b** 77
3[c]	*n*-C$_8$H$_{17}$	H	Me	**3b** 0
4	Me$_2$CH(CH$_2$)$_2$	H	Me	**3c** 60
5	*c*-C$_6$H$_{11}$	H	Me	**3d** 55
6	Ph(CH$_2$)$_2$	H	Me	**3e** 59
7	Cl(CH$_2$)$_4$	H	Me	**3f** 50
8	Cl(CH$_2$)$_9$	H	Me	**3g** 79
9	Br(CH$_2$)$_4$	H	Me	**3h** 60
10	MeO(CH$_2$)$_9$	H	Me	**3i** 34
11	AcO(CH$_2$)$_9$	H	Me	**3j** 48
12	PhCO$_2$(CH$_2$)$_9$	H	Me	**3k** 61
13	4-CF$_3$C$_6$H$_4$CO$_2$(CH$_2$)$_9$	H	Me	**3l** 64
14	3,5-(CF$_3$)$_2$C$_6$H$_3$CO$_2$(CH$_2$)$_9$	H	Me	**3m** 67
15	MeO$_2$C(CH$_2$)$_8$	H	Me	**3n** 44
16	3,5-(CF$_3$)$_2$C$_6$H$_3$O$_2$C(CH$_2$)$_8$	H	Me	**3o** 51
17	4-MeOC$_6$H$_4$	H	Me	**3p** 78
18	4-MeC$_6$H$_4$	H	Me	**3q** 62
19	Ph	H	Me	**3r** 41
20	4-CF$_3$C$_6$H$_4$	H	Me	**3s** 23
21	*n*-C$_7$H$_{15}$	Me	Me	**3t** 54
22	Ph	Me	Me	**3u** 84
23	Ph	Ph	Me	**3v** 65[d]
24	*n*-C$_8$H$_{17}$	H	Et	**3w** 39
25	*n*-C$_8$H$_{17}$	H	4-NO$_2$C$_6$H$_4$	**3x** 61[e]

[a] Conditions: an alcohol (5 equiv)/difluorobromane **2** (3 equiv)/BF$_3$−Et$_2$O (2 equiv)/Ar. [b] Isolated yields. [c] Difluoroiodane (*p*-CF$_3$C$_6$H$_4$IF$_2$), instead of **2**, was used. [d] *E*/*Z* ratio = 96:4. [e] *E*/*Z* ratio = 98:2.

A possible reaction mechanism shown in Scheme 2 involves an initial λ^3-bromane-induced oxidation of EtOH to acetaldehyde, which probably proceeds via (1) activation of λ^3-bromane **2** by the coordination of BF$_3$ that increases the polarization of the hypervalent F−Br−F bonding, (2) formation of the tetracoordinated species **4**, (3) generation of the alkoxy-λ^3-bromane **5** via ligand exchange on Br(III), and (4) reductive β-elimination of a λ^3-bromanyl group with a very high leaving group ability, producing acetaldehyde. [2 + 2] Cyclization of the aldehyde with alkynes, probably accelerated by HBF$_4$ generated *in situ*, would result in the regioselective formation of 2*H*-oxete **6**, because of steric factors, and finally the concerted electrocyclic conrotatory ring opening will afford the conjugated enones **3** selectively.

This mechanism expects that the terminal ethylidene group in **3b** originates from ethanol, while the α-vinylic hydrogen comes
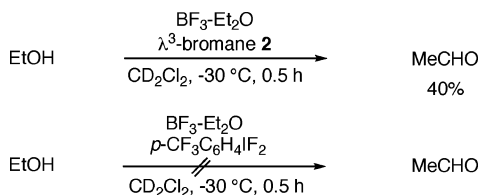
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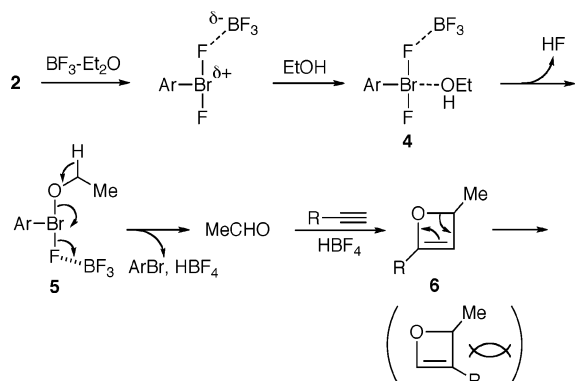
Scheme 3
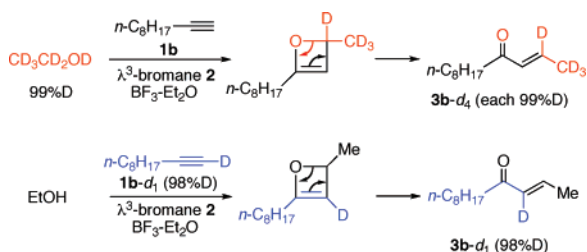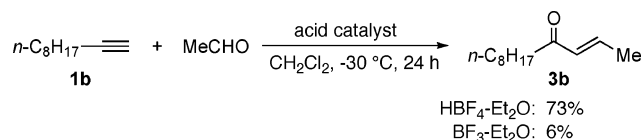

Scheme 4

Scheme 5

Scheme 6

from 1-decyne, which is compatible with the results obtained in the deuterium labeling experiments shown in Scheme 3.

Oxidation of EtOH to acetaldehyde with difluorobromane **2** does take place at −30 °C in the presence of BF_3−Et_2O, but in moderate yield (40%), probably because of the competing oxidative dimerization with formation of ethyl acetate (Scheme 4, Figure S1). Therefore, use of excess amounts of ethanol and bromane **2** is required for oxidative coupling with alkynes. Interestingly, the oxidation of EtOH also occurs even without using BF_3−Et_2O, when the reaction was carried out at room temperature (Figure S1). In marked contrast, difluoro-λ^3-iodane p-$CF_3C_6H_4IF_2$ showed no evidence for the formation of acetaldehyde and recovered the alcohol unchanged under the BF_3-catalyzed conditions, which is in good agreement with the result shown in Table 1, entry 3.[4]

Lewis acid catalyzed[5] or photochemical condensations[6] of carbonyl compounds with alkynes, producing α,β-unsaturated ketones, are well documented.[7] Intermediacy of a highly labile 2*H*-oxete has been firmly established by the isolation in a low-temperature reaction of hexafluoroacetone with ethoxyacetylene.[8] We found that the condensation of 1-decyne (**1b**) with acetaldehyde in dichloromethane at −30 °C is catalyzed by Brφnsted acid HBF$_4$−Et$_2$O yielding the enone **3b**, probably via the intermediate formation of 2*H*-oxete (Scheme 5). In contrast, Lewis acid BF_3−Et_2O was found to be less effective for the condensation.

Use of 1-propanol and *p*-nitrobenzyl alcohol in the oxidative coupling with **1b** afforded selectively the conjugated enones **3w** and **3x** in moderate to good yields (entries 24, 25); however, no formation of enones **3** was observed in the attempted reaction using
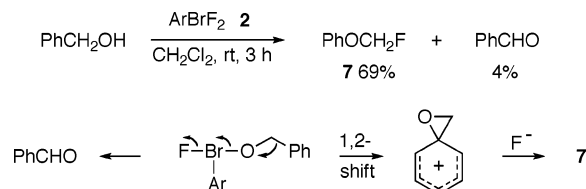
2-propanol and benzyl alcohol. Although 2-propanol is readily oxidized to acetone (70% yield) by difluorobromane **2** under the conditions, the subsequent [2 + 2] cyclization with **1b** does not take place, probably because of the increased steric demands of acetone. In the reaction of benzyl alcohol with **2**, oxidation to benzaldehyde competes with the more facile oxidative 1,2-phenyl rearrangement that produces fluoromethyl phenyl ether **7** (Scheme 6).[9] Decreased migratory aptitude of the *p*-nitrophenyl group favors oxidation of *p*-nitrobenzyl alcohol to the aldehyde, which, in turn, results in formation of the coupling product **3x**.

In summary, the difluoro-λ^3-bromane-induced oxidative coupling of alcohols with alkynes was shown to directly afford the construction of conjugated enones. The reaction is highly stereo- and regioselective and avoids the use of transition metal catalysts.

Supporting Information Available: Experimental details and Figures S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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