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Free-Radical-Initiated Coupling Reaction of Alcohols and Alkynes: Not C−O but C−C Bond Formation

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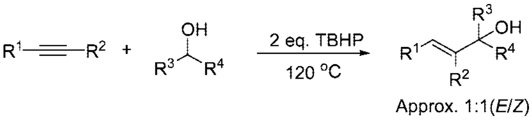
ABSTRACT



This work demonstrates an efficient method to prepare allylic alcohols via direct C−C bond formation using electron-rich alkynes and aliphatic alcohols initiated by *tert*-butyl hydroperoxide.

Addition of alcohols to alkynes promoted by mercury(II), generating one and/or two new carbon−oxygen bonds, has been known for 86 years.[1] Over the past decades, many efficient systems have been developed for this transformation.[2] Although it offers a powerful method to prepare enol ethers and acetals, alcoholysis of the triple bond seems to be the dominant interaction of alcohols and alkynes. Very few efficient protocols for direct radical-mediated carbon−carbon bond formation between alcohols and alkynes have been developed.[3] Uckun et al. found the unexpected product of an allylic alcohol in the thermolysis of 1,2-diethylnylbenzene in isopropyl alcohol at 165 °C.[3a] Later Nakagawa et al. also observed a C−C bond formation product in the reaction of alkynes and alcohols at 350 °C.[3b] Recently, Ishii et al. reported a coupling reaction of electron-deficient alkynes and alcohols by using the NHPI/Co^{II}/O_2 system.[3c] A month ago, Geraghty et al. reported a photoinduced C−C bond coupling reaction of alcohols and alkynes.[3d] However, these systems suffer from relatively high temperature,[3a,b] substrate limitation (alkynes with electron-withdrawing groups are necessary), and relatively low yields of the allylic alcohols.[3c,d] Recently, Krische et al.[3e] reported a very efficient ruthenium-catalyzed alcohol-alkyne C−C bond coupling. We wish to report herein an efficient reaction of alkynes and alcohols for direct sp^2−sp^3 C−C bond formation via peroxide-initiated C−H bond activation.

Radical initiators such as *tert*-butyl hydroperoxide (TBHP) and di-*tert*-butyl peroxide have been successfully used for

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(1) Reichert, J. S.; Bailey, J. H.; Niewland, J. A. *J. Am. Chem. Soc.* **1923**, *45*, 1552.

(2) For selected reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

(3) (a) Thoen, K. K.; Thoen, J. C.; Uckun, F. M. *Tetrahedron Lett.* **2000**, *41*, 4019. (b) Nakagawa, T.; Ozaki, H.; Kamitanaka, T.; Takagi, H.; Matsuda, T.; Kitamura, T.; Harada, T. *J. Supercrit. Fluids* **2003**, *27*, 255. (c) Oka, R.; Nakayama, M.; Sakaguchi, S.; Ishii, Y. *Chem. Lett.* **2006**, *35*, 1104. (d) Geraghty, N. W. A.; Hernon, E. M. *Tetrahedron Lett.* **2009**, *50*, 570. (e) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066–2067.

(4) (a) Urry, W. H.; Stacey, F. W.; Huyser, E. S.; Juveland, O. O. *J. Am. Chem. Soc.* **1954**, *76*, 450. (b) LaZerte, J. D.; Koshar, R. J. *J. Am. Chem. Soc.* **1955**, *77*, 910. (c) Walling, C.; Huyser, E. S. *Org. React.* **1963**, *13*, 91. (d) Stacey, F. W.; Harris, J. F. *Org. React.* **1963**, *13*, 150. (e) Curran, D. P. *Synthesis* **1988**, 489. (f) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (g) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (h) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (i) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (j) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci.* **2006**, *103*, 8928. (k) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505. (l) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (m) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497.

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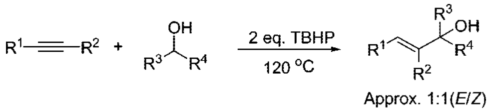
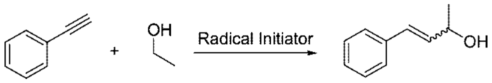
activation and/or functionalization of the sp^3 C−H bond and generation of α-hydroxyalkyl radicals from alcohols.[4] However, most of these procedures need a transition metal as the active catalyst. We successfully accomplished a metal-free, TBHP-initiated sp^2−sp^3 C−C bond formation via coupling of aliphatic alcohols with electron-rich alkynes (Scheme 1). To the best of our knowledge, this is the first example of a C−C bond formation via coupling of electron-rich alkynes with alcohols mediated by a radical initiator.

Scheme 1. C−C Bond Formation via Coupling of Alcohols with Alkynes



Initially, we chose ethanol and phenyl ethyne as standard substrates to optimize suitable conditions for this reaction (Table 1). The initial concentrations of phenyl ethyne demonstrated that 0.05 M (entry 2) was the ideal concentration for this reaction (entries 1−3). Reduction of the amount of TBHP gave relatively lower isolated yields (entries 4−6). The yields of the desired product decreased to 63% and 41% by using 2.0 and 0.2 equiv of TBHP (70% aqueous solution), respectively (entries 7 and 8). This indicated that the allylic alcohol could be obtained in moderate yield even in the presence of water, while the hydrolysis product was not observed. The use of di-*tert*-butyl peroxide instead of TBHP as an initiator gave only 14% yield of the product (entry 9). A 38% yield of the desired product was isolated when benzoyl peroxide (BPO) was used (entry 10). No products were detected by using $K_2S_2O_8$ as the radical initiator (entry 11). The coupling reaction did not proceed at a low temperature such as 90 °C (entry 12).

Table 1. Optimization of Typical Reaction Conditions[a]

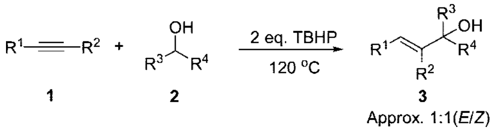


entry	initiators	concn (M)[b]	*t* (°C)	yield (%)[c]
1	2.0 equiv TBHP	0.1	120	73
2	**2.0 equiv TBHP**	**0.05**	**120**	**95**
3	2.0 equiv TBHP	0.01	120	76
4	0.2 equiv TBHP	0.05	120	75
5	0.5 equiv TBHP	0.05	120	60
6	1.0 equiv TBHP	0.05	120	68
7[d]	2.0 equiv TBHP	0.05	120	63
8[d]	0.2 equiv TBHP	0.05	120	41
9	2.0 equiv *t*BuOO*t*Bu	0.05	120	14
10	2.0 equiv BPO	0.05	120	38
11	2.0 equiv $K_2S_2O_8$	0.05	120	0
12	2.0 equiv TBHP	0.05	90	0

[a] Reaction conditions: phenylacetylene (0.5 mmol), TBHP (5−6 M in decane), unless otherwise noted, ethanol as solvent, 15 h. [b] Concentration of phenyl ethyne. [c] Isolated yield of the *E*/*Z* isomer; the ratio of the *E*/*Z* isomers was approximate 1:1 as analyzed by crude ^{1}H NMR. [d] TBHP (70% aqueous solution).

As depicted in Table 2, various alkynes and alcohols were tested as substrates for the coupling reaction under typical conditions. Reaction of terminal phenyl alkynes **1a**−**1d** and ethanol **2a** produced the desired product **3a**−**3d** in good to excellent yields (Table 2, entries 1−4). The electronic effect was not obvious as phenyl alkynes bearing an electron-withdrawing *p*-fluoro group **1c** or an electron-donating *p*-methoxy group **1d** gave similar yields of the product. Alkynes with internal triple bond such as 1-phenyl-1-propyne **1e** and diphenyl ethyne **1f** gave good isolated yields of the corresponding product **3e** and **3f** (entries 5 and 6). In the case of **1e**, the major product was not 3-phenyl-3-penten-2-ol but 4-phenyl-3-methyl-3-buten-2-ol **3e**, which may be due to the stability of the alkenyl radical intermediate. 2-Ethynyl pyridine **1g** was inactive in this system (entry 7). It is noteworthy that propargyl alcohol **1h** also produced the product **3g** in 70% yield (entry 8). In addition, only the *trans*-allylic diol **3g** was obtained. We next studied the coupling reaction of phenyl ethyne with various aliphatic alcohols (entries 9−13). Methanol did not give the desired product due to its relatively low reactivity (entry 9). *n*-Propanol and *n*-butanol gave the corresponding allylic alcohols **3h** and **3i** in good yields (entries 10 and 11), while isobutyl alcohol gave relatively lower yields of the products **3j** (entry 12). The corresponding allylic alcohol can be also obtained in moderate yield by using secondary alcohols such as isopropyl alcohol (entry 13). However, when benzyl alcohols were used as the substrates coupling with phenyl ethyne, the corre-

Table 2. Direct C−C Bond Formation by Using Alcohols with Alkynes[a]



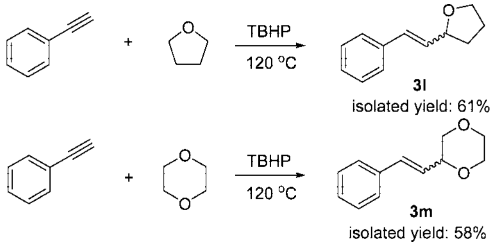
entry	alkynes (R^1, R^2)	alcohols	product	yield (%)[b]
1	R^1 = Ph, R^2 = H; **1a**	Ethanol	**3a**	95
2	R^1 = 4-MeC_6H_4, R^2 = H; **1b**	ethanol	**3b**	90
3	R^1 = 4-FC_6H_4, R^2 = H; **1c**	ethanol	**3c**	85
4	R^1 = 4-$OMeC_6H_4$, R^2 = H; **1d**	ethanol	**3d**	87
5	R^1 = Ph, R^2 = Me; **1e**	ethanol	**3e**	66
6	R^1 = Ph, R^2 = Ph; **1f**	ethanol	**3f**	65
7	R^1 = 2-Py, R^2 = H; **1g**	ethanol		0
8	R^1 = C(Ph)(Me)(OH), R^2 = H; **1h**	ethanol	**3g**	70[c]
9	**1a**	methanol		0
10	**1a**	*n*-propanol	**3h**	70
11	**1a**	*n*-butanol	**3i**	60
12	**1a**	*i*-butanol	**3j**	40
13	**1a**	*i*-propanol	**3k**	48

[a] Reaction conditions: alkynes (0.5 mmol), TBHP (5−6 M in decane, 1.0 mmol), alcohol (10 mL) as solvent, 120 °C, 15 h. [b] Isolated overall yield of the *E*/*Z* isomer; the ratio of the *E*/*Z* isomers was approximate 1:1 as analyzed by isolation of the pure isomer. [c] Only the *E* isomer was obtained.

sponding allylic alcohols were obtained in very low yields, and the appropriate solvent has not been found at present. Although the system is limited in alcohol scope and the *E*/*Z* ratio of the products is almost 1:1, the direct C−C bond construction and the sp^3 C−H bond activation features make this procedure very attractive.

It is believed that the alkoxyl radical would be generated in the procedure. Similar C−C coupling products were also obtained in the reactions of phenylacetylene **1a** with tetrahydrofuran (THF) and 1,4-dioxane (Scheme 2).

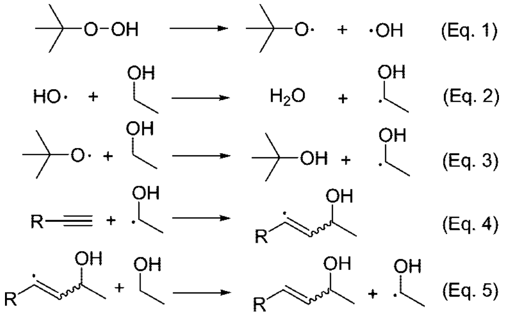
Scheme 2. Couplings of Phenylacetylene with THF and 1,4-Dioxane



A plausible mechanism for this coupling reaction is depicted in Scheme 3 and may involve a radical chain process. Homolytic cleavage of the radical initiator TBHP produces the alkoxyl radical and hydroxyl radical (eq 1). They abstract hydrogen from the alcohol, forming the α-hydroxyalkyl radical (eqs 2 and 3). Subsequently, an alkenyl radical is generated by addition of the α-hydroxyalkyl radical to the alkyne (eq 4). The hydroxyalkyl radical is regenerated via abstraction of hydrogen from alcohol by the alkenyl radical, and the radical chain grows (eq 5). The chain will be terminated once the alkyne is completely consumed.

In summary, this work demonstrates an efficient method to prepare allylic alcohols via direct C−C bond formation using electron-rich alkynes and aliphatic alcohols initiated by *tert*-butyl hydroperoxide. Compared with the traditional C−O bond formation reaction between alkynes and alcohols, the direct C−C bond construction via activation of the sp^3 C−H bond in this work might be novel and attractive in radical chemistry. Further investigation of this procedure including extension of the substrate scope is underway in our laboratory.

Scheme 3. Possible Mechanism for C−C Bond Formation via Coupling of Alcohols with Alkynes



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Supporting Information Available: Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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