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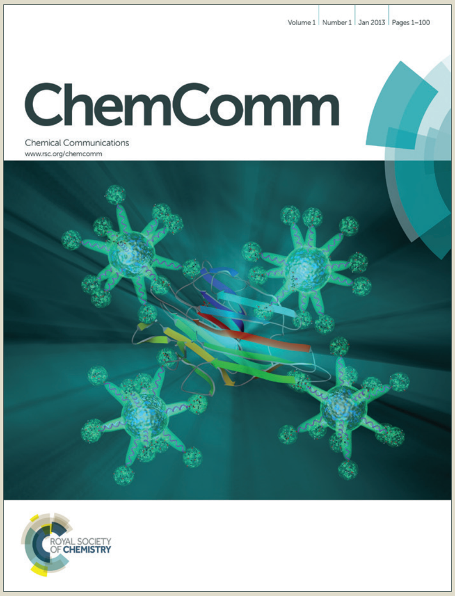

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

A Radical Anti-Markovnikov Addition of Alkyl Nitriles to Simple Alkenes via Selective sp^3C-H Bond Functionalization

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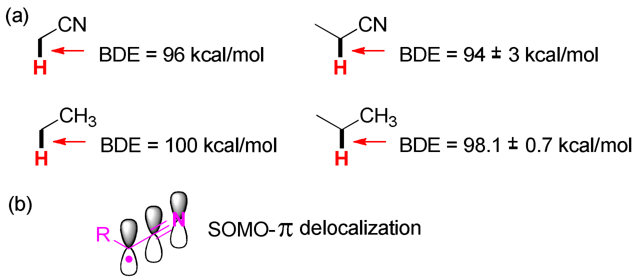
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

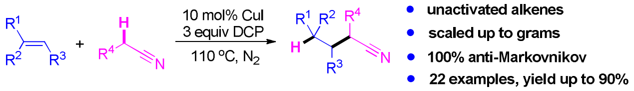
An efficient hydrocyanoalkylation of unactivated alkenes with alkyl nitriles was developed. Through this free-radical-initiated selective activation of the α-C(sp^3)-H bond of acetonitriles, an anti-Markovnikov addition of α-cyano C-centered radical to olefins has been achieved, which allows facile and convenient access to functionalized nitriles in large scales.

Nitriles are widely found in diverse areas of sciences such as materials, polymer as well as organic chemistry.[1] Direct functionalization of the α-C-H bond of simple nitriles represents one of the most efficient and low-toxic strategies for synthesis of substituted nitriles.[2] Due to the weak acidity of the α-proton of acetonitrile [p*K*a(MeCN) ≈ 31.3, DMSO], strong base-promoted α-functionalization of nitriles has been explored in the past decades.[3] However, most of these strategies are limited to reaction with electrophiles via their enolate form, which could generate organometallic complexes with transition metal salts.[4] As our continuous studies on free-radical-initiated C-C bond formations via sp^3 C-H bond activation,[5] we postulate that the α-C-H bond of alkyl nitriles could be selectively activated through electron transfer processes. Consideration of the bond dissociation energy (BDE) of the C-H bond[6] and stability of the radical intermediate, the cleavage of the α-C-H bond of alkyl nitriles would occur prior to other sp^3 C-H bonds (Scheme 1). The electrophilic α-cyano carbon-centered radical would be ready to undergo various free radical reactions.



Scheme 1. (a) Comparison of BDEs of C-H bond in nitriles and alkanes; (b) Stability of the α-cyano carbon-centered radical.

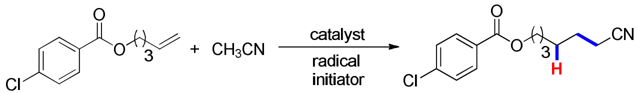
In fact, the addition of nitriles to alkenes has been very rarely investigated in the past years. Very few examples of radical addition of acetonitrile to norbornene[7], cycloalkenes[8] and styrene[9] were reported in the past decades. However, these systems suffered from very low yields, limited substrate scope, undesired by-products and extremely harsh conditions. Very recently, several copper-promoted radical reactions of alkyl nitriles with activated alkenes were studied by Gao and You,[10] Li,[11] Zhu[12] et al. Although these systems provide efficient accesses to cyano-substituted oxindoles, ketones, and ethers, these reactions are limited to activated alkenes such as *N*-arylacrylamides, diaryl allyl alcohols, and styrenes. More efficient cyanoalkylation of unactivated alkenes with alkyl nitriles remains highly desirable. Herein, we wish to report an efficient radical-initiated hydrocyanoalkylation of simple alkenes with alkyl nitriles (Scheme 2).



Scheme 2. Radical addition of alkyl nitriles to simple alkenes.

Initially, a series of reactions of pent-4-en-1-yl 4-chlorobenzoate with acetonitrile were carried out to optimize the reaction conditions (Table 1). It is found that the radical initiator is critically important to this reaction. The product can be isolated in 76% yield without catalyst (entry 1). 90% yield of the product was obtained by addition of 10 mol% of CuI, which was more efficient than other copper salts such as CuCl, CuBr, Cu_2O (entries 2-6). Interestingly, this reaction was found to be sensitive to the radical initiators (entries 7-11). Dicumyl peroxide (DCP) was proved to be more efficient than others, such as *tert*-butyl-hydroperoxide(TBHP), *tert*-butyl-peroxybenzoate (TBPB), di-*tert*-butyl peroxide (DTBP), and benzoyl peroxide (BPO) etc. Increasing the concentration of the reactants led to decrease of the yields (entries 12 and 13), which should be due to the cage effect of free radical reactions. No desired product was observed when the reaction was conducted at 80 °C (entry 14).

Table 1. Modification of the typical reaction conditions. [a]



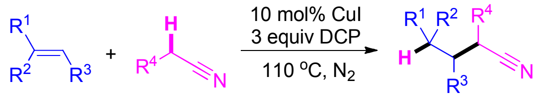
Entry	Catalyst (mol %)	Radical initiator (equiv)	Solvent (mL)	Yield (%)[b]
1	-	DCP (3)	5	76
2	CuCl(10)	DCP (3)	5	75
3	CuBr(10)	DCP (3)	5	70

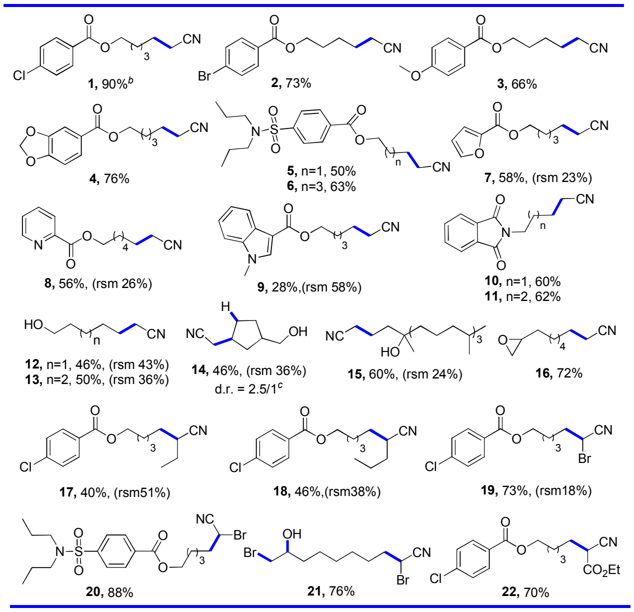
4	Cu_2O(10)	DCP (3)	5	78
5	**CuI (10)**	**DCP (3)**	**5**	**90**
6	CuI (2)	DCP (3)	5	79
7	CuI (10)	TBHP (3)	5	-
8	CuI (10)	TBPB (3)	5	22
9	CuI (10)	DTBP (3)	5	-
10	CuI (10)	BPO (3)	5	10
11	CuI (10)	DCP (2)	5	80
12	CuI (10)	DCP (3)	3	69
13	CuI (10)	DCP (3)	1	53
14[c]	CuI (10)	DCP (3)	5	-

[a] Reaction conditions: pent-4-en-1-yl 4-chlorobenzoate (1 equiv, 0.20 mmol), acetonitrile as solvent, N_2, 110 °C, sealed tube, 10 h, unless otherwise noted. [b] Isolated yields. [c] 80 °C.

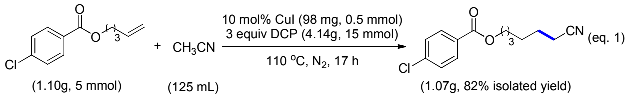
As illustrated in Table 2, a variety of simple alkenes and alkyl nitriles were applied in this system. Diverse functional groups such as halogen, ester, sulfonamide, heterocycle, amide, hydroxyl, epoxide etc can all be well survived (entries **1**-**16**). It is noteworthy that cyclic alkenes such as cyclopent-3-en-1-ylmethanol gave moderate yield of the desired product (entry **14**). Allylic alcohol such as isophytol gave the corresponding adduct in 60% yield (entry **15**). Notably, 1, 2-epoxy-7-octene reacted with acetonitrile gave the product **16** in 72% yield, and the strained three-membered ring was well-tolerated. In the case of nitriles, it is found that a wide range of alkyl nitriles are amenable to this system (entries **17**-**22**). Surprisingly, 2-bromoacetonitrile gave the desired products with retention of the Br-atom in high yields (entries **19**-**21**). It is also interesting that reaction of 2-epoxy-7-octene with 2-bromoacetonitrile afforded product **21** in 76% yield. Ring opening may happen via attack of epoxide by Br-atom. Ethyl 2-cyanoacetate also gave good yields of the product **22**. However, styrenes are not effective in this system. Finally, the reaction could be easily scaled up to gram level, which suggests that it possess an industrial prospect (equation 1).

Table 2. CuI-mediated Cyanoalkylation of Simple Alkenes[a]

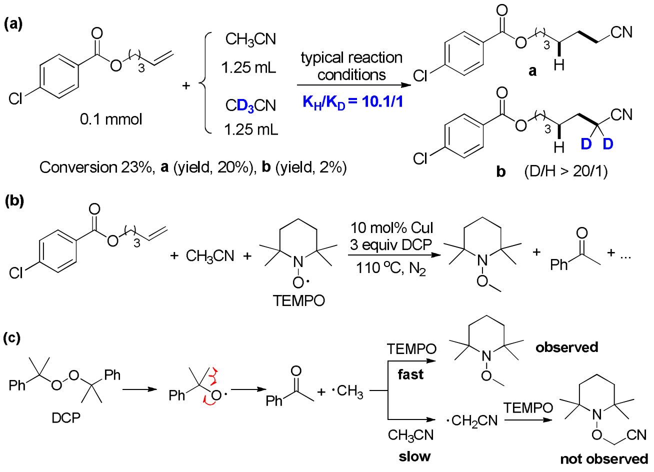




[a] Reaction conditions: Alkenes (1 equiv, 0.20 mmol), CuI (0.02 mmol), DCP (3 equiv, 0.60 mmol), 5 mL of nitriles as solvent, N_2, 110 °C, sealed tube, 10 h. [b] Isolated yields. [c] Obtained as a mixture of diastereoisomers and the diastereomeric ratio determined by ^1H NMR spectroscopy.

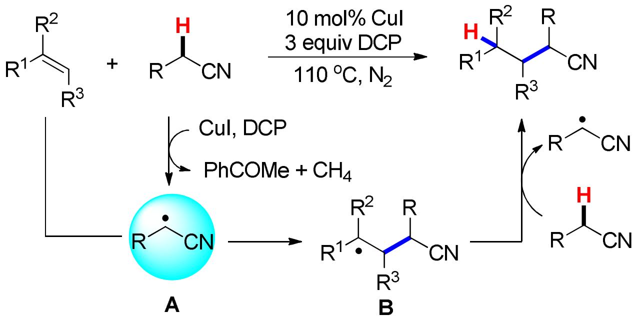


Finally, mechanistic studies indicate a free radical process might be involved in this reaction (Scheme 3, also see SI). We first studied the intermolecular competing kinetic isotope effect (KIE). The initial KIE is significant with $K_H/K_D = 10.1$, which suggests that the C_{sp3}-H bond cleavage might be involved in the rate-determining step of the reaction (Scheme 3a). Then radical trapping by addition of TEMPO into the system was carried out, and the reaction was completely inhibited. It is not the 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetonitrile but the 1-methoxy-2,2,6,6-tetramethylpiperidine was observed (Scheme 3b). It might be due to that the combination rate of methyl radical with TEMPO is faster than rate of hydrogen abstraction and/or reaction of acetonitrile radical with TEMPO (Scheme 3c).



Scheme 3. Mechanistic Studies.

Based on the experimental data and literatures precedent, a plausible mechanism is proposed in Scheme 4. The CuI-promoted homolysis of DCP followed by β-cleavage offers acetophenone and methyl radical. Hydrogen abstraction of acetonitrile by methyl radical gives methane and acetonitrile radical **A**. A carbon-centered radical **B** would be formed by addition of **A** to the alkene. Abstraction of the H-atom from acetonitrile by **B** would regenerate radical **A** and afford the final product. This radical chain propagation reaction of **B** with acetonitrile proceeds smoothly because radical **B** is more active than acetonitrile radical **A** which could be stabilized by SOMO-π delocalization. But in the case of styrene, the secondary free radical intermediate, benzyl radical should be more stable than acetonitrile radical. Hence, the radical chain propagation via hydrogen abstraction of acetonitrile by benzyl radical would not occur. That is why styrene and its derivatives are not effective in this system.



Scheme 4. Suggested Mechanism.

In summary, we have developed an efficient hydrocyanoalkylation of simple alkenes with alkyl nitriles via a free radical hydrogen atom transfer process. This strategy could be applied to preparing a wide range of substituted nitriles in very high selectivities and large scales. Further studies on free-radical-initiated C-C bond formation via sp^3 C-H activation of simple acetonitriles are ongoing in this laboratory.

This project is supported by the National Science Foundation of China (Nos. 21272096, 21472080).

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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