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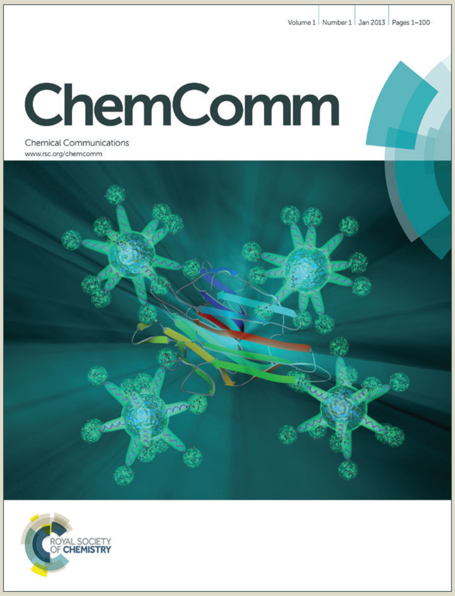

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Oxidative Radical 1,2-Alkylarylation of Alkenes with *α*-C(sp^3)-H Bonds of Acetonitriles Involving 1,2-Aryl Migration

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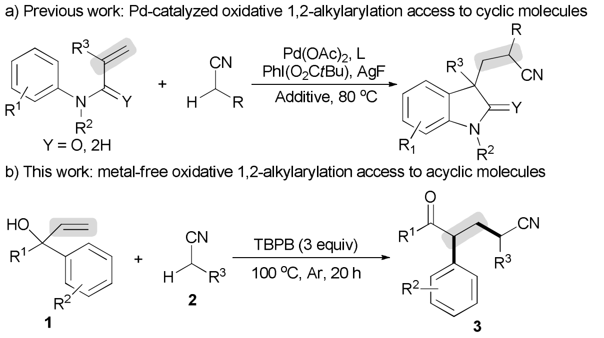
A novel metal-free oxidative 1,2-alkylarylation of unactivated alkenes with the *α*-C(sp^3)-H bonds of acetonitriles for the synthesis of 5-oxo-pentanenitriles is presented. In the presence of TBPB (*tert*-butyl peroxybenzoate), a variety of *α*-aryl allylic alcohols underwent the 1,2-alkylarylation reaction with acetonitriles, giving 5-oxo-pentanenitriles in good to excellent yields. This method proceeds via the C(sp^3)-H oxidative coupling with the C-C double bond and 1,2-aryl-migration, and represents a new access to acyclic molecules through metal-free oxidative alkene 1,2-alkylarylation.

The difunctionalization of alkenes has become a powerful strategy for the assembly of more complex structures in synthesis through simultaneously introduction of two functional groups across alkenes.[1] As a result, the discovery of new efficient strategies for the alkene difunctionalization has attracted much attention.[1-4] Of particular interest are the oxidative 1,2-alkylarylation transformations that proceed via direct oxidative coupling of the C-C double bond with a C(sp^3)-H bond[5] followed by incorporation of another aryl group.[2-4] However, the majority of these transformations proceed through the aryl intramolecular incorporation, thereby limiting to the synthesis of oxindoles and related heterocycles.[2,3] Moreover, only two papers using *α*-C(sp^3)-H bonds of acetonitriles for the oxidative alkylarylation of alkenes have been reported.[3] Liu and co-workers have first described a palladium-catalyzed oxidative alkylarylation of activated alkenes with acetonitriles to construct various oxindoles (Scheme 1a).[3a] Subsequently, they have extended this similar Pd-catalyzed oxidative strategy to alkylarylation of unactivated alkenes.[3b] However, the two oxidative alkylarylation methods are still restricted to the construction of oxindoles and related heterocycles as well as the requirement of expensive Pd catalysts. Thus, a new strategy for general alkylarylation of alkenes under metal-free leading to diverse complex molecules is highly desirable.

Herein, we wish to report a new metal-free oxidative 1,2-alkylarylation between the C-C double bonds of α-aryl allylic alcohols[4] and the *α*-C(sp^3)-H bonds of acetonitriles using TBPB as oxidant for the assembly of 5-oxo-pentanenitriles, useful build blocks in synthesis[6] (Scheme 1b); this method achieves the alkene 1,2-alkylarylation by the C(sp^3)-H oxidative coupling with the C-C double bond and 1,2-aryl-migration, and represents the first access to acyclic molecules by metal-free oxidative 1,2-alkylarylation of alkenes with *α*-C(sp^3)-H bonds of acetonitriles.



Scheme 1 Oxidative 1,2-Alkylarylation of Alkenes with Acetonitriles.

As shown in Table 1, the reaction between 1,1-diphenylprop-2-en-1-ol (**1a**) and acetonitrile (**2a**) was chosen as a model to explore the optimal reaction conditions. After a series of trials, the best results were obtained with 3 equiv TBPB at 100 °C under argon atmosphere for 20 h (entry 1). Under the standard conditions, conversion of alkene **1a** was completed through C(sp^3)-H oxidative coupling and 1,2-Ph-mirgation, giving the target alkene difunctionalization product **3aa** in 90% yield. Screening on the amount of TBPB revealed that the presence of 2 equiv TBPB decreased the yield from 90% (entry 1) to 55% (entry 2), and 4 equiv TBPB (entry 3) afforded the same results as those of 3 equiv TBPB. The effect of the reaction temperatures was found to affect the reaction (entry 1 vs. entries 4 and 5). Alkene **1a** at 120 °C remained high reactivity of (89% yield; entry 4). However, at 80 °C it lowered dramatically, decreasing the yield of product **3aa** to 34% (entry 5). It should be noted that the presence of air suppresses the reaction, and decreases the yield to 72% (entry 6). Finally, three other peroxides, including TBHP (*tert*-buty hydroperoxide), DTBP (di-*tert*-butyl peroxide) and BPO (benzoyl peroxide), were investigated (entries 7-9), and the results showed that they were less effective than TBPB. Both TBHP and DTBP had lower activity for the reaction in terms of yield (entries 7 and 8). Although BPO had a lower activity than TBPB, good yield of product **3aa** was still achieved (78% yield, entry 9).

After determining the standard reaction conditions, we next exploited the scope of this difunctionalization protocol with respect to α-aryl allylic alcohols (**1**) and acetonitriles (**2**) (Table 2). Initially, three other acetonitriles, including butyronitrile (**2b**), 2-phenylacetonitrile (**2c**) and 2-methoxyacetonitrile (**2d**), were examined in the presence of

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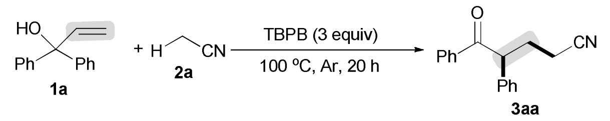
Table 1 Screening of the Optimal Conditions[a]



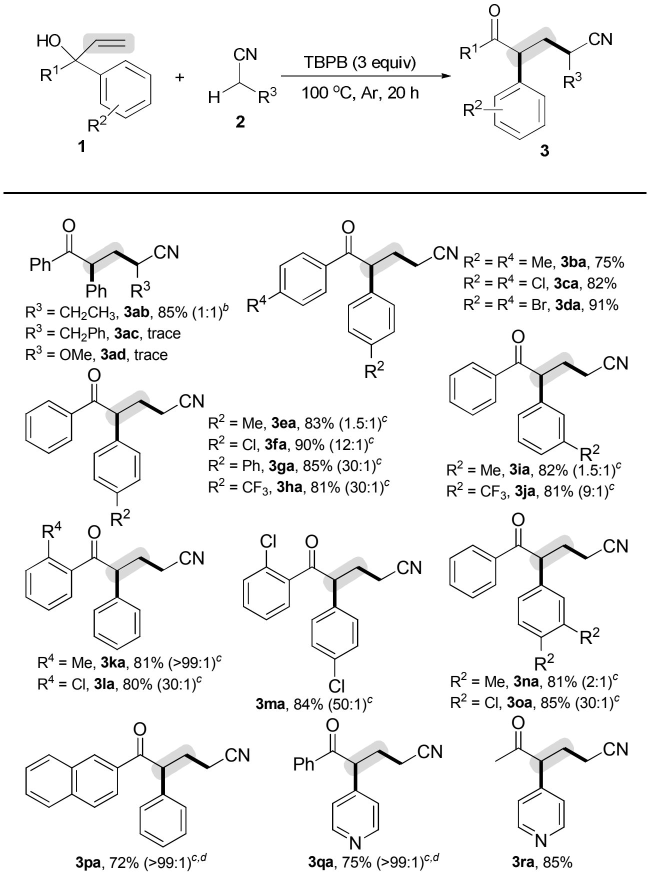
Entry	Variation from the standard conditions	Isolated yield (%)
1	none	90
2	TBPB (2 equiv)	65
3	TBPB (4 equiv)	88
4	at 120 °C	89
5	at 80 °C	34
6	air (1 atm) instead of argon	72
7[b]	TBHP (3 equiv) instead of TBPB	8
8	DTBP (3 equiv) instead of TBPB	16
9	BPO (3 equiv) instead of TBPB	78

[a] Reaction conditions: **1a** (0.3 mmol), MeCN **2a** (2 mL), and TBPB (3 equiv) under argon atmosphere at 100 °C for 20 h. [b] TBHP (5 M in decane).

1,1-diphenylprop-2-en-1-ol (**1a**) and TBPB (Products **3ab-ad**). Interestingly, butyronitrile (**2b**) was viable for reacting with 1,1-diphenylprop-2-en-1-ol (**1a**), furnishing the desired product **3ab** in 73% yield. However, both 2-phenylacetonitrile (**2c**) and 2-methoxyacetonitrile (**2d**) had no reactivity for the reaction (Products **3ac** and **3ad**).

Subsequently, a range of α-aryl allylic alcohols **1** were investigated in the presence of acetonitrile (**2a**) and TBPB (Products **3ba-sa**). Screening of the substitution effect suggests that which aryl group migration occurs depends on the electronic and sterical hindrance properties of substituents on the aryl ring: the aryl-migration reactivity based on the electronic property decreased from electron-deficient aryl groups to electron-rich aryl groups, and based on the sterical hindrance property decreased from *p*-substituted-Ph and *m*-substituted-Ph to Ph to *o*-substituted-Ph. Alcohols **1b-d**, which contain two same substituted aryl groups, such as two 4-MePh, two 4-ClPh or two 4-BrPh groups, on the *α* position delivered products **3ba-da** in high yields. Alcohols **1e-h** with a Ph group and a *p*-substituted-Ph group underwent the *p*-substituted-Ph group migration as the major process, giving the corresponding products **3ea-ha** in good yields. Similar migration process took place for alcohols **1i** and **1j** with a Ph group and a *m*-substituted-Ph group (Products **3ia** and **3ja**). However, alcohols **1k** and **1l** with a Ph group and a *o*-substituted-Ph group delivered the major Ph group-migration products **3ia** and **3ja** in 82% and 81% yields. This migration rule is suitable for alcohol **1m** with two different aryl groups, a *p*-substituted-Ph group and *o*-substituted-Ph group, which assembled the *p*-substituted-Ph group-migration product **3ma** in good yield. Interestingly, alcohols **1n** and **1o**, which contain two different substituted aryl groups, were also viable substrates for the reaction, and selectivity of their products **3na** and **3oa** toward the migrating 3,4-disubstituted-Ph group. It should be noteworthy that halogen functional groups, F, Cl and Br, were well-tolerated under the optimal conditions, thereby making the difunctionalization protocol more useful in organic synthesis due to additional modifications at the halogenated positions (Products **3ca**, **3da**, **3fa**, **3la**, **3ma** and **3oa**). In alcohols **1p** the migration of the Ph group had precedence over naphthalen-2-yl group in 72% yield (product **3pa**). The Ph- and pyridin-4-yl-substituted alcohol **1q** also worked well and mainly offered the pyridin-4-yl-migration product **3qa** in good yield. Gratifyingly, the reaction was applicable to 2-(pyridin-4-yl)but-3-en-2-ol (**1r**), exclusively furnishing the pyridin-4-yl-migrating product **3ra** in 85% yield.

Table 2 ,2-Alkylarylation of Alkenes (**1**) with Acetonitriles (**2**)[a]



[a] Reaction conditions: **1** (0.3 mmol), **2** (2 mL), and TBPB (3 equiv) under argon atmosphere at 100 °C for 20 h. [b] The d.r. value ratio of product **3ab** is given in parenthesis determined by GC-MS analysis of the crude product. [c] The ratio of product **3**/its isomer is given in parenthesis determined by GC-MS analysis of the crude product. [d] For 30 h.

To understand the mechanism for the current reaction, some control experiments were carried out (Scheme 2). As shown in Scheme 2, a mixture two different *α,α*-diaryl allylic alcohols **1a** and **1c** reacted with acetonitrile (**2a**) under the standard conditions was conducted (Eq 1). The results demonstrated that no cross aryl-migrating products were observed, suggesting that the 1,2-aryl migration proceeds via an intramolecular process. Moreover, among the reaction of alcohol **1a** with acetonitrile (**2a**), three radical inhibitors (4 equiv), TEMPO, hydroquinone and BHT, resulted in no conversion of alcohol **1a** into product **3aa** (Eq 2), suggesting that this current reaction may proceed via a radical process.

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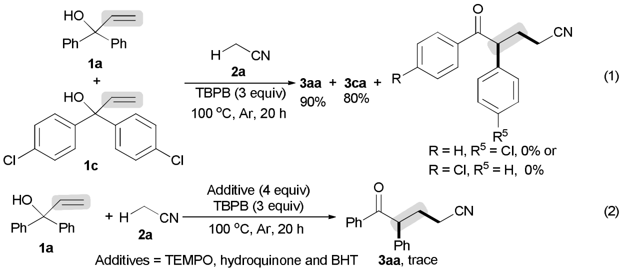
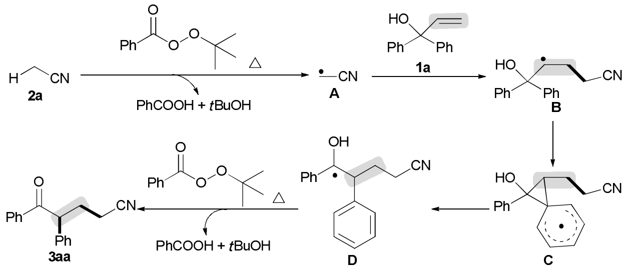


Scheme 2 Control Experiments.

The possible mechanism outlined in Scheme 3 was proposed for the oxidative difunctionalization reaction.[2-4] Initially, TBPB is split into ^{t}BuO· radical and PhCOO· radical under heating, supporting by the results of entries 1, 4 and 5 in Table 1. Subsequently, single-electron-transfer (SET) takes place to form alkyl radical **A**, followed by addition to the C-C double bond of substrate **1a** affords new alkyl radical **B**. Within alkyl radical intermediate **B**, 1,2-migration of aryl group occurs via spiro[2,5]octadienyl radical **C** to produce intermediate **D**.[4] Finally, intermediate **D** is easily converted into product **3aa** with the aid of TBPB under heating.



Scheme 3 Possible Mechanism.

In summary, we have illustrated the first oxidative 1,2-alkylarylation between the C-C double bonds of α-aryl allylic alcohols and the α-C(sp^3)-H bonds of acetonitriles using TBPB as oxidant under metal-free conditions. This method achieves the C(sp^3)-H oxidative coupling with the C-C double bond and 1,2-aryl-migration, and provides an efficient and highly atom-economic access to various acyclic molecules, 5-oxo-pentanenitriles, through the oxidative 1,2-alkylarylation of alkenes.

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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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