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Copper-catalyzed three-component oxycyanation of alkenes†

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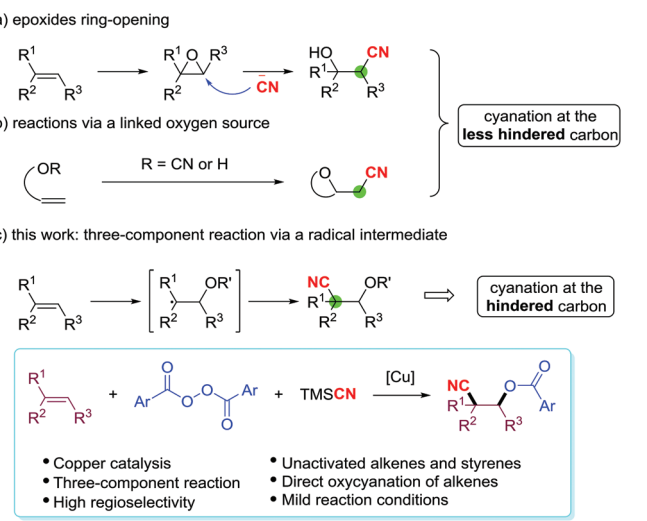
A copper-catalyzed, three-component reaction for the direct oxycyanation of various alkenes with aryl diacyl peroxides and trimethylsilyl cyanide has been developed. Both unactivated alkenes and styrenes are reliable substrates and produce β-cyanohydrin derivatives. An asymmetric version of this reaction has been conducted and proceeds well.

Nitriles are important molecules that are structural motifs in natural products and pharmaceuticals.[1] They are also one of the most versatile types of compounds in organic synthesis because the cyano group can be easily transformed into other different functional groups to afford valuable organic compounds.[2] In view of the abundant supply of alkenes, direct vicinal cyanofunctionalization of C=C double bonds is a straightforward strategy for the construction of nitriles. The cyanofunctionalization of the C=C double bond has drawn much attention and significant advances have been achieved in the hydrocyanation[3] and carbocyanation[4] of alkenes through either an intramolecular or an intermolecular process.[5]

The direct vicinal oxycyanation of alkenes is a remarkable strategy which simultaneously incorporates a cyano group and an oxygen-containing group into the C=C double bond, forming versatile β-cyanohydrins or their derivatives. A common and versatile approach to β-cyanohydrins is the nucleophilic ring-opening of strained triangular epoxides with a cyanide anion source (Scheme 1a).[6] The cyanide anion prefers to regioselectively attack the less substituted carbon center in the epoxide. In recent years, successful oxycyanation of alkenes has also been developed. Nakao *et al.*[7] and Shi's group[8] independently disclosed a palladium-catalyzed intramolecular oxycyanation of C=C double bonds (Scheme 1b). Both the methods are proposed to involve the cleavage of the O-CN bond by an electron-rich Pd(0) catalyst, as depicted in their mechanisms. On the other hand, two-component oxycyanation of alkenes with a linked oxygen source has been reported by Alexanian,[9] Han,[5g] and Zhu[10] (Scheme 1b). However, these oxycyanation reactions are limited by their tendency to generate β-cyanohydrin derivatives with the cyano group attached to the less substituted carbon center.

An attraction of three-component oxycyanation of alkenes is that it uses a one-step process to assemble multifunctional structures from various compounds, and this can greatly broaden the utility of the method. Recently, Liu *et al.* described an electron donor–acceptor (EDA) complex enabled three-component oxycyanation of C=C double bonds.[11] Electron-rich vinyl ethers are the key substrates in this reaction, but the direct oxycyanation of alkenes in a three-component model with generic unactivated alkenes is a valuable process. Herein, we report the three-component, copper-catalyzed oxycyanation of unactivated alkenes and styrenes with



Scheme 1 Oxycyanation of alkenes.

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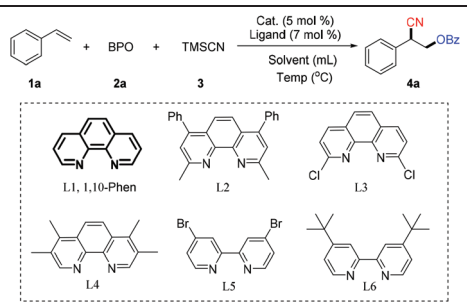
aryl diacyl peroxides as the oxygen source and trimethylsilyl cyanide (TMSCN) as the cyano source (Scheme 1c). Mechanistic studies suggest that the O-radical attacks the double bond first and the reaction produces the β-cyanohydrin derivatives with the cyano group at the more substituted carbon center.

We began by examining the scope of copper catalysts, ligands, solvents and temperature, using the model reaction of styrene with benzoyl peroxide[12] (BPO, **2a**) and TMSCN (**3**). The details of the optimization of the conditions are provided in Table 1. Copper catalysts were screened with 1,10-phenanthroline (**L1**) as the ligand and CH_3CN as the solvent at 50 °C. Cu$(CH_3CN)_4PF_6$ was the most effective catalyst tested with which the reaction provided the desired oxycyanation product (**4a**) in 47% yield (entries 1–3). Solvents such as HFIP (hexafluoroisopropanol) and 1,4-dioxane were less efficient than CH_3CN, but TFEA (2,2,2-trifluoroethanol) provided the highest yield (entries 4–6). The yield of **4a** was increased to 77% by using higher concentrations of the substrates (entries 7–9). Other ligands were evaluated, and it was found that 1,10-phenanthroline is the most effective ligand (entries 10–14 *vs.* entry 9). The yield of the desired product (**4a**) was further improved to 83% by using two equivalents of TMSCN (entry 15). In the absence of any ligand, the catalytic efficiency drops dramatically (entry 16).

Table 1 Optimization of the reaction conditions[a]



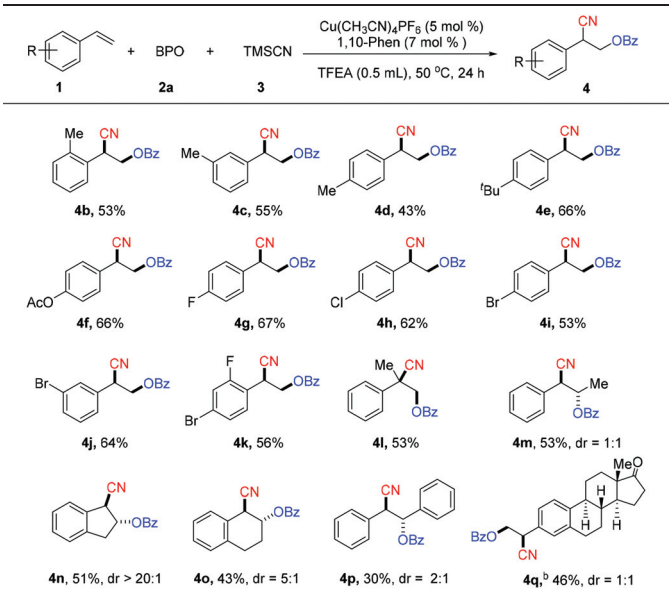
Entry	Cat.	Ligand	Solvent (mL)	Yield[b] (%)
1	Cu$(CH_3CN)_4PF_6$	**L1**	CH_3CN (2)	47
2	CuTc	**L1**	CH_3CN (2)	17
3	CuOAc	**L1**	CH_3CN (2)	2
4	Cu$(CH_3CN)_4PF_6$	**L1**	HFIP (2)	33
5	Cu$(CH_3CN)_4PF_6$	**L1**	Dioxane (2)	23
6	Cu$(CH_3CN)_4PF_6$	**L1**	TFEA (2)	54
7	Cu$(CH_3CN)_4PF_6$	**L1**	TFEA (1.5)	60
8	Cu$(CH_3CN)_4PF_6$	**L1**	TFEA (1)	67
9	Cu$(CH_3CN)_4PF_6$	**L1**	TFEA (0.5)	77
10	Cu$(CH_3CN)_4PF_6$	**L2**	TFEA (0.5)	38
11	Cu$(CH_3CN)_4PF_6$	**L3**	TFEA (0.5)	35
12	Cu$(CH_3CN)_4PF_6$	**L4**	TFEA (0.5)	66
13	Cu$(CH_3CN)_4PF_6$	**L5**	TFEA (0.5)	69
14	Cu$(CH_3CN)_4PF_6$	**L6**	TFEA (0.5)	71
15[c]	Cu$(CH_3CN)_4PF_6$	**L1**	TFEA (0.5)	83(81)
16	Cu$(CH_3CN)_4PF_6$	—	TFEA (0.5)	13

[a] Reaction conditions: **1a** (0.50 mmol, 1 equiv.), **2a** (1.5 equiv.), **3** (1.5 equiv.), cat., ligand, and solvent, at 50 °C for 24 h. [b] Yield was determined by ^{1}H NMR analysis. [c] 2 equiv. of **3** were used; an isolated yield in parentheses.

With the optimized reaction conditions in hand, the substrate scope of the reaction with respect to vinylarenes was investigated (Table 2). The reactions of *o*-, *m*- or *p*-alkyl-substituted vinylarenes with BPO afforded the corresponding oxycyanation products (**4b–4e**) in moderate yields. Vinylarenes bearing an ester substituent also underwent this reaction, affording the product (**4f**) in 66% yield. When a halogen, such as fluorine, chlorine, or bromine, was attached to the phenyl ring, the reaction afforded the desired products (**4g–4k**) in moderate yields. A 1,1-disubstituted vinylarene was also examined and it was found to be a suitable substrate in the reaction, producing the product (**4l**) in 53% yield. Acyclic or cyclic 1,2-disubstituted vinylarenes were also compatible under the reaction conditions, giving the corresponding oxycyanation products (**4m–4p**) in moderate yields. This reaction can proceed with more complex substrates. For example, the oxycyanation product (**4q**) can be produced in 46% yield with the substrate that is a derivative from the natural product estrone.[13]

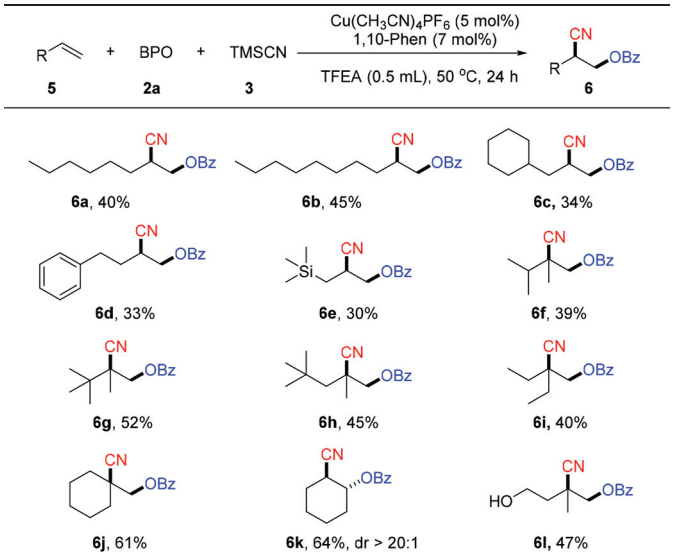
We next examined unactivated alkenes, a class of challenging but useful substrates (Table 3). In general, the reactions of a variety of unactivated alkenes afford the corresponding products with less efficiency than the reactions of styrenes. Unactivated alkenes with an alkyl chain could afford the desired oxycyanation in moderate yield (**6a–6c**). 1,1-Disubstituted unactivated alkenes were suitable substrates for this reaction, producing the oxycyanation products (**6f–6j**) in yields of 39–61%. Notably, this reaction can use not only terminal alkenes as the substrates, but also internal alkenes. For example, cyclohexene is a good substrate for the reaction, affording the desired product (**6h**) in 61% yield. Substrates

Table 2 Scope for oxycyanation of styrenes[a]



[a] Reaction conditions: **1** (0.50 mmol, 1 equiv.), **2a** (1.5 equiv.), and **3** (2 equiv.) in TFEA (0.5 mL) at 50 °C for 24 h. [b] Addition of 5 mol% of Hantzsch ester.

Table 3 Scope of the oxycyanation reaction with unactivated alkenes[a]



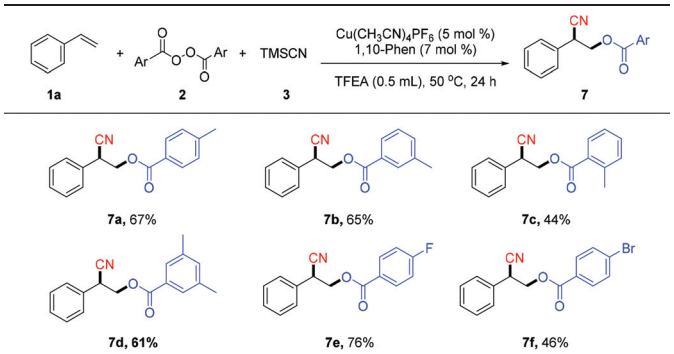
[a] Reaction conditions: **5** (0.50 mmol, 1 equiv.), **2a** (1.5 equiv.), and **3** (2 equiv.) in TFEA (0.5 mL) at 50 °C for 24 h.

with a phenyl group (**6d**), a trimethylsilyl group (**6e**) or a free hydroxyl group (**6l**) are compatible with the reaction, making it a powerful method for the difunctionalization of alkenes.

The scope of diacyl peroxides in this oxycyanation reaction was also examined (Table 4). A variety of diacyl peroxides can afford the corresponding oxycyanation products (**7a–7f**) in moderate yields.[12a]

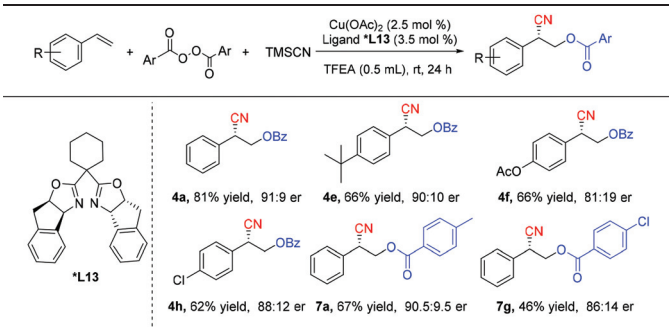
The copper-catalyzed asymmetric oxycyanation of alkenes was also evaluated.[12c,14] After considerable evaluation (for details, see the ESI†), a combination of a Cu(II) species and a bisoxazoline ligand (***L13**) was found to be the most efficient catalyst system, and the results are summarized in Table 5. The copper-catalyzed asymmetric oxycyanation of alkenes could afford the desired products with an er value of 91 : 9. However, under the asymmetric conditions, almost no enantiomeric excess was obtained with an aliphatic alkene (**5d**).

Table 4 Scope of the oxycyanation reaction with diacyl peroxides[a]



[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), and **3** (1.0 mmol) in TFEA (0.5 mL) at 50 °C for 24 h.

Table 5 Asymmetric oxycyanation of alkenes[a]

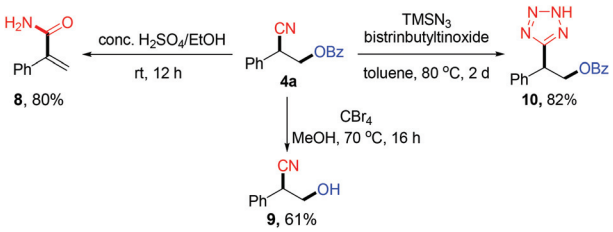


[a] **1** (0.5 mmol), **2** (0.75 mmol), and **3** (1.0 mmol) in TFEA (0.5 mL) at rt for 24 h.

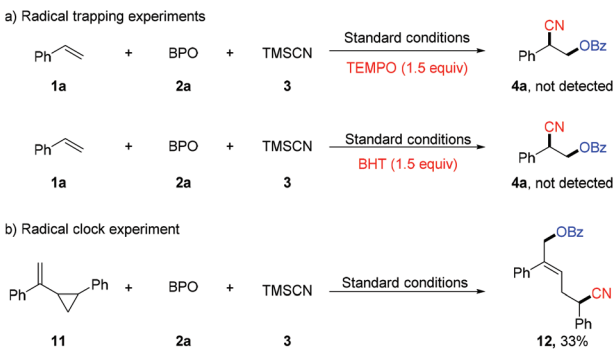
The absolute configuration of the products (R-form of **4e**, CCDC 2040065†) was confirmed by X-ray single crystal diffraction.

In order to demonstrate the potential synthetic value of the oxycyanation reactions, we investigated the subsequent transformations of compound **4a**. As shown in Scheme 2, the oxycyanation product (**4a**) efficiently engaged in selective olefination, deprotection or cyano functionalization to afford an α,β-unsaturated primary amide (**8**), a β-cyanohydrin (**9**), or a tetrazole (**10**).[15] These results demonstrate the potential of this method to provide valuable synthetic compounds.

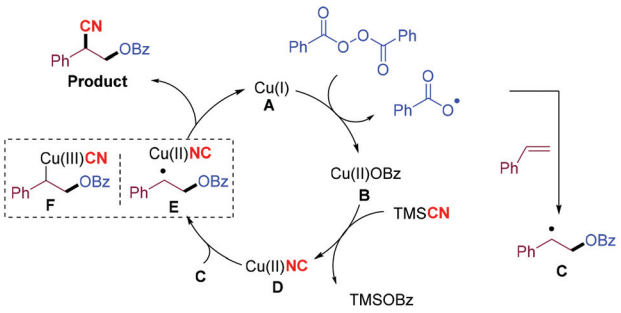
Preliminary experiments were performed to probe the mechanism of the oxycyanation reaction (Scheme 3). First,



Scheme 2 Synthetic applications of the oxycyanation products.



Scheme 3 Preliminary mechanistic studies.



Scheme 4 Plausible catalytic cycle for the oxycyanation of alkenes.

radical trapping experiments were conducted and found that TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (2,6-di-*tert*-butyl-4-methylphenol) inhibit the formation of the oxycyanation product[16] (Scheme 3a). The results are consistent with the involvement of radical species. To further support this hypothesis, compound **11** bearing a cyclopropylmethyl moiety was tested as a radical clock (Scheme 3b).[17] The reaction of compound **11** with BPO and TMSCN afforded the ring-opening product (**12**) in 33% yield, further supporting the involvement of radical species in the reaction.

Based on these mechanistic studies, a catalytic mechanism† for the oxycyanation reaction is proposed (Scheme 4). Initially, a copper(I) species (**A**) undergoes single-electron transfer with BPO to afford the copper(II) species (**B**) and a benzoyl radical,[12a,18] which can be trapped by an alkene to produce a more stable carbon-centered radical (**C**). Upon ligand exchange with TMSCN, the copper(II) species (**B**) is converted into a copper(II) species (**D**),[12c,19] which then undergoes cyano group transfer with the stabilized carbon-centered radical (**C**) through an intermediate (**E**) to afford the oxycyanation product, and regenerate the copper catalyst. The oxycyanation product can also be formed through the reductive elimination of the copper(III) species (**F**).[20]

Conclusions

In conclusion, we have developed a copper-catalyzed three-component reaction which leads to direct oxycyanation of various alkenes with aryl diacyl peroxides and TMSCN. Both unactivated alkenes and styrenes are reliable substrates under the mild reaction conditions, affording β-cyanohydrin derivatives in moderate to good yields. The utility of these direct oxycyanation products has been demonstrated with further synthetic applications. The copper-catalyzed asymmetric oxycyanation of alkenes has been conducted and proceeds well.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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