Synthetic Methods

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Copper-Catalyzed Intermolecular Carboetherification of Unactivated Alkenes by Alkyl Nitriles and Alcohols**

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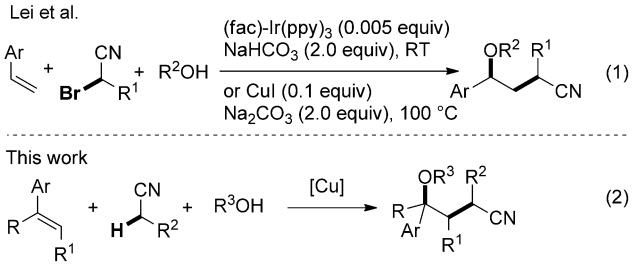
Abstract: *A three-component carboetherification of unactivated alkenes has been developed allowing the rapid building of complexity from simple starting materials. A wide range of α-substituted styrenes underwent smooth reactions with unactivated alkyl nitriles and alcohols to afford γ-alkoxy alkyl nitriles with concomitant generation of a quaternary carbon center. A radical clock experiment provided clear-cut evidence that the reaction proceeds through a tertiary alkyl radical intermediate.*

Due to their prevalence, alkenes represent an attractive building block for the construction of structurally diverse molecules.[1] In this context, carboetherification of alkenes is a powerful transformation as it allows a one-step introduction of a carbon–carbon and a carbon–oxygen bond. Whereas metal-catalyzed carboetherification reactions initiated by intramolecular alkoxypalladation followed by trapping of the resulting organometallic intermediate are well investigated,[2,3] the development of intermolecular variants based on the same principle turned out to be challenging. Indeed, most of the three-component carboetherifications of alkenes focus on oxytrifluoromethylation[4] and Meerwein-type oxyarylation[5] involving radicals generated from Togni's reagent[6] and arenediazonium or aryliodonium salts, respectively. To the best of our knowledge, there are very few examples of multicomponent carboetherification reactions that allow the introduction of more synthetically versatile functional handles.[7,8] Very recently, Lei and co-workers described the carboetherification of styrenes using α-bromo alkyl nitriles and alcohols as reaction partners [Eq. (1), Scheme 1].[8] This is of particular interest because the cyano group is robust yet readily converted to many other functional groups.[9]



Scheme 1. Three-component carboetherification of alkenes.

Although formation of organometallic complexes (Ln, Rh, Fe, Ru) by activating the α-C–H bond of acetonitrile has been documented,[10] the α-functionalization of nitriles is limited mainly to its enolate chemistry requiring a strong base [pK_a(MeCN) ≈ 31.3, DMSO] for its formation. There are only a few examples that utilize the direct C–H functionalization of alkyl nitriles.[11,12] In connection with our ongoing project on metal-catalyzed functionalization of carbon–carbon multiple bonds,[13] we have recently launched a research program aimed at developing new processes that are initiated by copper-catalyzed direct coupling of alkenes with nitriles through the formation of a C_{sp^3}–C_{sp^3} bond.[14] In this report, we describe the first examples of three-component oxyalkylation of alkenes by alkyl nitriles and alcohols. The reaction generated one C_{sp^3}–C_{sp^3}, one C_{sp^3}–O bond and a quaternary carbon center to afford γ-alkoxy alkyl nitriles, which are otherwise difficult to access [Eq. (2), Scheme 1].[15]

We began our study by examining the three-component reaction of 1,1-diphenylethylene (**1a**) with acetonitrile and methanol. No difunctionalized product was detected when $Cu(OAc)_2$ was used as a catalyst (Table 1, entry 1).[14a] Using $Cu(OTf)_2$ (0.5 equiv) under otherwise identical conditions afforded the three-component adduct **2a** in 23% yield (entry 2). Interestingly, lowering the amount of potassium carbonate proved to be beneficial providing **2a** in 55% yield (entry 3). Significantly, performing the reaction in the absence of base afforded product **2a** in 83% yield (entry 4). As expected, lowering the catalyst loading led to a slight decrease in yield (entries 4 to 6). Therefore, catalyst loading of 20 mol% was chosen for further optimization (see the Supporting Information). The results of this survey allowed us to conclude that a) $Cu(OTf)_2$ in combination with 1,10-Phen (mol ratio 1:2) gave the best results. b) The optimum ratio of MeCN/MeOH is 1:1. d) Inert conditions proved to be critical. When the reaction was run under aerobic conditions, product **2a** was obtained in only 45% yield together with a substantial amount of benzophenone.[16] Overall, heating a solution of **1a** in MeCN/MeOH (v/v = 1:1) in the presence of $Cu(OTf)_2$ (0.2 equiv), 1,10-Phen (0.4 equiv), and DTBP

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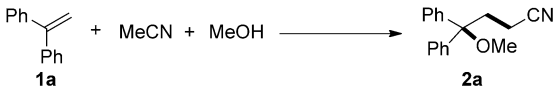
Table 1: Optimization of reaction conditions.[a]



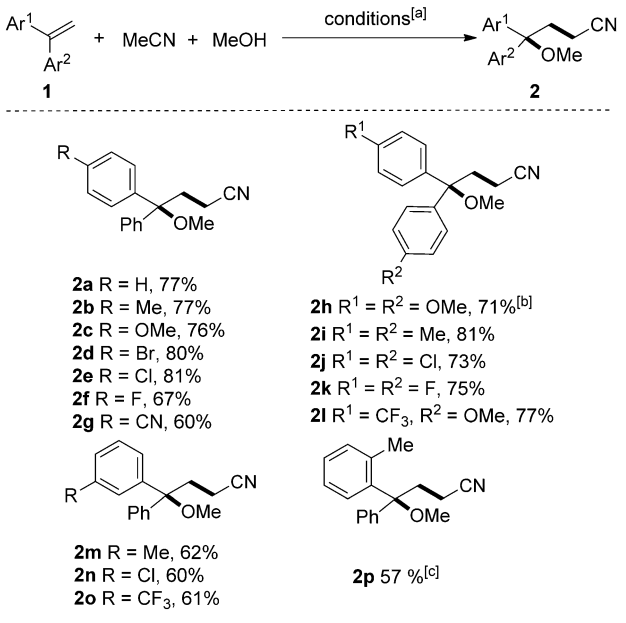
1a **2a**

Entry	Cu (equiv)	Ligand (equiv)	Base (equiv)	MeCN/MeOH	Yield[b]
1	$Cu(OAc)_2$ (0.2)	Phen (0.4)	K_2CO_3 (1.0)	4:1	0
2	$Cu(OTf)_2$ (0.5)	Phen (1.0)	K_2CO_3 (1.0)	4:1	23
3	$Cu(OTf)_2$ (0.5)	Phen (1.0)	K_2CO_3 (0.2)	4:1	55
4	$Cu(OTf)_2$ (0.5)	Phen (1.0)	none	4:1	83
5	$Cu(OTf)_2$ (0.2)	Phen (0.4)	none	4:1	72
6	$Cu(OTf)_2$ (0.1)	Phen (0.2)	none	4:1	60
7	$Cu(OTf)_2$ (0.2)	Bipy (0.4)	none	4:1	60
8	$Cu(OTf)_2$ (0.2)	DiMeObipy (0.4)	none	4:1	68
9	$Cu(OTf)_2$ (0.2)	Phen (0.4)	none	1:1	83 (77)[c]

[a] Reaction was performed in a sealed tube: **1a** (0.1 mmol), DTBP (2.0 equiv), $Cu(OTf)_2$, and ligand in MeCN/MeOH (0.1 M), 120 °C, 16 h. [b] Yield was determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] Yield of the isolated product. Phen = 1,10-phenanthroline; Bipy = 2,2′-bipyridine; DiMeObipy = 4,4′-dimethoxybipyridine; DTBP = di-*tert*-butyl peroxide.

(2.0 equiv) under inert atmosphere at 120 °C afforded **2a** in 77% yield (entry 9).

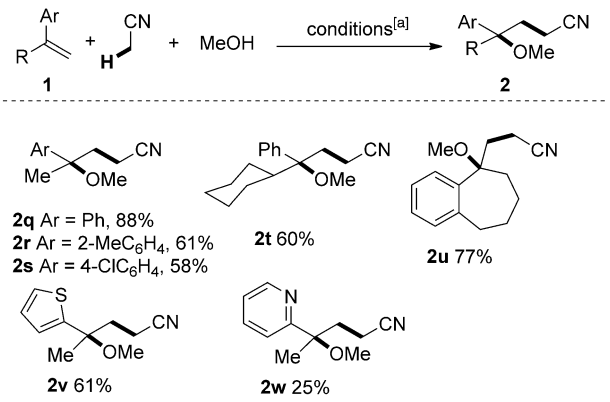
With the optimized conditions, the scope of the copper-catalyzed methoxycyanomethylation of unactivated alkenes was examined. Both electron-donating (OMe, Me) and electron-withdrawing (Br, Cl, F, CN) groups on the aromatic rings of 1,1-diarylethylenes were tolerated to afford the expected products (**2b** to **2l**, Scheme 2). The position of the substituent, however, impacted the yield of the reaction. Substitution at the *meta*-position led to decreased product yields (**2m** to **2o**). Compound **2p** with an *ortho*-methyl-substituted phenyl ring was obtained in only 57% yield.



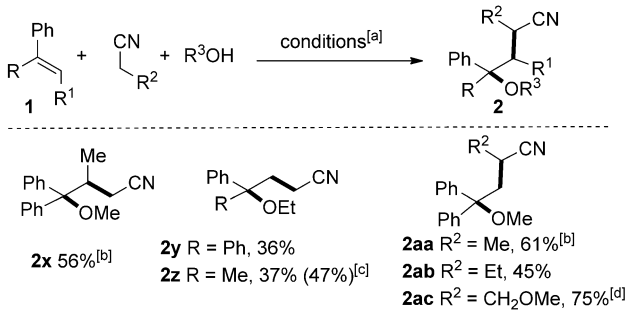
Scheme 2. Carboetherification of *gem*-biaryl alkenes. [a] Reaction conditions: **1** (0.50 mmol, 1 equiv), DTBP (2 equiv), $Cu(OTf)_2$ (0.2 equiv), 1,10-Phen (0.4 equiv), MeCN/MeOH (1:1, *c* 0.1 M), 120 °C, 16 h. [b] $Cu(OTf)_2$ (0.3 equiv) and 1,10-Phen (0.6 equiv), 24 h. [c] $Cu(OTf)_2$ (0.4 equiv) and 1,10-Phen (0.8 equiv) for 24 h.

α-Alkylstyrene derivatives are also appropriate substrates for this transformation (Scheme 3). α-Methyl, α-cyclohexyl, and methylene benzocycloheptane were all successfully difunctionalized to provide the corresponding three-component adducts (**2q**–**2u**). Heterocyclic arene-substituted olefins underwent the desired methoxycyanomethylation albeit with reduced synthetic efficiency. However, α-unsubstituted styrene failed to participate in this reaction presumably due to its facile polymerization.

A trisubstituted olefin can also be methoxycyanomethylated (**2x**, Scheme 4) and ethanol can be used to functionalize both α-phenylstyrene and α-methylstyrene (**2y**, **2z**), albeit with reduced efficiency. Propionitrile, butyronitrile, and 2-methoxypropionitrile participated in the reaction to give the corresponding three-component adducts (**2aa**–**2ac**). The



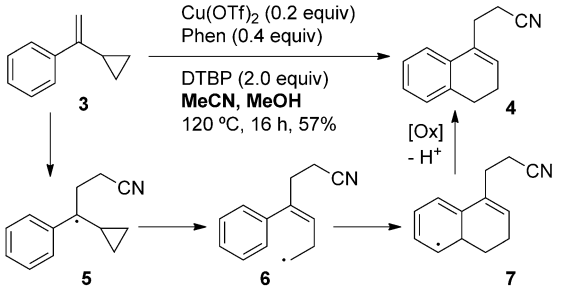
Scheme 3. Carboetherification of α-alkyl-substituted styrenes. [a] Reaction conditions: **1** (0.50 mmol), DTBP (2.0 equiv), $Cu(OTf)_2$ (0.2 equiv), 1,10-Phen (0.4 equiv), MeCN/MeOH (1:1, *c* = 0.1 M), 120 °C.



Scheme 4. Additional examples of carboetherification of alkenes. [a] $Cu(OTf)_2$ (0.3 equiv) and 1,10-Phen (0.6 equiv), DTBP (2.0 equiv), R^2CH_2CN/R^3OH = 1:1, 120 °C; [b] $Cu(OTf)_2$ (0.2 equiv) and 1,10-Phen (0.4 equiv) were used; [c] DTBP (3.0 equiv) was used; [d] 3-methoxypropionitrile (11.0 equiv) in MeOH.

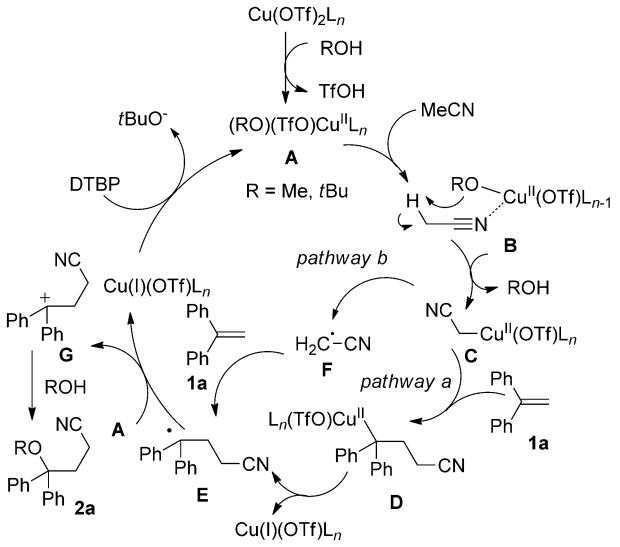
formation of compound **2x** is particularly significant, as it represents the first example of a trisubstituted alkene being successfully oxyalkylated.

Control experiments showed that the reaction of **1a** did not proceed in the absence of copper catalyst. The product **2a** was still formed in the absence of peroxide albeit with low conversion indicating that the peroxide is not directly involved in the acetonitrile activation. Significantly, submitting (1-cyclopropylvinyl)benzene (**3**) to the standard conditions afforded dihydronaphthalene **4** in 57% yield (Scheme 5). The formation of **4** can be accounted for by invoking the benzylic radical **5** that underwent fragmentation to homoallylic radical **6**. Cyclization of the latter to **7** followed by rearomatization would then afford the observed product **4**.[17]



Scheme 5. Radical clock experiment.

On the basis of the above experimental results, a working mechanism was proposed as shown in Scheme 6. Complexation of $Cu(OTf)_2$ with 1,10-Phen followed by ligand exchange with alcohol would give complex **A**. Coordination of alkyl nitrile to Cu^{II} followed by deprotonation would afford cuprate **C**.[11a,b] Carbocupration of alkene **1a**[18] by **C** would provide **D** which upon homolytic cleavage would furnish tertiary radical **E**.[3a,19] Alternatively, cuprate **C** could undergo homolytic cleavage to provide cyanomethyl radical that upon addition to olefin would produce benzylic radical **E**. The presence of the intermediate **E** is clearly evidenced by our radical clock experiment (Scheme 5). Oxidation of radical **E** followed by trapping of the resulting tertiary carbocation by alcohol would afford the carboetherification product **2a**.[20] Oxidation of Cu^{I} by DTBP would regenerate the Cu^{II} species.[21,22]



Scheme 6. Proposed mechanism of alkoxycyanomethylation of alkenes.

In conclusion, we reported the first copper-catalyzed three-component reaction of alkenes with unactivated alkyl nitriles and alcohols allowing the one-step formation of both a C_{sp^3}–C_{sp^3} and a C_{sp^3}–O bond with concomitant creation of a quaternary carbon center.[23] The reaction is applicable to a wide range of styrene derivatives to provide γ-alkoxy alkyl nitriles that are otherwise difficult to access.

Experimental Section

General procedure: The alkene (**1**, 0.5 mmol), $Cu(OTf)_2$ (0.2 equiv), and 1,10-phenanthroline (0.4 equiv) were dissolved in dry and degassed MeOH and MeCN (v/v = 1:1, 0.1M). DTBP (2.0 equiv) was added and the tube was sealed and heated to 120 °C for 16 h under inert atmosphere. The reaction mixture was diluted with EtOAc and washed with an aqueous solution of NH_4OH/NH_4Cl (sat) (v/v = 1:1). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to give compound **2**.

Keywords: alkenes · carboetherification · copper catalysts · difunctionalization · oxyalkylation

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