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Copper-Catalyzed Cyanomethylation of Allylic Alcohols with Concomitant 1,2-Aryl Migration: Efficient Synthesis of Functionalized Ketones Containing an α-Quaternary Center**

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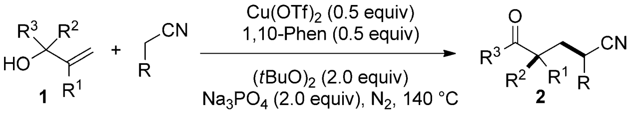
Abstract: *A copper-catalyzed alkylation of allylic alcohols by alkyl nitriles with concomitant 1,2-aryl migration was developed. Formation of the alkyl nitrile radical was followed by its intermolecular addition to alkenes and the migration of a vicinal aryl group with the concomitant generation of a carbonyl functionality to complete the domino sequence. Mechanistic studies suggested that 1,2-aryl migration proceeded through a radical pathway (neophyl rearrangement). The protocol provided an efficient route to functionalized ketones containing an α-quaternary center.*



Scheme 1. Copper-catalyzed coupling reaction between α,α-disubstituted allylic alcohols and alkyl nitriles with concomitant 1,2-aryl migration. 1,10-Phen = 1,10-phenanthroline, Tf = trifluoromethanesulfonyl.

Alkenes and nitriles are two of the most ubiquitous chemical feedstocks and are essential in different domains of chemistry, such as polymers,[1] agrochemicals, and pharmaceuticals.[2] Therefore, many important chemical transformations of these compounds have been developed.[3] Powerful synthetic methodologies have been developed on the basis of the metal-catalyzed oxidative vicinal difunctionalization of unactivated alkenes;[4–7] however, examples of the copper-mediated/catalyzed difunctionalization of alkenes with the generation of a $C(sp^3)-C(sp^3)$ bond remain scarce.[8] On the other hand, although the formation of organometallic complexes (Ln, Rh, Fe, Ru) by activation of the α-C–H bond of acetonitrile has been documented,[9] the synthetic use of nitriles is limited mainly to their enolate form,[10] the formation of which requires a strong base [$pK_a(\mathrm{MeCN}) \approx 31.3$, DMSO]. We recently initiated a project aimed at the development of methods for the direct coupling of unactivated alkenes with alkyl nitriles and disclosed a copper-mediated/catalyzed oxyalkylation of unactivated alkenes with alkyl nitriles and amides/acids as reaction partners for the synthesis of functionalized phthalides, isochromanones, and γ-lactones.[11,12] We report herein a novel copper-catalyzed coupling reaction of allylic alcohols with alkyl nitriles that leads to ketones with the concomitant creation of an α-quaternary center (Scheme 1). Although alkylation-induced 1,2-aryl migration has recently been reported for the conversion of allylic alcohols into ketones,[13] examples of the generation of homologated ketones with the creation of an α-quaternary center are rare.[13h]

2-Methyl-3-phenylbut-3-en-2-ol (**1a**) and acetonitrile were initially used as test substrates. When we applied our previously developed alkylative lactonization conditions [$Cu(OTf)_2$ (2.0 equiv), BiPy (1.0 equiv), DTBP (2.0 equiv), K_3PO_4 (2.0 equiv), H_2O (11.0 equiv), air, 140 °C, CH_3CN (0.1 M)], ketone **2a** was formed together with epoxide **3a** in 61 % yield in a 1.9 : 1 ratio. Although the usefulness of the formation of epoxide **3a** is evident,[14] we focused our attention on ketone **2** in this study. Conditions were systematically surveyed by varying the copper salt, the ligand, the base, and the temperature under an inert atmosphere.[15] The use of sodium phosphate instead of potassium phosphate resulted in a slight improvement in the ketone/epoxide ratio and the overall yield (Table 1, entry 2 versus entry 1). A result with important mechanistic implications was that the reaction took place in the absence of DTBP, albeit with lower conversion (Table 1, entry 3). On the other hand, only degradation was observed in the absence of a base (Table 1, entry 4). The use of 4,4′-dimethoxy-2,2′-bipyridine as the ligand provided epoxide **3a** as the major product, thus indicating the dramatic effect of the ligand (Table 1, entries 5–8). Neither **2a** nor **3a** was formed in the absence of $Cu(OTf)_2$ and 1,10-Phen. Reasoning that the methyl group has a low migratory aptitude, we investigated the reaction between 2-methyl-1,1-diphenylprop-2-en-1-ol (**1b**) and acetonitrile. Gratifyingly, the desired ketone **2b** was isolated in 84 % yield under the following conditions: $Cu(OTf)_2$ (0.5 equiv), 1,10-Phen (0.5 equiv), Na_3PO_4 (2.0 equiv), DTBP (2.0 + 2.0 equiv), CH_3CN (0.1 M), 140 °C (Table 1, entry 10). At a lower catalyst loading (0.2 equiv), the reaction remained clean, but the conversion was lower within the same reaction time (51 % or 85 % based on conversion; Table 1, entry 11).

We investigated the scope of the copper-catalyzed coupling reaction of α,α-disubstituted allylic alcohols with alkyl nitriles under the optimized conditions (Scheme 2). The presence of electron-withdrawing groups (m-CF_3, m-F, p-Cl)

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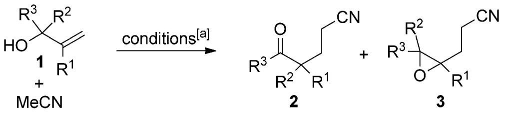
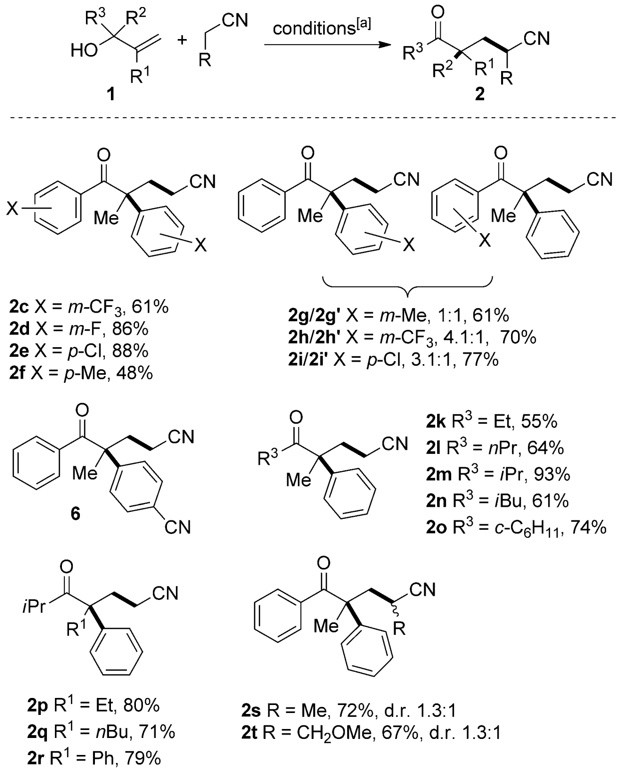
Table 1: Arylalkylation of alkenes: Survey of reaction conditions.



1a $R^2 = R^3 = Me$, $R^1 = Ph$; **1b** $R^2 = R^3 = Ph$, $R^1 = Me$

Entry	**1**	Ligand	Base	**2**/**3**	Yield of **2** + **3** [%][b,c]
1	**1a**	1,10-Phen	K_3PO_4	1.9 : 1	(58)
2	**1a**	1,10-Phen	Na_3PO_4	2.3 : 1	(64)
3	**1a**	1,10-Phen	Na_3PO_4	2.9 : 1	(34)[d]
4	**1a**	1,10-Phen	–	–	degradation
5	**1a**	1,10-Phen	$CsOH{\cdot}H_2O$	2.2 : 1	(35)
6	**1a**	Bpym	Na_3PO_4	3.0 : 1	(38)
7	**1a**	dtbpy	Na_3PO_4	1.8 : 1	(41)
8	**1a**	OMebpy	K_3PO_4	1 : 2.7	(70)
9	**1b**	1,10-Phen	Na_3PO_4	only **2b**	55
10	**1b**	1,10-Phen	Na_3PO_4	only **2b**	84[e,f]
11	**1b**	1,10-Phen	Na_3PO_4	only **2b**	51[e,g]

[a] Reactions were carried out on a 0.05 mmol scale in a sealed tube. Standard conditions: $Cu(OTf)_2$ (2.0 equiv), ligand (2.0 equiv), DTBP (2.0 equiv), base (2.0 equiv), N_2, 140 °C, CH_3CN (0.1 M). [b] Yields in parentheses were calculated from ^1H NMR spectra by using CH_2Br_2 as an internal standard. [c] The yield is given for a mixture of **2** and **3**. [d] No DTBP was used. The reaction reached 40% conversion according to ^1H NMR spectroscopy. [e] DTBP was added in two portions (the second portion after 2 h). [f] $Cu(OTf)_2$ (0.5 equiv), 1,10-Phen (0.5 equiv). [g] $Cu(OTf)_2$ (0.2 equiv), 1,10-Phen (0.2 equiv), 85% based on conversion (60%). Bpym = 2,2′-bipyrimidine; dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine; OMebpy = 4,4′-dimethoxy-2,2′-bipyridine; DTBP = di-*tert*-butyl peroxide.

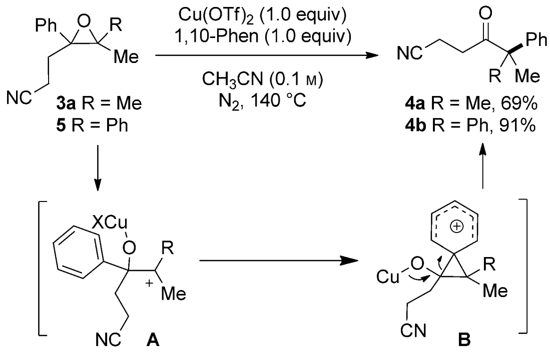


Scheme 2. Scope of the copper-catalyzed coupling reaction of allylic alcohols with alkyl nitriles. [a] Reactions were carried out on a 0.05 mmol scale in a sealed tube. Reaction conditions: $Cu(OTf)_2$ (0.5 equiv), 1,10-Phen (0.5 equiv), DTBP (4.0 equiv, added in two portions), Na_3PO_4 (2.0 equiv), RCH_2CN (solvent, 0.1 M), N_2 atmosphere, 140 °C.

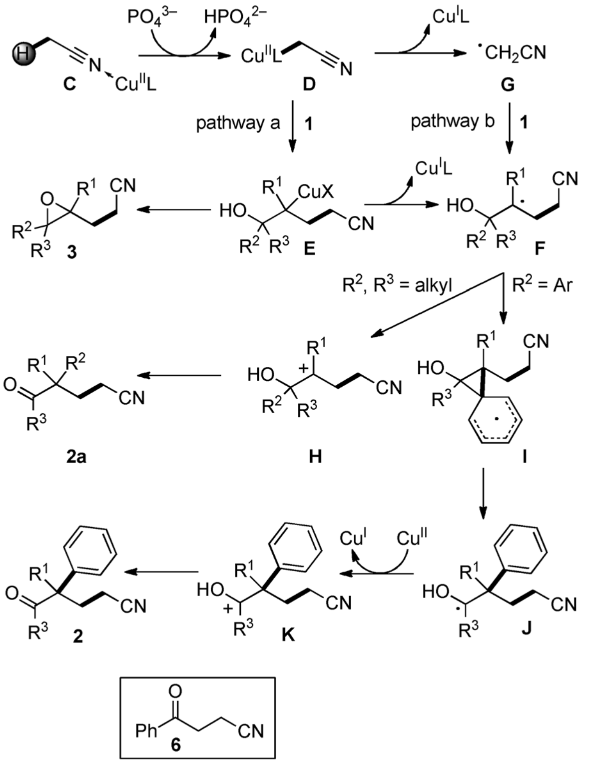
on the α-aryl group was well-tolerated, and the desired α-quaternary ketones **2c–e** were formed in up to 88% yield. Interestingly, the reaction of electron-rich 2-methyl-1,1-di-*p*-tolylprop-2-en-1-ol with acetonitrile furnished migration product **2f** in lower yield (48%). When two different aromatic substituents were incorporated into tertiary alcohol **1**, the electron-poor aryl group migrated in preference to the electron-rich aryl group. In the case of 4-(1-hydroxy-2-methyl-1-phenylallyl)benzonitrile (**1j**, $R^1 = Me$, $R^2 = p$-cyanophenyl, $R^3 = Ph$), only one product, resulting from the migration of the electron-poor *para*-cyano-substituted phenyl group, was formed (product **2j**, 76% yield). It is well-known that electron-rich aryl groups have a high migratory aptitude in Wagner–Meerwein-type rearrangements involving cationic intermediates.[16] In contrast, electron-poor aryl groups migrate preferentially in neophyl rearrangements involving radical intermediates.[17] Therefore, our experimental results indicated that the 1,2-aryl shift might occur via a radical rather than a cationic intermediate. Only the aryl group migrated when α-aryl-α-alkyl-substituted tertiary allylic alcohols were used, regardless of the nature of the alkyl group (products **2k–r**). Alkyl groups other than Me at the internal position of the double bond were also well-tolerated (Et, *n*Bu, Ph), with the formation of the desired ketones in 71–80% yield (products **2p–r**). However, the reaction failed with a monosubstituted olefin ($R^1 = H$). Gratifyingly, other alkyl nitriles, such as propionitrile and 3-methoxypropionitrile, participated in this reaction to give the desired functionalized ketones (products **2s**,**t**) in up to 72% yield, albeit with low diastereoselectivity (d.r. 1.3 : 1). In none of these examples was an epoxide isolated.

Mechanistically, ketone **2a** could be generated by a copper triflate catalyzed Meinwald rearrangement of epoxide **3a**.[18] However, a control experiment showed that epoxide **3a** was stable under our optimized reaction conditions. On the other hand, **3a** was converted into ketone **4a**, rather than ketone **2a**, in 69% yield in the absence of a base (Scheme 3). Preferential formation of a carbocation **A** stabilized via phenonium ion **B** could explain the formation of **4a**. The same regioselectivity in the rearrangement of **5** (R = Ph) was observed to afford ketone **4b** in 91% yield. These results indicated that epoxide **3a** was not the precursor of ketone **2a** and that these two compounds were formed through two competitive processes.

Possible reaction pathways are depicted in Scheme 4. Coordination of copper(II) triflate to the nitrile followed by the deprotonation of complex **C** by sodium phosphate would produce the organocopper species **D**.[19] Carbocupration of **1** by **D**[20] would lead to **E**, which could subsequently be converted into epoxide **3** or undergo homolytic cleavage to give radical **F**. Alternatively, the cyanomethyl radical **G** could also be generated from **D**, and upon addition to **1** would produce intermediate **F**. When both R^2 and R^3 are alkyl substituents (**1a**, $R^2 = R^3 = Me$), **F** would be further oxidized to carbocation **H**,[21] which upon alkyl migration would be converted into ketone **2a**. With aryl-substituted allylic



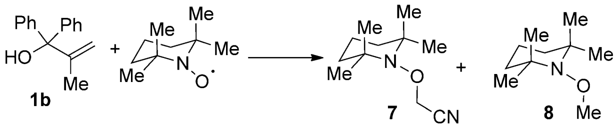
Scheme 3. Cu(OTf)$_2$-promoted rearrangement of epoxides **3a** and **5**.



Scheme 4. Possible reaction pathways of the copper-catalyzed coupling reaction of allylic alcohols with alkyl nitriles to give ketones **2**.

alcohols, a neophyl rearrangement via a spiro[2,5]octadienyl radical intermediate **I** might predominate in accord with the experimental observations. The radical **J** resulting from the 1,2-aryl migration could be further oxidized to carbocation **K** and therefore to ketone **2**. Finally, the Cu^I species could be oxidized to regenerate the Cu^{II} salt.[22–24] The fact that a variable amount of 4-oxo-4-phenylbutanenitrile (**6**) was produced when the reaction of **1a** and acetonitrile was performed in air was indicative of the presence of the radical intermediate **F**.[25]

When the reaction of **1b** was performed in MeCN in the presence of TEMPO (2.0 equiv) under otherwise identical conditions, 2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]acetonitrile (**7**) and 1-methoxy-2,2,6,6-tetramethylpiperidine (**8**) were obtained in yields of 14 and 7%, respectively (exp. 1, Scheme 5). The formation of ketone **2b** was not observed



		7	8
exp. 1	standard conditions	14%	7%[a]
exp. 2	without Cu(OTf)$_2$ and 1,10-Phen	4%	16%

Scheme 5. Trapping experiments with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO). [a] Yield based on TEMPO.

when the reaction was quenched before the consumption of TEMPO (after 1 h). On the other hand, compound **8** became the major product (16% yield) when the same reaction was performed in the absence of the copper salt and the ligand (exp. 2). The results of these trapping experiments are in favor of pathway b (Scheme 4) involving a cyanomethyl radical and support the notion that the copper catalyst is responsible for the generation of this radical under our reaction conditions.

In summary, we have developed a copper-catalyzed oxidative coupling of allylic alcohols **1** with alkyl nitriles for the synthesis of functionalized ketones **2**. The reaction involves the copper-catalyzed formation of alkyl nitrile radicals, followed by their intermolecular addition to alkenes and 1,2-aryl migration with the concurrent generation of a carbonyl functionality. Electron-poor aryl groups underwent the 1,2-shift in preference to electron-rich aryl groups in accordance with the mechanism of the neophyl rearrangement. The protocol provides an efficient route to functionalized ketones containing an α-quaternary center.

Experimental Section

DTBP (2.0 equiv) was added to a mixture of an allylic alcohol **1**, Cu(OTf)$_2$ (0.5 equiv), 1,10-Phen (0.5 equiv), and Na$_3$PO$_4$ (2.0 equiv) in RCN (0.1 M). The tube was sealed and the mixture stirred at 140 °C for 2 h, and then another portion of DTBP (2.0 equiv) was added, and the mixture was stirred for an additional 2 h. The reaction mixture was then partitioned between ethyl acetate and aqueous NH$_3$ (25%). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed twice with aqueous HCl (2.0 N), aqueous NaOH (3.0 N), and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford ketone **2**.

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Keywords: alkyl nitriles · allylic alcohols · copper triflate · ketones · neophyl rearrangement

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Synthetic Methods

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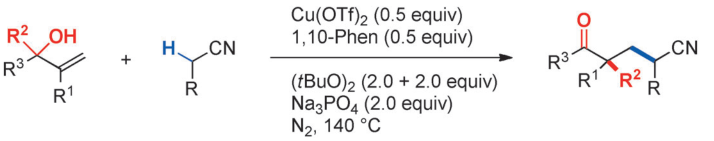
Copper-Catalyzed Cyanomethylation of Allylic Alcohols with Concomitant 1,2-Aryl Migration: Efficient Synthesis of Functionalized Ketones Containing an α-Quaternary Center



A shift in gear: Ketones with an α-quaternary center were synthesized by the title copper triflate catalyzed alkylation of alkenes with non-activated alkyl nitriles (see scheme; 1,10-Phen = 1,10-phenanthroline). The reaction involves the copper-catalyzed formation of an alkyl nitrile radical, its addition to the alkene, and the migration of a vicinal aryl group with the concomitant generation of a carbonyl functionality.