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Transforming Olefins into γ,δ-Unsaturated Nitriles by Cu-Catalysis

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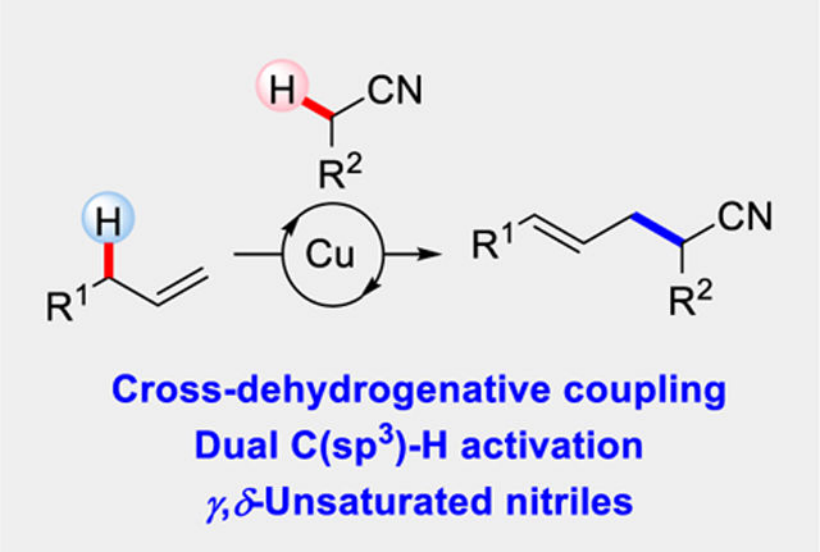
Abstract

We developed a strategy to transform olefins into homoallylic nitriles by a mechanism that combines copper catalysis with alkyl nitrile radicals. The radicals are easily generated from alkyl nitriles in the presence of a mild oxidant, di-*tert*-butyl peroxide. This cross-dehydrogenative coupling between simple olefins and alkylnitriles bears advantages to the conventional use of halides and toxic cyanide reagents. With this method, we showcase the facile synthesis of a flavoring agent, natural product, and polymer precursor from simple olefins.

Graphical Abstract

Functionalizing alkenes for pennies: A copper catalyzed cross-dehydrogenative coupling of unactivated olefins with alkylnitriles was developed by dual sp^3 C–H bond cleavage.



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Conflict of interest

The authors declare no conflict of interest.

Keywords

copper; alkenes; alkylnitriles; cross-dehydrogenative coupling; radicals

While radicals play a key role in biochemistry,[1] their potential for use in organic synthesis remains vast, with new concepts emerging,[2] including applications in cross-coupling.[3] By combining Cu-catalysis with radicals, Heck-type transformations have been achieved, including allylic trifluoromethylation,[4] arylation,[5] and alkylation.[6] These radical transformations enable bond constructions previously impossible and provide an attractive approach for olefin synthesis (Figure 1). Inspired by versatility of nitriles,[7] we designed a strategy for transforming simple olefins into γ,δ-unsaturated nitriles by taming the reactivity of a cyanoalkyl radical. Rather than requiring functionalized halides and toxic cyanide reagents, this transformation enables olefin feedstocks to be coupled with alkyl nitriles to generate homoallylic nitriles in a single-step, using an earth-abundant metal-catalyst (Figure 1).[8]

The nitrile functional group is common in both materials[9] and medicines,[10] while being a useful handle for elaboration.[7] As shown in Figure 1, we proposed a cross-dehydrogenative coupling (CDC)[11] between an olefin and acetonitrile.[12] Initial oxidation of an alkylnitrile forms the corresponding cyanoalkyl radical, which can add to an olefin to give alkyl radical **A**.[13–16] Radicals such as **A** have been implicated in olefin hydrocyanoalkylations[13] and bifunctionalizations, such as oxycyanoalkylation[14] and cyanoalkylation/arylation.[1516] In the presence of a copper(II) catalyst, Koichi first showed that radicals can be trapped to generate an alkylcopper(III) intermediate **B**.[17] Koichi's kinetic studies suggest that alkyl radicals can be trapped by copper with rate constants in excess of 10^6 $M^{-1}s^{-1}$.[17] Theoretical studies on the CF_3 allylic functionalization invoke a triflate counterion-assisted elimination.[4b] On the basis of these studies, we reasoned that the appropriate counterion would be critical for controlling regio-and stereochemistry in the final elimination.

With this mechanistic hypothesis in mind, we focused on the copper-catalyzed allylic cyanoalkylation of 1-dodecene in acetonitrile, using di-*terf*-butyl peroxide (DTBP) as the oxidant.

DTBP is a convenient and inexpensive radical initiator in synthetic and polymer chemistry, commonly used for generating radicals from acetonitrile.[13–16] [It might make more sense to move Zhu's work here because you are saying that he also used copper and peroxides. Zhu demonstrated that Cu/peroxide can generate cyanoalkyl radicals from alkylnitriles, which can then add to alkenes through an intermolecular process.[14a,b,d,e,16] In Zhu's work, the generated alkyl radical is typically trapped to afford hydrocyanoalkylations and bifunctionalizations, such as xxxx.. But we imagine diverting intermediate **A** to achieve dehydrogenative olefin-functionalization.

In the absence of copper, treatment of 1-dodecene with DTBP afforded the known hydrocyanoalkylation product **4a** in 25% yield, with no desired cyanoalkene **3a**. Copper(I) and copper(II) complexes bearing weak counterions provided **4a** as the major product (28–70% yields) (Table 1), in accordance with reported studies on hydrocyanoalkylation.[13]

Catalysts used by Zhu were not effective in our proposed allylic cyanoalkylation.[14a,b,d,e,16] In contrast, the (thiophene-2-carbonyloxy)copper(I) (CuTc) (previously used as catalyst in allylic trifluoromethylation[4b]) provided the cyanoalkene **3a** as the major product in 30% yield. In comparison to copper(I) acetate, we found that copper(II) acetate showed higher efficiency and chemoselectivity by providing **3a** in 47% yield, >20:1 regioselectivity. By replacing acetate with more basic pivalate, the desired alkene was obtained in 65% yield, >20:1 regioselectivity. Other oxidants such as *terf*-butyl hydroperoxide (TBHP) and dicumyl peroxide (DCP) were ineffective. Using an electron-rich benzonitrile derivative as an additive further improved efficiency, presumably by improving catalyst solubility. In the presence of one equivalent of veratronitrile, **3a** was obtained in 90% yield, >20:1 *rr* and 4:1 *E/Z.* Only trace amount of **4a** was observed (<5% yield). These results support the notion that a carboxylate counterion facilitates the elimination and enables >20:1 regioselectivity to provide the γ,δ-unsaturated nitrile. A *syn*-elimination affords the *E*-isomer as the major product.[18]

With this protocol, we elaborated a wide-range of terminal olefins (Scheme 1). Unactivated linear terminal olefins gave the corresponding γ,δ-unsaturated nitriles (**3a-c**) in 80–86% yields with >20:1 *rr* and 4:1 *E/Z* ratio. For the substrates bearing ester (**3d**, **3e**), amide (**3f**), cyano (**3g**) and ether (**3h**) groups, regioselective CDC reactions with acetonitrile provided the corresponding products in 75–82% yields. Increasing the steric hindrance at the 4-position of the olefins slightly decreased the yields but increased the *E/Z* ratios of the products (**3i** 7:1 E/Z; **3j** 11:1 E/Z; **3k** >20:1 E/Z). With a tert-butyl group at the 3-position, we observed >20:1 regioselectivity and >20:1 *E/Z* selectivity (**3k**). The regioselectivity is unaffected by the increased steric hindrance at the 4-position of the olefins. 3-Aryl substituted substrates gave the corresponding nitriles (**3l-n**) in 40–46% yields with >20:1 *E/Z* selectivity. A substrate with an electron-withdrawing group on the phenyl ring (**3n**) showed slightly higher reactivity than the one with an electron-donating group (**3m**). Trisubstituted-alkenyl nitriles were synthesized in 50–77% yields from 3,3- or 1,1-disubstituted olefins (**3o-r** and **3t**). A series of nitriles were also tested as coupling partners and solvent. Propionitrile and butyronitrile show decreased reactivity compared to acetonitrile, most likely due to steric effects and a lower solubility of the copper catalyst in these nitriles (**3v**, **3w**). Only trace amount of hydrocyanoalkylation product **4** were observed with the olefins shown in Scheme 1. With facile access to various nitriles, we next focused on applying them as building blocks.

Due to the versatility of the nitrile group, we can now use simple olefins to access a range of motifs, including an industrial flavor agent, a natural product, and a polymer precursor (Scheme 2). For example, treatment of **3b** with TMSCl in ethanol provided the pear-flavored agent, ethyl 4-decenoate **7**, in 85% yield.[19] The 4-alkyl γ-lactones are members of a large family of natural flavors, widely used in food industry.[20] From the same compound **3b**, γ-decalactone **8** was obtained in 73% yield by a one-pot, hydrolysis and intramolecular hydroacyloxylation. Our strategy provides an efficient route to fatty acids. For example, lyngbic acid, isolated from the marine cyanophyte Lyngbya majuscule,[21] exhibits antimicrobial activity.[22] By hydrolysis of the cyano group in compound **3h**, lyngbic acid **9**

can be obtained in 87% yield. Ru-catalyzed hydrogenation of **3d** provided the nylon 9 precursor **10** in 75% yield.[23]

Next, we examined internal olefins (Scheme 3). With (*E*)-5-decene, the reaction gave cyanoalkene **3x** in 62% yield with with >20:1 *rr* and 12:1 *E/Z* ratio after 24 hours (Scheme 3a). With (Z)-5-decene, (*E*)-isomer **3x** was obtained as the major product in a similar yield and *E/Z* selectivity as the (*E*)-olefin substrate (60% yield, 11:1 E/Z) (Scheme 3b). The C–C bonds were formed at the 5-position of the substrates. No 3-propylnon-4-enenitrile **5** was observed from potential allylic radical **F** or π-allylcopper intermediate **G** by allylic C–H bond activation (Scheme 3c). We saw no carbocation rearrangement type products **6**, which would arise from carbocation intermediate **H** (Scheme 3d).[24] Nor were these 1,2-hydride shift products detected in experiments yielding compounds **3o-q** shown in Scheme 1. These observations suggest that an allylic radical or carbocation are most likely not key intermediates in our cross-coupling.

To gain more insight into the mechanism, we performed a radical trapping and radical clock experiments (Scheme 4). The allylic cyanoalkylation reactions were suppressed in the presence of radical inhibitors TEMPO or BHT (Scheme 4a). In addition, compound **12** was obtained in 60% yield from (1-cyclopropylvinyl)benzene **11** via sequential ring-opening of cyclopropylmethyl radical intermediate and cyclization (Scheme 4b).[13b] These observations suggest that a radical pathway is involved in this cross-coupling (Scheme 5).

Addition of the cyanoalkyl radical to the olefin generates radical intermediate **A**. To explain the regioselectivity, we propose that π-bonding of cyano group to copper(III)[25] shields the H at the β-position to direct the pivalate to abstract the H at the δ-position.

In summary, we have developed a copper catalyzed cross-dehydrogenative coupling of unactivated olefins with alkylnitriles by dual sp^3 C–H bond cleavage. High chemo- and regioselectivity for an E_2-type elimination was achieved by (1) the pivalate counterion and (2) the directing effect of cyano group. By using a catalyst derived from earth abundant salts, we can access 4-alkenylnitriles from simple olefins. Both terminal and internal olefins can be transformed into γ,δ-unsaturated nitrile, versatile synthetic building blocks. These studies contribute to the emerging use of radicals for catalytic cross-coupling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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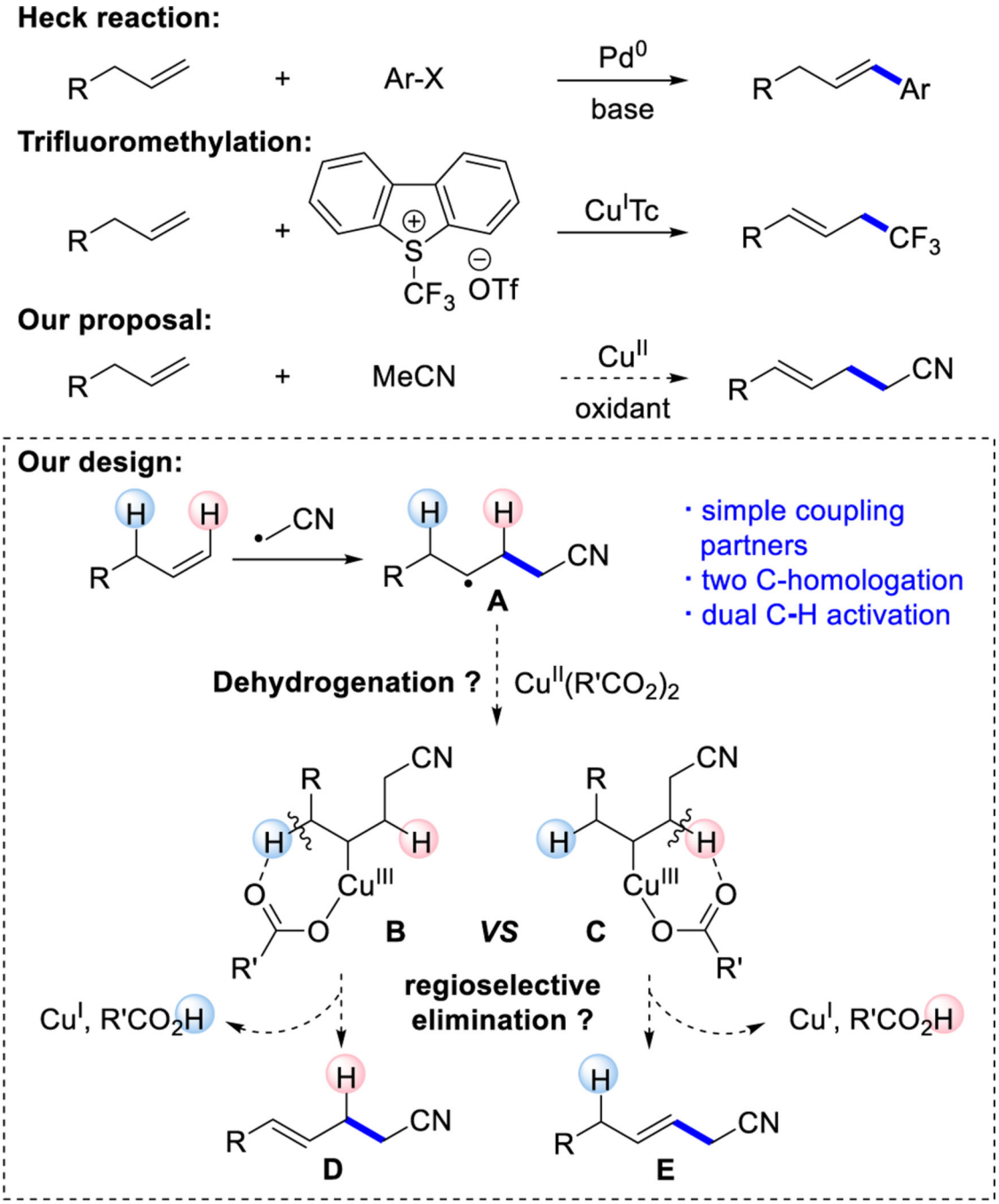
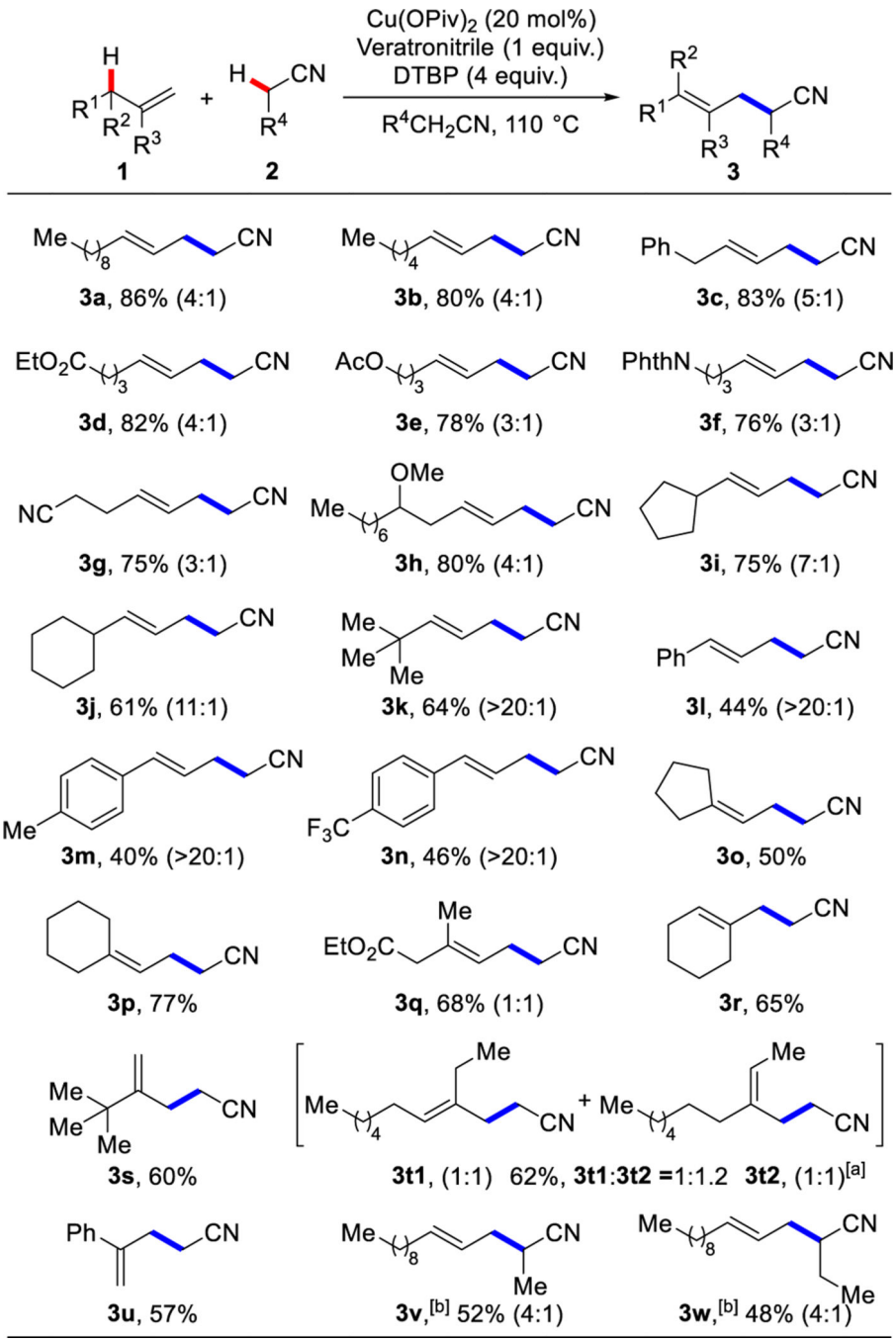
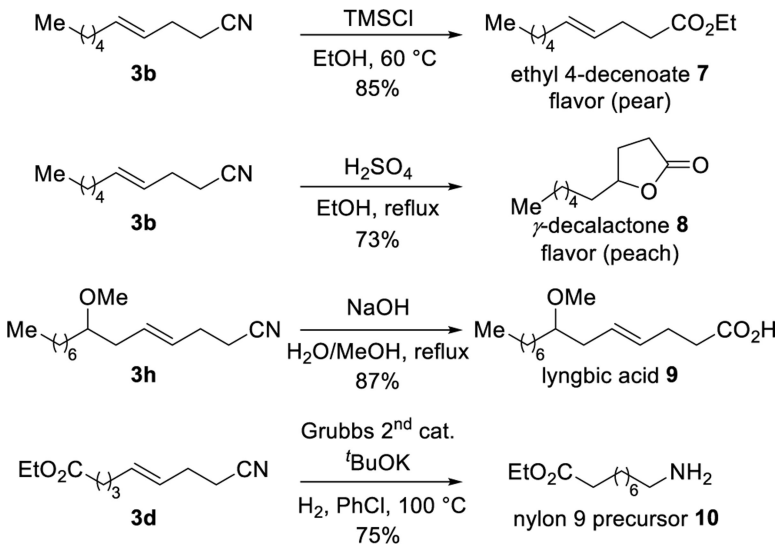


Figure 1.
Allylic cyanoalkylation using alkylnitrile.



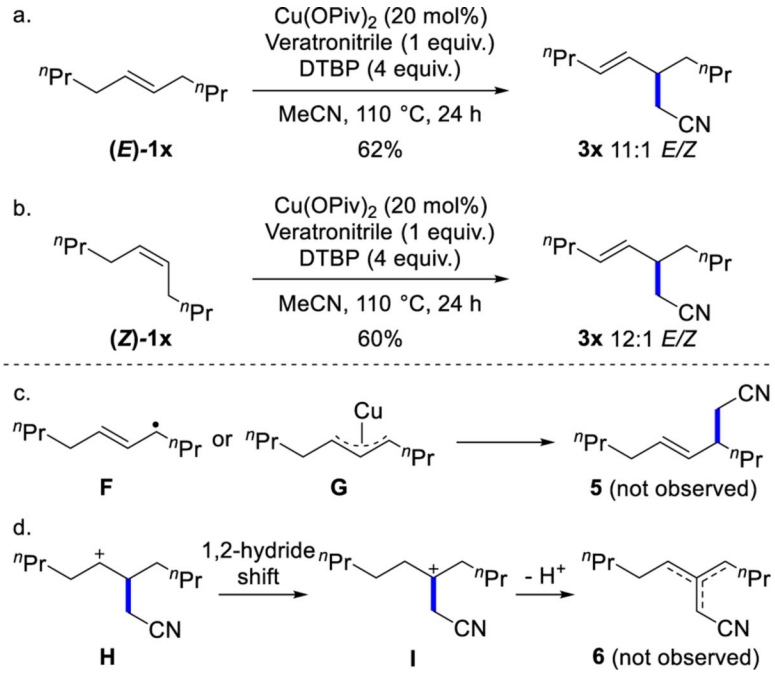
Scheme 1.

Allylic cyanoalkylation of terminal olefins. Reaction conditions: **1** (0.20 mmol), $Cu(OPiv)_2$ (20 mol%), DTBP (0.80 mmol) and veratronitrile (0.20 mmol) in alkylnitrile **2** (1.5 mL), 110 °C, 6 h. *E/Z* ratios determined by NMR analysis of the unpurified reaction mixture are shown in parentheses. [a] **3t1** and **3t2** were isolated as a mixture. [b] 24 h.

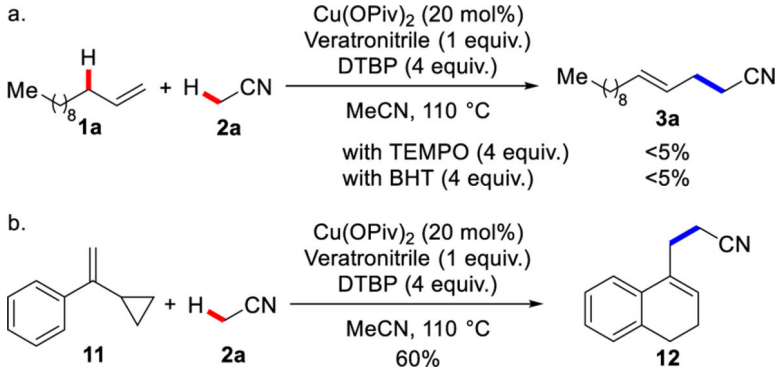


Scheme 2.

Applications of the γ,δ-unsaturated nitriles.

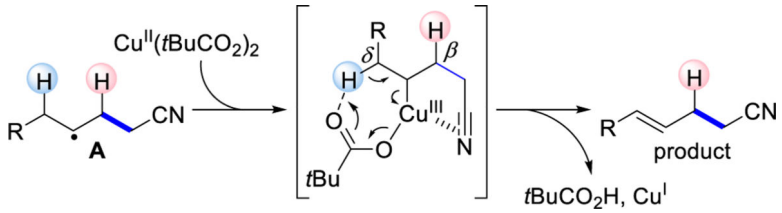


Scheme 3.
Allylic cyanoalkylation of internal olefins.



Scheme 4.

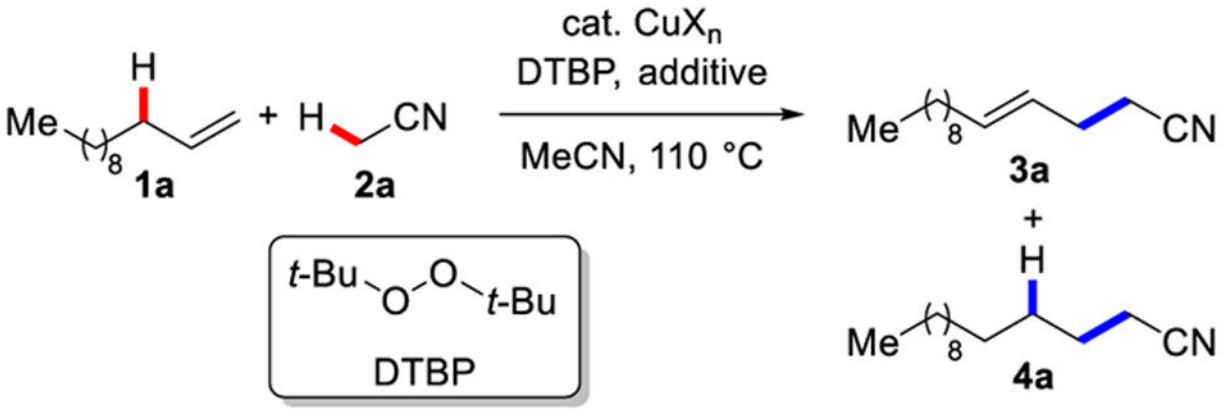
Intermediate trapping and radical clock experiments.



Scheme 5.
Proposed rationale for regioselectivity.

Table 1:

Counterion effects on Cu-catalyzed allylic cyanoalkylation[a,b]



		CuOTf[c]	CuI	CuTc	CuOAc
Cu(I)	3a	0%	0%	30%	35%
	4a	47%	28%	10%	7%

more coordinating

		$Cu(OTf)_2$	$Cu(OAc)_2$	$Cu(iPrCO_2)_2$	$Cu(OPiv)_2$
Cu(II)	3a	0%	47%	58%	65% 90%(86%)[d]
	4a	70%	<5%	<5%	<5% <5%[c]

[a] Reaction conditions: **1a** (0.20 mmol), CuX_n (20 mol%) and DTBP (0.80 mmol) in acetonitrile **2a** (1.5 mL), 110 °C, 6 h.

[b] Yields were determined by NMR analysis of the unpurified reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield is shown in parentheses.

[c] $(CuOTf)_2$ PhMe (10 mol%).

[d] With veratronitrile (0.20 mmol). A 4:1 *E/Z* ratio was determined by NMR analysis of the unpurified reaction mixture.