Direct Oxidation of Aryl Malononitriles Enabling a Copper-Catalyzed Intermolecular Alkene Carbochlorination

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Abstract

A copper-catalyzed carbochlorination of alkenes with aryl malononitriles and chloride is disclosed. This net oxidative transformation proceeds with activated and unactivated alkenes with moderate to excellent yields. Mechanism experiments suggest addition of the malononitrile radical to form a secondary carbon radical which is intercepted by a chloride source. The resultant products can be transformed into biologically important γ-lactones in one further step.

Graphical Abstract
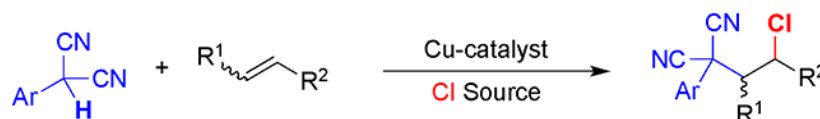
- **30 examples with yield up to 92%** • **Easy access to γ-lactones**

Owing to the high abundance of alkenes, their functionalization to efficiently generate complex molecular scaffolds is a very attractive transformation. In this regard, transition metal catalyzed functionalization of alkenes has been extensively studied in recent years.[1] Among different approaches, the addition of radicals to alkenes represents a versatile entry to many adducts with the most work focused on carbon-carbon bond formation. Similarly, carbohalogenation reactions of alkenes have also been investigated.[2] These reactions generate valuable organic synthons.[3] Despite the advancements in this field, the majority of transformations are restricted to intramolecular alkene functionalization/cyclization.

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Single-electron oxidation of a-carbonyls to carbon-centered radicals using transition metals is a well-established strategy.[4] Using alkenes as a radical acceptor, vicinally functionalized motifs can be accessed in the presence of a suitable radical trap.[5] Early work by the Jahn group showed that electron-rich lithium malonates undergo an intramolecular oxidative carbo-chlorination with tethered alkenes (Scheme 1a).[6] They also reported an efficient synthesis of terpenoid analogues through the radical cyclization of ester enolates.[7] Similarly, the Burton group demonstrated the oxidative cyclization of 4-pentenylmalonates to form lactones in presence of manganese acetate.[8] Recently, the Lin group reported an electrochemical manganese catalyzed chloro-alkylation of alkenes (Scheme 1b).[9] However, reactions with aryl malononitriles were unsuccessful or resulted in addition of two equivalents of the malononitrile to the alkene in this electrochemical system. Despite the breadth of these studies, only limited work has been done with malononitriles and the carbon center radicals generated by oxidation of a-aryl malononitriles have not been investigated in alkene functionalization.

Nitriles are common functional groups occurring in natural products and bioactive molecules.[10] In addition, they can be transformed to other important functional groups like aldehydes, esters, amides etc.[11] Therefore, reactions that incorporate these groups are highly desirable. Previously our group discovered the oxidative coupling of toluene and alkylnitriles with aryl malononitriles, oxindoles, and related substrates.[12] These reactions are believed to proceed by the formation of dimer intermediate that is in equilibrium with the reactive species, the captodative radical monomer, in solution at higher temperatures.[13] Inspired by the importance of the nitrile functional group, we proposed to utilize the captodative radical generated from the aryl malononitriles in alkene functionalization. In this work we described a copper-catalyzed alkene carbochlorination reaction. Mechanistic studies were also performed and the synthetic utility was highlighted by post-modification of the product.

We began our investigation by combining 2 equiv copper chloride ($CuCl_2$), 4-phenyl-1-butene, and 2-p-methoxyphenyl (PMP) malononitrile in acetonitrile. After heating at 100 °C for 24 h, the alkene functionalized product **3a** was isolated in 86% yield (Table 1, entry 1). Shorter reaction times resulted in incomplete consumption of the malononitrile. Lesser amounts of $CuCl_2$ decreased the yield (entries 2 and 3). Lowering the reaction temperature to 60 °C was ineffective giving low yield (entry 4). Other metal salts like $FeCl_3$ and CuCl proved ineffective (entry 5). Acetonitrile was found to be the best solvent relative to others (entries 6 and 7). The alkene was used in excess to obtain better reaction rates, and excess alkene could be recovered. Water-free conditions were superior as undried solvents led to lower yields.

With the optimized conditions, the scope of this reaction was examined (Scheme 2). Initially, the same aryl malononitrile (PMP malononitrile) was surveyed and was found to provide moderate to excellent yields with different unactivated alkenes (**3a**-**3s**). Notably, straight chain aliphatic alkenes proceed in good yield (**3l**- **3m**). The regioselectivity was confirmed from an X-ray crystal structure of **3d** which showed addition of the carbon and chlorine to the terminal and internal positions of the alkene, respectively. Unlike, the previously reported electrochemical alkene carbochlorination,[9] this transformation worked well with a

diene selectively functionalizing only one double bond (**3n**). The reaction was able to tolerate functional groups including ester (**3o**) and *N*-protected amines (**3p**). In addition, internal alkenes also provided moderate yields of products and good diastereoselectivity (**3q-3s**). The X-ray crystal structure of **3s** indicates the formation of the *trans*-isomer as the major diastereomer. Other electron-donating and electron-withdrawing groups on the aryl of the malononitrile gave rise to excellent yields (**3t-3u**).

Further studies were undertaken to determine if the reaction was feasible with a catalytic amount of copper. Upon screening oxidants and chloride sources, it was discovered that $K_2S_2O_8$ and KCl were the best oxidant and chloride source respectively affording 68% isolated yield of the carbochlorinated product in presence of 15 mol % $Cu(OTf)_2$ and 20 mol % 4,4'-di-tert-butyl-2,2'-bipyridine (dtbbpy) as ligand (See Supporting Information for details). In the absence of copper, no product was observed indicating that the $K_2S_2O_8$ oxidant alone is not sufficient for the reaction to occur. Acetonitrile remained the best solvent.

Like the stoichiometric version, this catalytic process was effective with diverse alkenes and aryl malononitriles (Scheme 3). Again excess alkene was utilized to obtain sufficient rates; upon complete consumption of the limiting malononitrile, the balance of the alkene was recovered as both the unreacted form and the dichlorinated adduct (see below). The reaction can employ allyl phenyl ether (**4b-4c**). Again, only one double bond of a diene substrate was functionalized (**4e**), with the remainder of the diene being recovered or undergoing dichlorination of just one double bond. Notably, the reaction conditions are compatible with thio groups (**4e**); thioethers are often not well-tolerated in oxidative or copper-catalyzed processes. Electron-withdrawing and electron-donating groups on the malononitriles had no adverse effect(**4a-4i**). A trisubstituted alkene, 1-methylcyclohexene resulted mainly in the malononitrile dimer with trace product. The reaction of vinyl pyridine resulted in polymerization and <10% carbonchlorination. With 1-phenyl-1,3-butadiene, a mixture of products was observed that could not be separated by column chromatography. With aryl cyanoacetates instead of an aryl malononitrile, the reaction with styrene shows moderate yield; however, the product could not be purified. As aryl malononitrile can be transformed to the cyanoacetates, this avenue was not investigated further. A larger scale reaction to form **3a** proceeded in lower yield (1 mmol, 46%) presumably due to the heterogeneity of the reaction mixture (KCl, $K_2S_2O_8$ not fully soluble).

To determine the possible reaction pathway, the aryl malononitriles dimers were investigated as intermediates since aryl malononitriles are known to readily dimerize under oxidative conditions.[12] In addition, dimers formed in the absence of alkene and were observed in reactions with alkene when they were halted prior to completion. With dimer **5** in place of the aryl malononitrile under the standard conditions, 36% yield of product **3a** was obtained indicating that dimer could be an intermediate in this reaction (Scheme 4a). A control reaction without the aryl malononitrile formed (3,4-dichlorobutyl)benzene **6** in 34% yield (Scheme 4b). To determine if this dihalide is an intermediate,[14] compound **6** was subjected to the standard reaction conditions in place of the alkene. With or without copper salts, no product formed indicating that an S_N2 displacement of the terminal chloride by the malononitrile anion is unlikely (Scheme 4c).

Both the aryl malononitrile radical (see above) and the aryl malononitrile cation can form under oxidizing conditions. To determine which is involved, the addition to radical probe, 2-(vinylcyclopropyl)benzene, was undertaken (Scheme 5). Under catalytic condition, 24% yield of the cyclopropyl ring opening product **7** was observed (Scheme 5a). Stoichiometric copper conditions gave rise to diene **9** (Scheme 5b). The diene could be formed after the cyclopropane ring opening followed by dehydrochlorination. In support of this hypothesis, diene **9** was observed upon subjecting **7** to condition B. The direct carbochlorination product **8** was not observed under either set of conditions. These results are consistent with addition of aryl malononitrile radical to the alkene forming a secondary alkyl radical that can be intercepted by the copper catalyst.

Based on the above studies and the literature,[15] a possible reaction pathway is outlined in Scheme 6. Initially, the aryl malononitrile oxidizes to form dimer, which is known to be in equilibrium with the carbon center radical **A** at higher temperature.[12] This radical **A** adds to the terminal carbon of the alkene to generate secondary radical **B**. This radical combines with the Cu(II) catalyst to provide Cu(III) intermediate **C**. Reductive elimination from **C** forms product and generates Cu(I), which can be reoxidized to Cu(II). However, the formation of product through a Cu(II) to Cu(I) pathway could also be possible.[16] A pathway involving further oxidation of radical **B** to a cation is also plausible. To interrogate this possibility, an oxidation resistant nucleophile that could only trap the carbocation, not the radical **B**, was investigated. Thus, KCN was used in place of KCl under the conditions from Scheme 3 with *para*-methoxyphenylmalononitrile in combination with both styrene, which can form a stabilized radical/carbocation, and 4-phenyl-1-butene, which would not. Under these conditions, only malononitrile dimer was observed and no alkene addition adducts were seen, which points away from a carbocation mechanism.[17]

To highlight the synthetic utility of this reaction, further modifications of the carbochlorinated products were undertaken. Using precedented procedures,[18] selective hydrolyses of one of the nitrile groups in the products **3c** and **3a** were performed to generate amides **10** and **12**, respectively (Scheme 7). Further cyclization of the amide oxygen onto the chloride formed γ-lactones **11** and **13**. Thus, the reaction products from this method allow access to the γ-lactone backbone with quaternary centers.[19]

In summary, a copper-catalyzed carbochlorination of alkenes has been developed. A carbon-centered radical generated from oxidation of aryl malononitrile is intercepted by an alkene followed by chloride allowing a three-component coupling. A simple, inexpensive chloride source KCl, is employed. Highlights of the method include the ability to monofunctionalized dienes and conditions that are orthogonal to halides and thioanisoles, the latter of which normally do not tolerate oxidative conditions. Mechanism experiments suggests the formation of radical intermediate after addition of the malonyl radical which further recombines with chloride in a copper-mediated process. The products can be readily transformed to form γ-lactones with highly substituted carbon centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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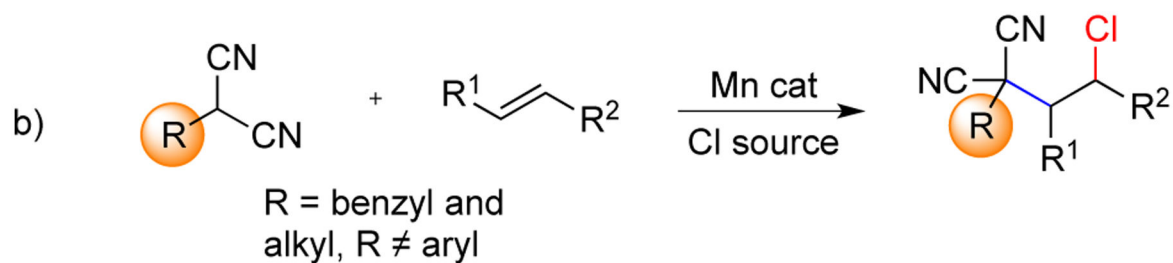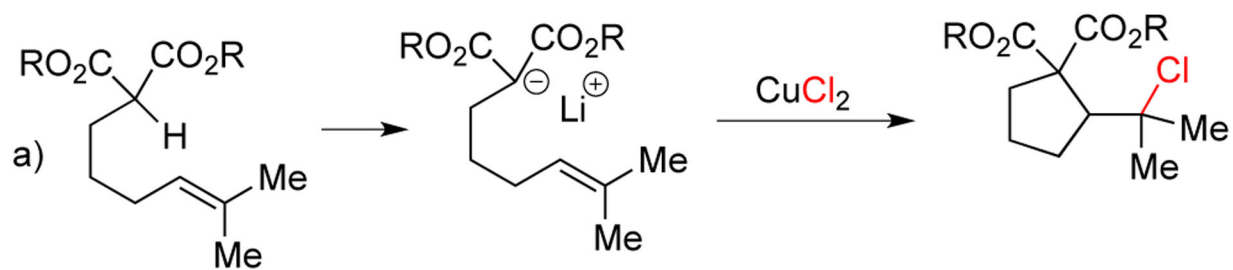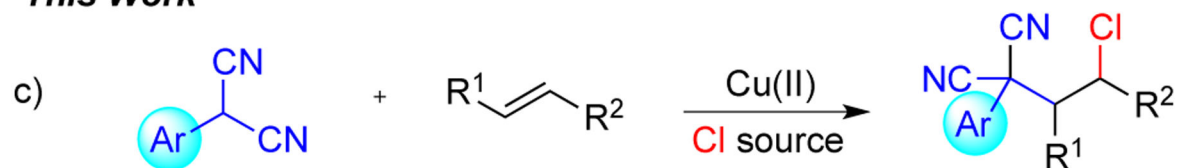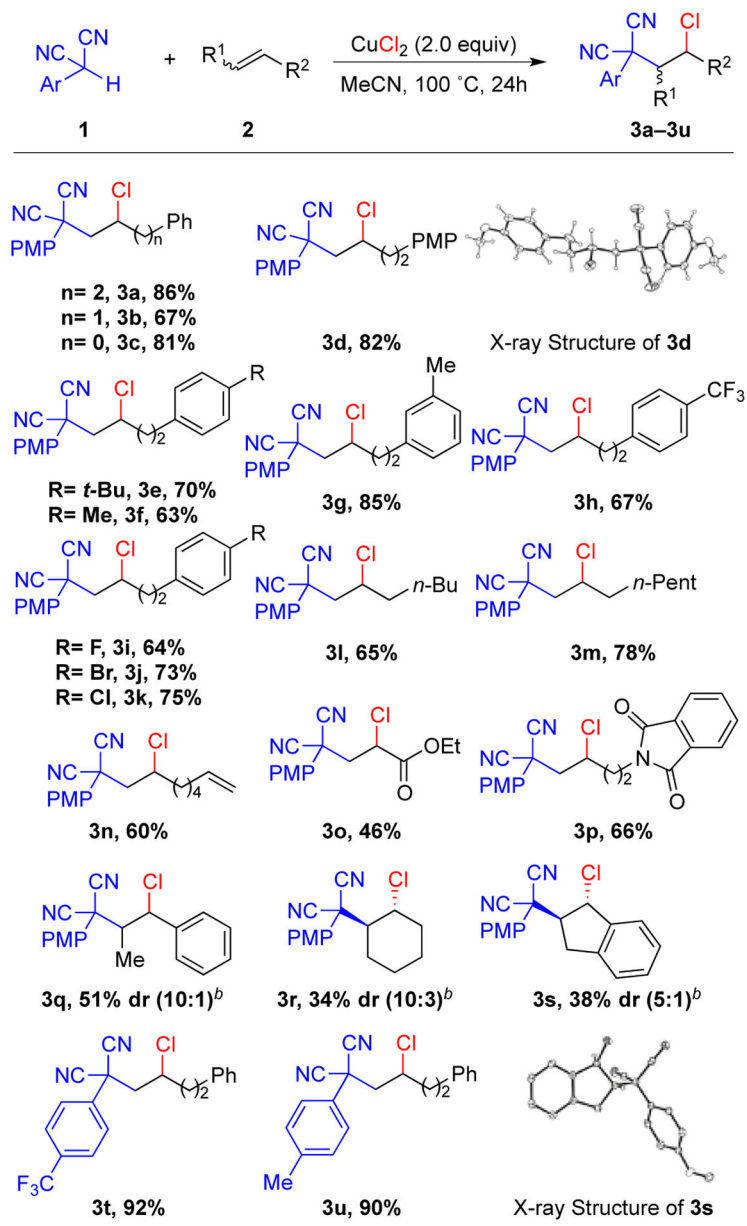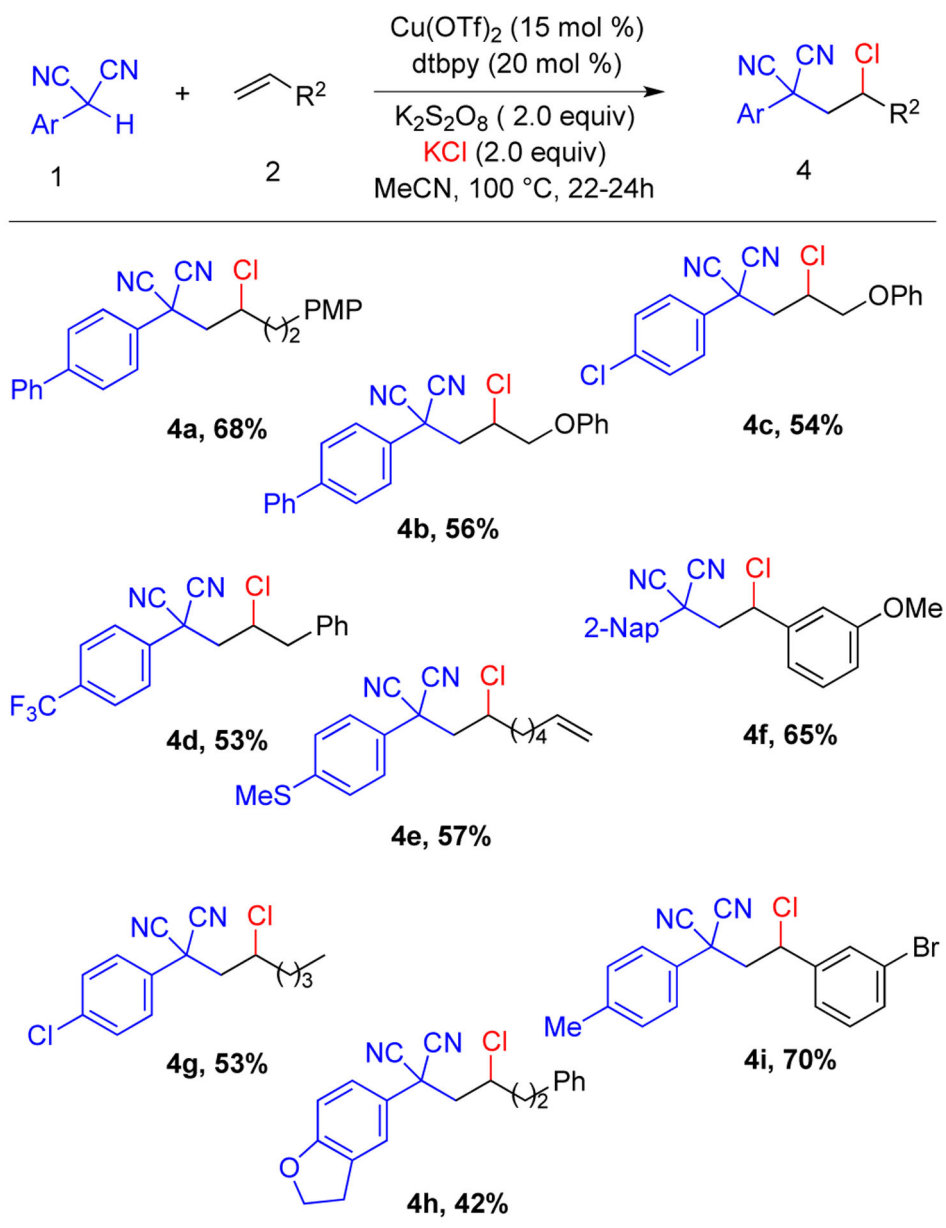
Scheme 1.
Known Alkene Carbohalogenation Reactions vs This Work

Scheme 2. Substrate Scope of Alkene Carbochlorination[a]

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol, 2.5 equiv), CuCl$_2$ (0.4 mmol, 2.0 equiv), MeCN (1 mL), 100 °C, 24 h. [b]80 °C.
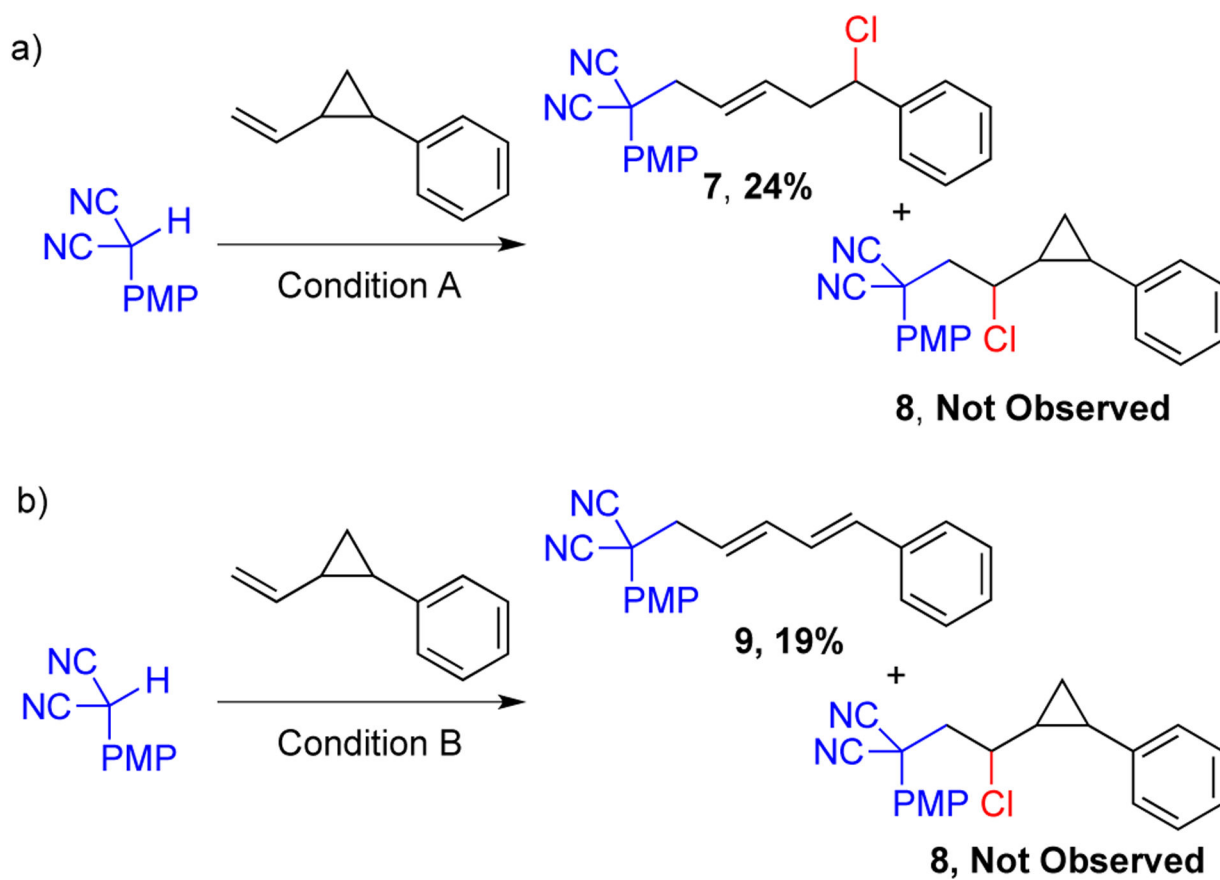
Scheme 3. Substrate Scope under Catalytic Conditions[a]

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol, 2.5 equiv), Cu(OTf)$_2$ (0.03 mmol), dtbbpy (0.04 mmol), K$_2$S$_2$O$_8$ (0.4 mmol), KCl (0.4 mmol), MeCN (1 mL), 100 °C, 20–24 h.
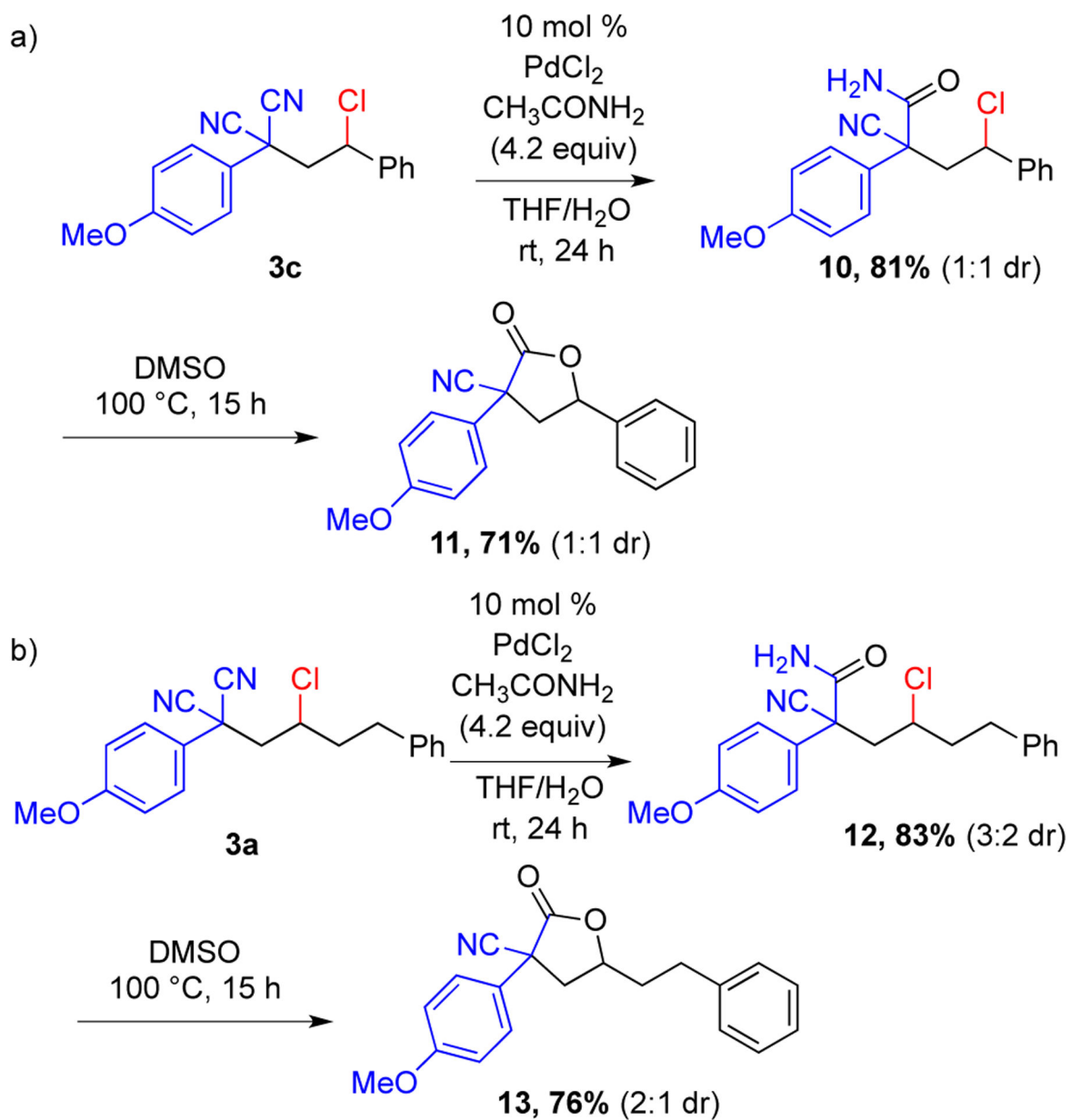
a)

b)

c)
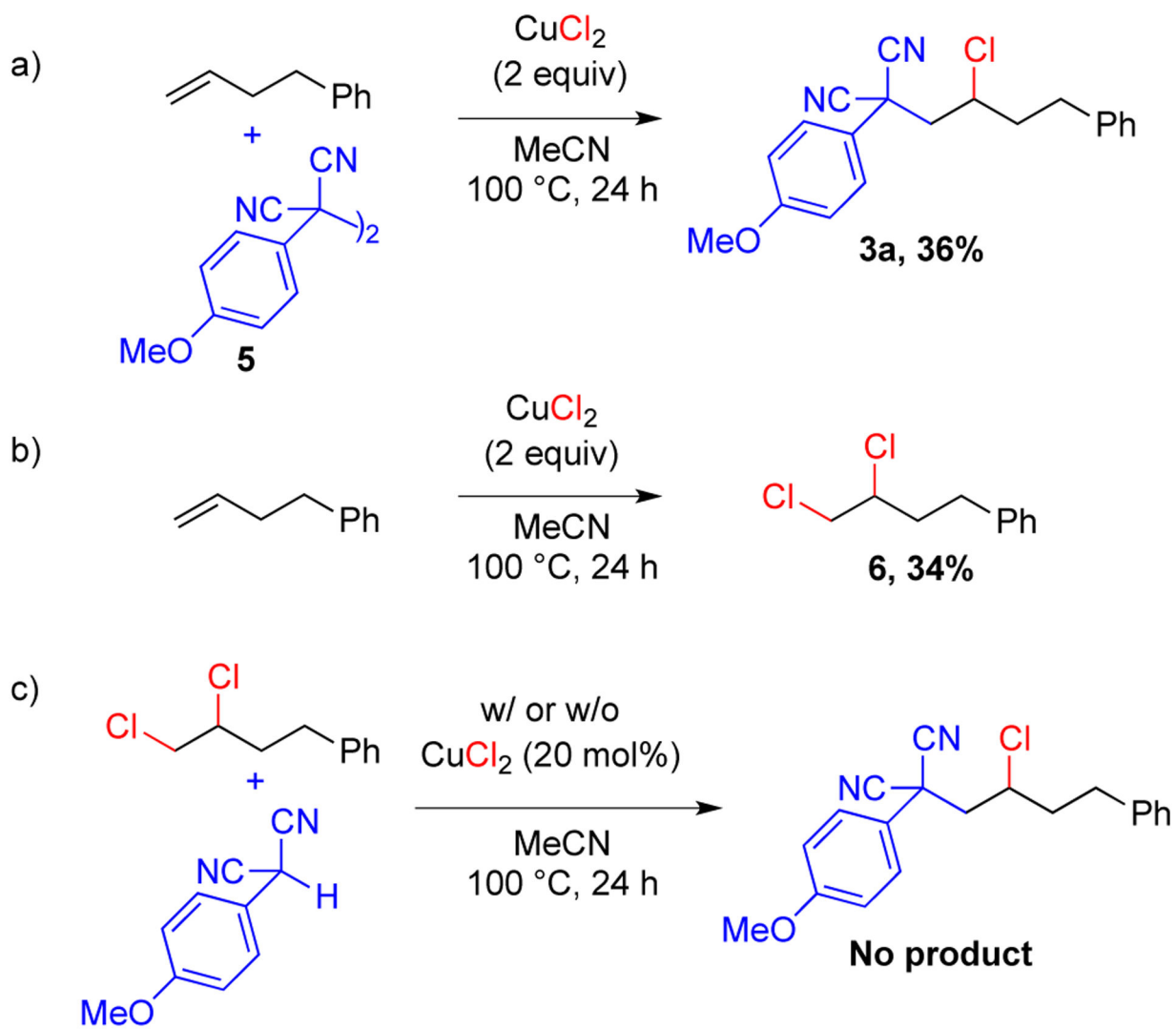
Scheme 4.
Control Experiments

Scheme 5. Radical Probe Experiments
Condition A = Cu(OTf)$_2$ (15 mol %), dtbbpy (20 mol %), K$_2$S$_2$O$_8$ (2 equiv) KCl (2 equiv), MeCN, 100 °C, 22 h. **Condition B** = CuCl$_2$ (2 equiv), MeCN, 100 °C, 24 h.
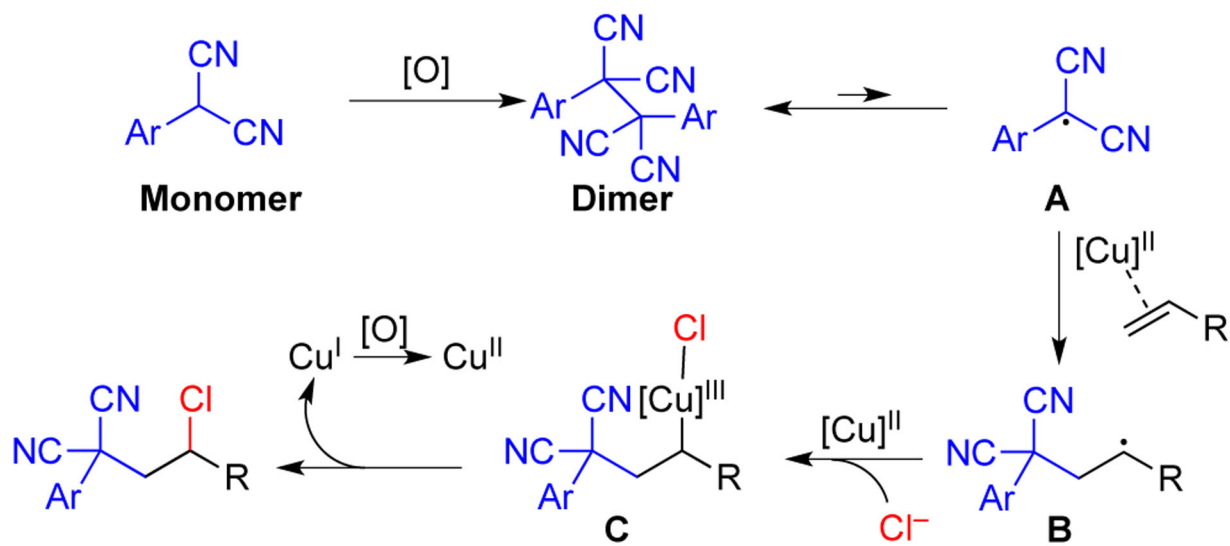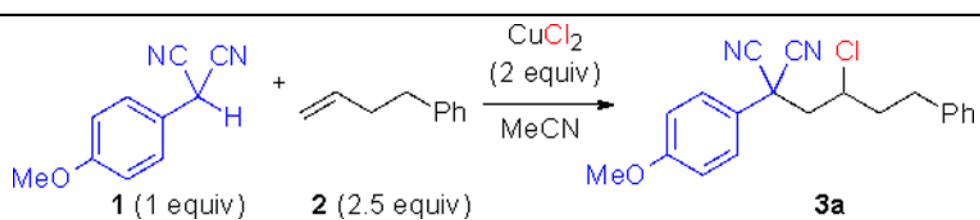
Scheme 6.
Proposed Mechanism

Scheme 7.
Post-Modification of Alkene Carbochlorination Products

Table 1:

Reaction Development

entry	change to conditions	T (°C)	t (h)	yield 3a (%)[b]
1	None	100	24	88 (86)
2	$CuCl_2$ (1.0 equiv)	100	24	42
3	$CuCl_2$ (1.5 equiv)	100	24	63
4	None	60	24	20
5	$FeCl_3$ or CuCl instead of $CuCl_2$	100	24	0
6	DMSO instead of MeCN	100	24	40
7	DMF instead of MeCN	100	24	44

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.25 mmol,), $CuCl_2$ (0.2 mmol), MeCN (1 mL), 100 °C, 24 h.

[b] Yields as judged by ^{1}HNMR spectrocscopy with CH_2Br_2 as internal standard. Yield in parentheses is the isolated yield.