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## Copper-catalysed direct radical alkenylation of alkyl bromides

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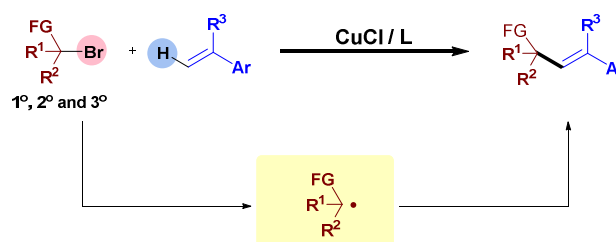
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**A copper-catalysed direct radical alkenylation of various benzyl bromides and  $\alpha$ -carbonyl alkyl bromides has been developed. Compared with the recent radical alkenylations which mostly focused on secondary or tertiary alkyl halides, this transformation shows good reactivity to primary alkyl halides and tertiary, secondary alkyl halides were also tolerated. The key initiation step of this transformation is a copper-induced single-electron reduction of C-Br bonds to generate alkyl radical species.**

Direct alkenylation of alkyl halides is one of the challenging fields and has been extensively studied. Although the palladium-catalysed Heck reaction has been widely applied in organic synthesis,<sup>1</sup> the alkenylation of alkyl halides by palladium still remains a major challenge.<sup>2</sup> In addition to the oxidative addition pathway for palladium-catalysed alkenylation of alkyl halides, a radical-mediated approach can serve as a complementary model for the alkenylation from alkyl halides because the alkyl halides can be easily activated to generate the key intermediate alkyl radical species which have high activity to alkenyl acceptors.<sup>3</sup> Generally, alkyl halides are divided into primary, secondary and tertiary alkyl halides. The reactivity of alkyl halides can be correlated with bond dissociation energy (BDE) and generally depends on degree of the substitution (primary < secondary < tertiary).<sup>4</sup> Among the recent development of radical alkenylations,<sup>5</sup> the alkyl halides were mostly limited to secondary alkyl halides or tertiary alkyl halides which attributed to the generation of relative stable alkyl radicals.<sup>6</sup> The alkenylation of primary halides was hard to achieve through a radical process because of its low reactivity. Therefore, the development of radical alkenylation to expand the application and solve the low reactivity of

alkyl bromides such as primary alkyl halides is a challenging and important task.

Copper has been a general catalyst to initiate conversion of alkyl halides to alkyl radicals, which have been widely applied in copper-catalysed atom-transfer radical addition (ATRA)<sup>7</sup> and atom-transfer radical polymerization (ATRP).<sup>8</sup> Though copper catalysts can be promising catalysts for the alkyl radical generation, the application of copper catalysts in the radical alkenylation of alkyl halides is very rare. Recently, Takashi Nishikata and co-workers have reported the first copper-catalysed radical Heck-type alkenylation reaction.<sup>9</sup> However, the alkyl halides were mostly limited to tertiary alkyl halides and the ligand used was very special. Herein, we demonstrate our progress in this copper-catalysed radical mediated direct alkenylation of various tertiary, secondary and primary alkyl halides by using easy available 1,10-phenanthroline (phen) as the ligand (Scheme 1).

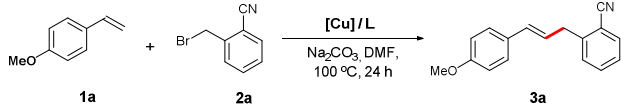


**Scheme 1.** Copper-catalysed radical alkenylation of alkyl bromides

We commenced our studies with 4-methoxystyrene **1a** and 2-(bromomethyl)benzotrile **2a** as model substrates. The best yield of the desired product **3a** could be achieved in the presence of 20 mol% CuCl, 40 mol% phen, 2 equiv Na<sub>2</sub>CO<sub>3</sub> and DMF as the solvent at

100 °C (Table 1, entry 4) and other selected results are summarized in Table 1. Various copper catalyst precursors were screened (Table 1, entries 1-4). The Cu(I) catalysts were effective for this alkenylation transformation in which CuCl was found to be the most effective catalyst precursor, while Cu(II) catalyst proved to be ineffective. In addition, different ligands such TMEDA and Acac (acetoacetate) ligand were not effective for this reaction, and the product was in less than 5% yield (Table 1, entry 5 and 6). Finally, control experiments in the absence of copper catalyst (Table 1, entry 7) or ligand (Table 1, entry 8) confirmed that these species played a critical role in this transformation.

**Table 1.** Optimization of conditions for the reaction of 4-methoxystyrene **1** and 2-(bromomethyl) benzonitrile **2a**<sup>a</sup>

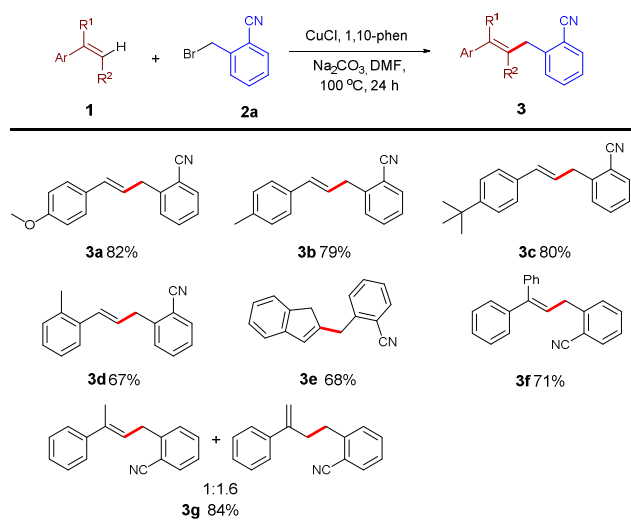


Entry	[Cu]	L	Yield [%]
1	CuCl <sub>2</sub>	Phen	5
2	CuI	Phen	79
3	CuBr	Phen	82
<b>4<sup>b</sup></b>	<b>CuCl</b>	<b>Phen</b>	<b>83(80)</b>
5	CuCl	Acac	< 5
6	CuCl	TMEDA	< 5
7	no	Phen	n.d. <sup>c</sup>
8	CuCl	no	n.d. <sup>c</sup>

<sup>a</sup> Reaction conditions: **1** (1.0 mmol), **2a** (0.5 mmol), catalyst (20 mol%), ligand (40 mol%), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), DMF (2.0 mL), 100 °C, N<sub>2</sub>, 24 h. GC yield. <sup>b</sup> The yield in the parentheses was isolated yield. <sup>c</sup> n.d. = no desired product.

With the optimal conditions established, various alkenes **1** were tested to react with 2-(bromomethyl)benzonitrile **2a** to form the corresponding alkenylation products **3** (Table 2).

**Table 2.** Scope of copper-catalysed radical alkenylation of different alkenes **1** and 2-(bromomethyl) benzonitrile **2a**<sup>a</sup>

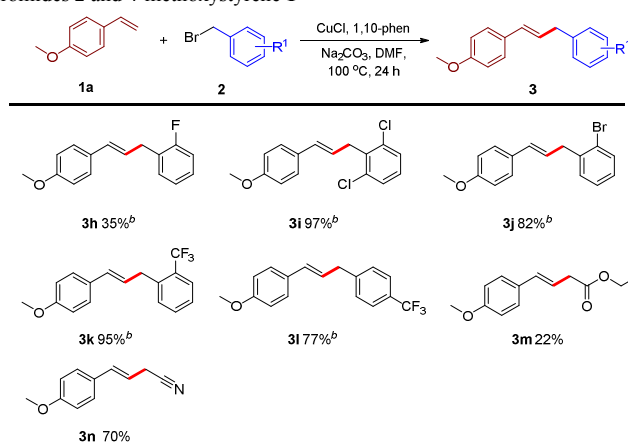


<sup>a</sup> Reaction condition: **1** (1.0 mmol), **2a** (0.5 mmol), CuCl (20 mol%), 1,10-phen (40 mol%), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), DMF (2.0 mL), 100 °C, N<sub>2</sub>, 24 h. Isolated yield.

This reaction was successfully amenable to a wide range of substituted styrenes, and moderate to good yields were achieved with substrates bearing functional groups such as OMe (**3a**), Me (**3b**) and <sup>t</sup>Bu (**3c**). In addition, the effect of steric with substituents ortho to the olefin (**3d**) also provided moderate yield. Interestingly, indene could also be employed to get the target alkenylation product without any difficulties (**3e**). Furthermore, the 1,1-disubstituted olefins (**3f** and **3g**) were suitable for this reaction and the corresponding products were obtained in good yields.

Next, we investigated the copper-catalysed radical alkenylation reactions of different benzyl bromides **2** (Table 3). Under the standard conditions, a wide range of functional groups, including the C-Br, C-Cl, C-F, CF<sub>3</sub> and CN groups were compatible with this method. In addition, the primary  $\alpha$ -carbonyl alkyl bromides were also tested under the optimized reaction conditions. The bromoacetonitrile (**3n**) provided the target product in moderate yield, while the ethyl bromoacetate afforded a poor yield (**3m**) because of the low reactivity.

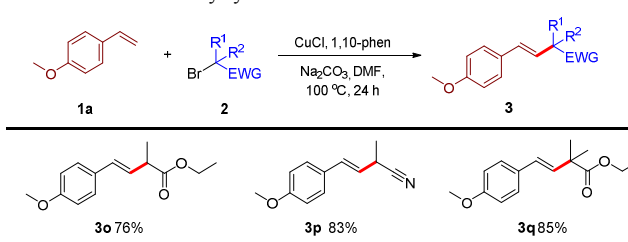
**Table 3.** Scope of copper-catalysed radical alkenylation of different benzyl bromides **2** and 4-methoxystyrene **1a**<sup>a</sup>



<sup>a</sup> Reaction conditions: **1a** (1 mmol), **2** (0.5 mmol), CuCl (20 mol%), 1,10-phen (40 mol%), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), DMF (2.0 mL), 100 °C, N<sub>2</sub>, 24 h. Isolated yield. <sup>b</sup> NMR yield

Inspired by the positive results of primary alkyl halides, we next extended this alkenylation reaction to secondary and tertiary  $\alpha$ -carbonyl alkyl bromides as well (Table 4). Under the optimized reaction conditions described above, secondary  $\alpha$ -carbonyl alkyl bromides bearing ester and cyano groups were shown to react with 4-methoxystyrene in good yields (**3o** and **3p**). Furthermore, a tertiary  $\alpha$ -carbonyl alkyl bromide bearing ester underwent the alkenylation transformation with **1a** smoothly in 85% yield (**3q**).

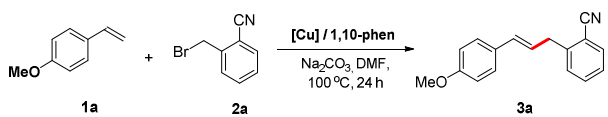
**Table 4.** Scope of copper-catalysed radical alkenylation of  $\alpha$ -carbonyl alkyl bromides **2** and 4-methoxystyrene **1a**<sup>a</sup>



<sup>a</sup> Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), CuCl (20 mol%), 1,10-phen (40 mol%), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), DMF (2.0 mL), 100 °C, N<sub>2</sub>, 24h. Isolated yield.

To gather some insights into this radical alkenylation reaction, radical scavengers, such as TEMPO and BHT, were employed in the reaction (Table 4). As a result, the reactions were completely shut down, which could indicate that this transformation involved radical intermediates.

**Table 5.** Radical inhibiting experiments.

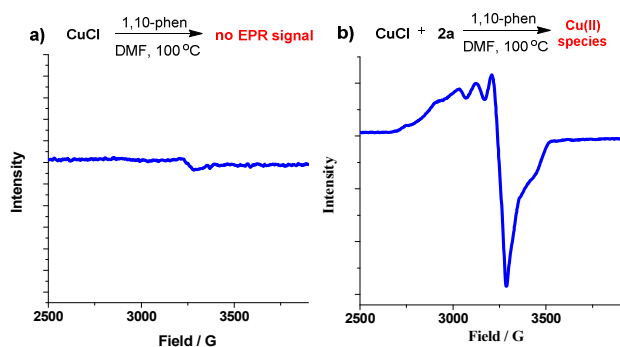


Additive	Yield of <b>3a</b> <sup>a</sup>
none	80%
TEMPO (2 equiv)	0
BHT (2 equiv)	0

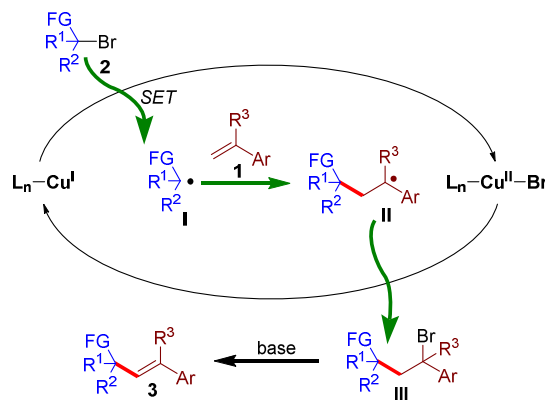
<sup>a</sup> Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), CuCl (20 mol%), 1,10-phen (40 mol%), additive (1.0 mmol), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), DMF (2.0 mL), 100 °C, N<sub>2</sub>, 24 h. GC yield.

The electron paramagnetic resonance (EPR) was also used to study this radical process. As shown in Figure 1(a), no EPR signal was observed when CuCl, 1,10-phen were tested in 2.0 mL DMF at 100 °C for 1 hour. However, when the mixture of CuCl, 1,10-phen and **2a** under the same condition, a strong Cu(II) EPR signal could be detected (Figure 1(b)). In addition, the homo-coupling of **2a** had also been detected by GC-MS, which indicated the formation of alkyl radical. Therefore, this transformation is Cu(I)-induced single-electron reduction of C-Br bonds to generate alkyl radical species and Cu(II) species.

**Figure 1.** EPR spectra.



According to the previous reports and the above results, a proposed mechanism for this copper-catalysed radical alkenylation is described in Scheme 2. The alkyl radical **I** is generated by the reaction between Cu(I) species and the alkyl bromide **2** through single-electron transfer process. After the generation of alkyl radical **I**, the addition of alkyl radical **I** to alkene **1** gives the radical intermediate **II**, which then reacted with Cu(II) species to form the brominated intermediate **III** and Cu(I) species. Meanwhile, Cu(I) species is regenerated to complete the catalytic cycle. Subsequently, the brominated intermediate **III** elimination with the base to obtain the desired product **3**.



**Scheme 2.** Proposed mechanism.

## Conclusions

In conclusion, we have demonstrated a copper-catalysed radical alkenylation of various benzyl bromides and  $\alpha$ -carbonyl alkyl bromides to furnish  $\alpha$ -vinyl carbonyls and allylbenzene derivatives. Specifically, this transformation shows good regioselectivity to primary alkyl halides and tertiary, secondary alkyl halides that bear  $\beta$ -hydrides are also tolerated. The key initiation step of this transformation is copper-induced single-electron reduction of C-Br bonds to generate alkyl radical species.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: General procedures, spectral data and other supplementary information. See DOI: 10.1039/b000000x/

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