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Copper-Catalyzed Amination of Alkenyl Halides: Efficient Method for the Synthesis of Enamines

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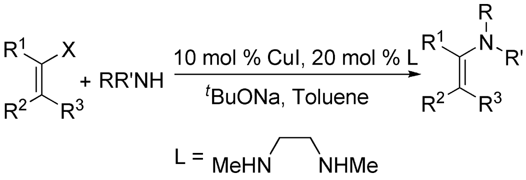
ABSTRACT



A copper-catalyzed method for the coupling of alkenyl halides with secondary amines has been developed. This protocol used a combination of 10 mol % copper iodide and 20 mol % *N,N′*-dimethylethane-1,2-diamine as catalyst. The reaction proceeded with various aromatic amines and alkenyl bromides or alkenyl iodides, and the enamines were formed in high yields with excellent regioselectivity and stereoselectivity under the reaction conditions.

Enamines are valuable intermediates in organic synthesis.[1] They are extensively employed as nucleophiles in Michael-type additions, intermediates in the synthesis of heterocycles, and precursors of chiral amines upon asymmetric transformations and intermediates in natural product synthesis.[2] The classical approach for the synthesis of enamines is the condensation of a secondary amine with a carbonyl compound, which usually happens under acid catalysis.[3] However, this method presents several limitations, such as harsh reaction conditions, lack of regio- and chemoselectivity, and low functional group tolerance. Alternative methods for the synthesis of enamines are hydroaminations of alkynes[4] and methylenation of amides.[5]

On the other hand, in recent years, great interest has been devoted to the development of metal catalyzed cross-coupling reactions of aryl halides with *N*-centered nucleophiles. In particular, the high stability and low cost of the copper catalysts enable these transformations[6,7] to be a useful complement to the more extensively studied palladium-catalyzed processes.[8] The application of the same cross-coupling reaction to alkenyl halides would furnish enamines or imines. This protocol has concentrated on the formation of enamines or imines with only a few examples of palladium-catalyzed vinylation of amines.[9] However, copper-catalyzed amination of alkenyl halides for formation of enamines has been scarcely studied, to the best of our knowledge, although copper-catalyzed the reactions of an alkenyl halide with amides[10,11]

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and azoles[12] have been previously reported. Herein we report the copper-catalyzed alkenylation of amines with various vinyl halides to afford enamines.

On the basis of our previous work on the copper-catalyzed reaction of an alkenyl halide with azoles,[12a] we felt that the use of an appropriate ligand and base would allow us to achieve a mild and general procedure for the synthesis of enamines. Using 1,2-diphenyl-1-iodobut-1-ene (**1a**) and diphenylamine (**2a**) as the prototypical substrate combination, an initial ligand screen was carried out with CuI as a precatalyst and ^{t}BuONa as a base. To our delight, among the five ligands examined, *N*,*N*′-dimethylethane-1,2-diamine (DMEDA) (**L4**) gave an excellent result (Figure 1). 2,2′-Bipyridine (**L1**), ethane-1,2-diamine (**L3**), and tetramethylethane-1,2-diamine (**L5**) also gave satisfying results. In the absence of ligand, the reaction can also proceed in 60% yield under the reaction conditions. Next, the applicability of other bases and solvents was also evaluated (Table 1). Clearly, ^{t}BuONa proved to be superior to KOH, Cs_2CO_3, and K_3PO_4 (entries 2 and 4−6). Na_2CO_3 proved to be inefficient (entry 7). The reaction also showed a strong solvent dependence. Except toluene, other solvents such as NMP, DMF, DMSO, and 1,4-dioxane proved to be inappropriate (entries 8−11). The reaction also showed a significant dependence on temperature. When the reaction was treated at 80 °C, the reaction did not proceed (entry 12). When the reaction mixture was warmed to 110 and 125 °C, the desired product was formed in 33% and 68% yields, respectively (entries 13 and 14). Reducing the amount of CuI to 5 mol % and 1 mol % within 16 h also afforded good yields (entries 15 and 16). It is noteworthy that when CuI was not used, the reaction did not proceed (entry 17).

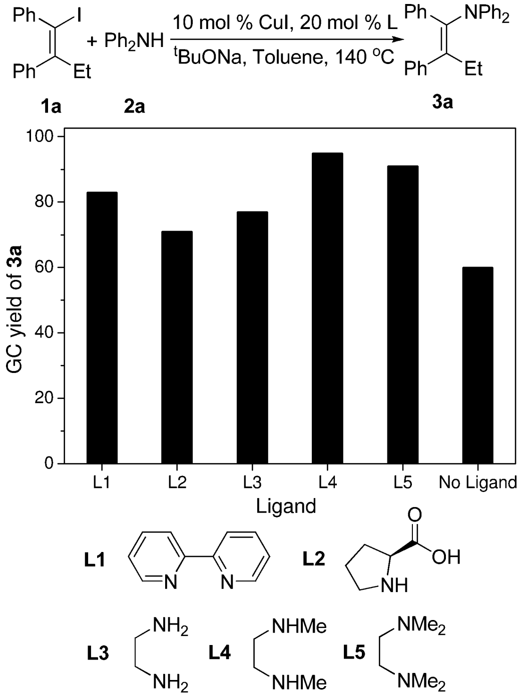
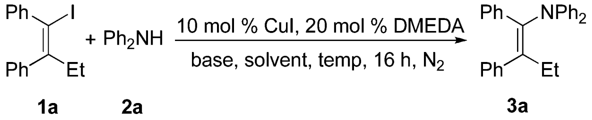


Figure 1. Comparison of ligands in CuI-catalyzed coupling of diphenylamine and 2,2-diphenyl-1-iodobut-1-ene.

Table 1. Base, Solvent, Temperature, and Time Optimization for Coupling of **1a** and **2a**



entry	base	solvent	temp (°C)	time (h)	yield^a (%) of **3a**
1	^{t}BuONa	toluene	140	24	95
2	^{t}BuONa	toluene	140	16	93
3	^{t}BuONa	toluene	140	8	73
4	NaOH	toluene	140	16	65
5	Cs_2CO_3	toluene	140	16	60
6	K_3PO_4	toluene	140	16	40
7	Na_2CO_3	toluene	140	16	NR
8	^{t}BuONa	NMP	140	16	21
9	^{t}BuONa	DMF	140	16	10
10	^{t}BuONa	DMSO	140	16	NR
11	^{t}BuONa	dioxane	140	16	NR
12	^{t}BuONa	toluene	80	16	NR
13	^{t}BuONa	toluene	110	16	33
14	^{t}BuONa	toluene	125	16	68
15	^{t}BuONa	toluene	140	16	86^b
16	^{t}BuONa	toluene	140	16	80^c
17	^{t}BuONa	toluene	140	16	NR^d

^{a} GC yield. ^{b} 5 mol % of CuI was added. ^{c} 1 mol % of CuI was added. ^{d} without the addition of CuI.

On the basis of these results, the optimal conditions involved the following parameters: CuI as precatalyst, ^{t}BuONa as base, *N*,*N*′-dimethylethane-1,2-diamine as ligand, and toluene as solvent, with reaction temperature at 140 °C. Under these

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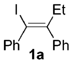
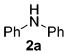
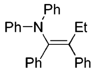
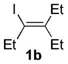
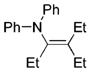
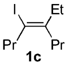
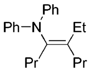
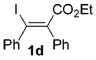
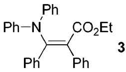
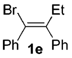
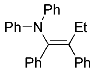
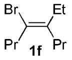
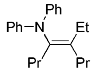
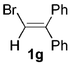
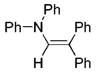
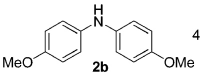
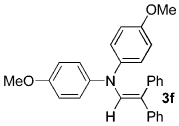
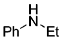
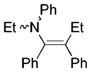
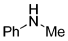
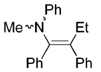
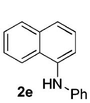
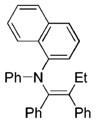
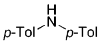
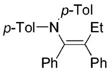
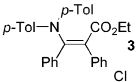
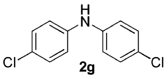
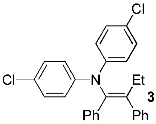
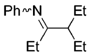
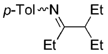
optimized conditions, a study on the substrate scope was carried out, and the results are summarized in Table 2.

Table 2. Expanding the Substrate Scope of the Coupling of Vinyl Halides with Amines

entry	alkenyl halide	amine	time (h)	product	yield (%)[a]
1	 **1a**	 **2a**	16	 **3a**	93(89)
2	 **1b**	**2a**	16	 **3b**	91(63)
3	 **1c**	**2a**	36	 **3c**	70(42)
4	 **1d**	**2a**	36	 **3d**	75(55)
5	 **1e**	**2a**	36	 **3a**	85(60)
6	 **1f**	**2a**	60	 **3c**	79(67)
7	 **1g**	**2a**	24	 **3e**	95(89)
8	**1g**	 **2b**	48	 **3f**	80(75)
9	**1a**	 **2c**	72	 **3g**	82(71)[b] (3:2)
10	**1a**	 **2d**	36	 **3h**	88(85)[b] (85:15)
11	**1a**	 **2e**	48	 **3i**	92(87)
12	**1a**	 **2f**	24	 **3j**	89(81)
13	**1d**	**2f**	24	 **3k**	87(67)
14	**1a**	 **2g**	48	 **3l**	88(81)
15	**1b**	Ph—NH$_2$ **2h**	24	 **3m**	95(64)[b] (*Z*:*E* = 1:1)
16	**1b**	*p*-Tol—NH$_2$ **2i**	24	 **3n**	97(88)[b] (*Z*:*E* = 1:1)

[a] GC yield; isolated yields are given in parentheses. [b] Combined yield of two isomers.

First, various alkenyl iodides were coupled with diphenylamine (**2a**). (*E*)-(1-Iodobut-1-ene-1,2-diyl)dibenzene (**1a**), 3-ethyl-4-iodohex-3-ene (**1b**), (*E*)-4-ethyl-5-iodooct-4-ene (**1c**), and (*Z*)-ethyl 3-iodo-2,3-diphenylacrylate (**1d**) proved to be suitable substrates, and the corresponding products were formed in excellent yields (entries 1−4). The reaction of alkenyl bromides with amines also afforded enamines in excellent yields (entries 5−8). To the best of our knowledge, this is the first example of the copper-catalyzed amination of an unactivated alkenyl bromide. It is worth noting that this protocol could proceed with di- and trisubstituted vinyl halides under the reaction conditions and afford the desired enamines in excellent yields. In contrast, when alkenyl halides bearing β-hydrogen, such as α-bromostyrene and β-bromostyrene, were treated with diphenylamine under the same reaction conditions, the desired products were not observed. A small amount of enyne was examined by GC−MS, which occurred to undergo an E2-type elimination and coupling reaction.[12e,13] Furthermore, the reaction of alkenyl chloride with **2a** did not proceed.

Besides the diphenylamine **2a**, other substituted anilines were all viable substrates. Excellent results were obtained for the aromatic substituted *N*-ethylaniline (**2c**) and *N*-methylaniline (**2d**) (entries 9 and 10). In these reactions, the products were formed as a mixture of two isomers. Coupling reaction of *N*-naphthalenylaniline (**2e**) with **1a** afforded an exclusive enamine in high yield (entry 11) due to increased steric hindrance. The coupling reaction also proceeded in excellent yields with bis(4-methoxyphenyl)amine (entry 8), di(*p*-tolyl)-amine (entries 12 and 13), or bis(4-chlorophenyl)amine (entry 14). To our delight, the crystal of **3j** was suitable for single-crystal analysis, and its structure was fully characterized by the X-ray diffraction analysis. Coupling reaction of alkenyl halides with primary amines gave rise to imines as a mixture of two isomers (as confirmed by NMR spectroscopy) after tautomerization of the initially formed enamine (entries 15 and 16). However, aliphatic amines were not suitable substrates for such reaction to form enamines under the reaction conditions. In this case, amines are remained.

In summary, we have developed the copper-catalyzed cross-coupling reaction of amines with alkenyl iodides and alkenyl bromides. The enamines were formed in high yields with excellent regioselectivity and stereoselectivity under the reaction conditions.

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Supporting Information Available: Experimental procedures and full characterization including ^{1}H NMR and ^{13}C NMR data for compounds **3a−n**. NMR spectra for **3a−n**. X-ray crystallography data for complex **3j** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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