



## Copper oxide nanoparticles catalyzed vinylation of imidazoles with vinyl halides under ligand-free conditions

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### ABSTRACT

Recyclable copper oxide nanoparticles catalyzed most efficient and straightforward protocol for the vinylation of imidazoles with vinyl halides under ligand-free conditions. Utilizing this protocol various imidazoles were cross-coupled with different substituted vinyl halides to get the corresponding products in excellent yields with the retention configuration.

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*N*-Vinylimidazoles are important building blocks in the synthesis of many biologically active molecules and a wide variety of industrially valuable organic compounds.<sup>1</sup> These compounds also exhibit remarkable antifungal and antiparasitic properties.<sup>2</sup> In addition, *N*-vinylimidazoles are widely used in the synthesis of polymeric materials with various properties. For example, poly(*N*-vinylimidazoles) have found growing applications in the preparation of polymeric dyes, catalysts, and ion-exchange resins.<sup>3</sup>

Thus, these wide ranges of applications led to various types of processes for the synthesis of *N*-vinylimidazoles. Traditional methods involve direct addition of imidazole to alkynes,<sup>4</sup> copper-catalyzed C–N bond cross-coupling of benzimidazole with vinylboronic acid<sup>5</sup>, and olefination of  $\beta$ -hydroxyimidazoles.<sup>6</sup> The most commonly employed strategy involves the vinylation of imidazoles with vinyl halides.<sup>7</sup> These procedures are rather limited in scope and selectivity. Notable amongst them is the well-defined Cu/L-proline as a recyclable system developed by Bao and co-workers for the synthesis of *N*-vinylimidazoles in ionic liquids at 110 °C for 20 h.<sup>7a</sup>

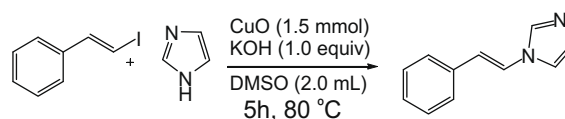
Over recent years great strides have been made in the field of transition-metal-catalyzed vinylation of imidazoles with vinyl halides. The combination of transition metals and ligands has been used to facilitate the transformation at higher temperatures.<sup>6</sup> Most of these metal-catalyzed reactions involve expensive and moisture-sensitive catalytic systems and ligands, longer reaction times, metal contamination of the final product, and non recyclability of the catalyst, thus increasing the cost and limiting the scope of the reaction. From the synthetic point of view, it is desirable to find novel recyclable catalytic system especially under ligand-free conditions for the synthesis of such highly useful organic compounds.

In the past few years, tremendous efforts have been made in the heterogeneous catalysis for various organic transformations.<sup>8</sup> We have recently described an efficient method for C–Se cross-coupling

of phenyl diselenide with various aryl halides by using recyclable CuO nanoparticles under ligand-free conditions.<sup>8a</sup> In continuation of our work on metal-catalyzed cross-coupling reactions, we have explored the CuO-catalyzed synthesis of *N*-vinylimidazoles under ligand-free conditions. In general, heterogeneous catalysts offer higher surface area and lower coordinating sites, which are responsible for the higher catalytic activity.<sup>9</sup> Furthermore, heterogeneous catalysis has the advantage of high atom efficiency, easy product purification, and reusability of the catalyst. However, until now, the investigation of nanoparticles as catalysts is of limited scope.

We report, herein, the synthesis of *N*-vinylimidazoles by using recyclable CuO nanoparticles as catalyst under ligand-free conditions (Scheme 1). To the best of our knowledge, this is the first recyclable copper oxide nanoparticles-catalyzed cross-coupling of vinyl halides with imidazoles.

Initially, the reaction between vinyl halides (1.0 mmol) and imidazole (1.0 mmol) was investigated to optimize the reaction conditions. In the first instance, the amount of catalyst necessary to promote the reaction efficiently was examined (Table 1). It is observed that the variation in the amount of CuO nanoparticles had an effective influence. While 0.5 and 1.0 mol afforded the desired product in moderate yields (entries 1 and 2), 1.5 mol % of the catalyst gave the desired product in 98% yield (entry 3). When the amount of CuO nanoparticles was increased to 2.0 mol %, the yield of the compound was not changed significantly and afforded the desired product in 99% (entry 4).



**Scheme 1.** CuO nanoparticles-catalyzed cross-coupling reaction of *trans*- $\beta$ -iodostyrene with imidazole.

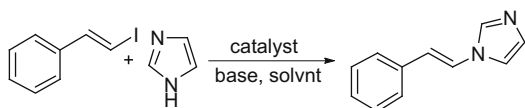
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**Table 1**  
Amount of CuO used for synthesis of *N*-vinylimidazole<sup>a</sup>

Entry	CuO (mol %)	Yield (%)
1	0.5	61
2	1.0	80
3	1.5	98
4	2.0	98

<sup>a</sup> Reaction conditions: *trans*- $\beta$ -iodostyrene (1.0 mmol), imidazole (1.0 mmol) CuO (1.5 mol, KOH (1.0 equiv), DMSO (2.0 mL), 80 °C, 5 h.

**Table 2**  
Screening of different copper catalysts<sup>a</sup>

Entry	Base	Solvent	Copper source	Time (h)	T (°)	Yield <sup>b</sup> (%)
1	KOH	DMSO	CuO	24	110	25
2	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	CuO	24	110	0
3	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	CuO	24	110	14
4	K <sub>3</sub> PO <sub>4</sub>	DMSO	CuO	24	110	10
5	Cs <sub>2</sub> CO <sub>3</sub>	THF	CuO	24	110	0
6	KOH	DMF	CuO	24	110	10
7	Cs <sub>2</sub> CO <sub>3</sub>	DMF	CuI	24	110	15
8	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	CuI	24	110	0
9	KOH	DMSO	CuI	24	110	0
10	KOH	DMSO	Cu(acac) <sub>2</sub>	24	110	9
11	KOH	DMSO	Nano CuO	5	80	98
12	KOH	DMSO	Nano CuO	5	40	66
13	KOH	DMSO	Nano CuO	5	rt	20
14	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	Nano CuO	5	80	49
15	K <sub>3</sub> PO <sub>4</sub>	DMSO	Nano CuO	5	80	31
16	KOH	DMF	Nano CuO	5	80	55
17	KOH	DMSO	—	24	80	0
18	—	DMSO	Nano CuO	24	80	25
19	KOH	Water	Nano CuO	24	80	0

<sup>a</sup> Reaction conditions: *trans*- $\beta$ -iodostyrene (1.0 mmol), imidazoles (1.0 mmol) CuO (1.5 mol), base (1.0 equiv), solvent (2.0 mL) under N<sub>2</sub>.

<sup>b</sup> Isolated yield.

Different solvents, base, as well as reaction temperature have been screened. Interestingly, we found that the reaction proceeded efficiently only when DMSO was used as the solvent (Table 2, entry 11). Other solvents such as DMF were also effective but the yields were not encouraging (Table 2, entries 6, 7, and 16), and no products were formed in the case of THF or water (Table 2, entries 5 and 19). The choice of KOH as the base was vital for this coupling reaction (Table 2, entry, 11), as Cs<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub> though catalyze the reaction, the yields were discouraging (Table 2, entries 3, 4, 14, and 15). The reaction when conducted at room temperature and 40 °C, the yields observed were very low. The reaction proceeds smoothly at 80 °C (Table 2, entry 11).

Then the reaction was screened with several copper catalytic systems for the synthesis of *N*-vinylimidazoles, and the results are summarized in Table 2. It was observed that the combination of nano CuO with KOH in DMSO provided the best results. However, the coupling reaction with ordinary CuO, CuI, and Cu(acac)<sub>2</sub> gave only trace amount of the desired product. The yield was highly dependent upon the reaction temperature, base, solvent, and catalyst.<sup>10</sup> The optimal reaction conditions for the vinylation of imidazoles with vinyl halides were achieved using a combination of CuO (1.5 mol), KOH (1.0 equiv), and DMSO (2.0 mL) with stirring for 5 h at 80 °C (Table 2, entry 12).

To expand the scope of this novel transformation, we examined various vinyl halides with different imidazoles and benzimidazoles for cross-coupling (Table 3).<sup>11</sup> This protocol efficiently cross coupled *trans*- $\beta$ -iodostyrene having electron-rich, electron-neutral, and electron-poor functionalities with various imidazoles and benzimidazoles under the optimized reaction conditions and generated the desired products in excellent yields (Table 3). However, the reaction of imidazoles having electron-withdrawing substituents such as 4-nitrile imidazole with *trans*- $\beta$ -iodostyrene did not proceed. Even in the case of 4-nitro-imidazole, the product was obtained in very low yields (Table 3, entry 15). All attempts to couple alkyl vinyl iodides with imidazoles were not successful (Table 3, entry 16). We further tested the coupling of *trans*- $\beta$ -bromostyrenes with imidazoles under the same conditions. The reaction of

**Table 3**  
Vinylation of imidazoles with *trans*- $\beta$ -iodostyrene<sup>a</sup>

Entry	Iodides	Imidazoles	Product	Yield <sup>b</sup> (%)
1				98
2				87
3				90
4				91
5				93

Table 3 (continued)

Entry	Iodides	Imidazoles	Product	Yield <sup>b</sup> (%)
6				90
7				89
8				91
9				88
10				85
11				88
12				84
13				86
14				—
15				10
16				—

<sup>a</sup> Reaction conditions: *trans*- $\beta$ -iodostyrene (1.0 mmol), imidazoles (1.0 mmol) CuO (1.5 mol), KOH (1.0 equiv), DMSO (2.0 mL) under N<sub>2</sub>.

<sup>b</sup> Isolated yield.

*trans*- $\beta$ -bromostyrenes with imidazoles proceeded smoothly to afford the desired product in reasonable yield (Table 4). However, the coupling reaction of various imidazoles with vinyl bromides required longer reaction times to get reasonable yields of *N*-vinylimidazoles whereas shorter reaction times led to decreased yields (Table 4, entries 1 and 2). Furthermore, the double bond geometry of the vinyl imidazoles was retained in all the cases and the structures of all the products were determined from their analytical and spectral (IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR) data and by direct comparison with authentic samples.<sup>12</sup>

Copper oxide nanoparticles were used directly in the next cycle. After each cycle, the catalyst was recovered by simple centrifugation, washed with acetone, and then dried in vacuo. The recovered nano CuO was then taken to the next cycle. The catalyst was found to be recyclable without loss of catalytic activity up to four cycles (Table 5).

In conclusion, we have developed a clean and efficient straightforward protocol for cross-coupling of imidazoles with phenyl-substituted vinyl halides catalyzed by copper oxide nanoparticles as recyclable catalyst under ligand-free conditions with retention

**Table 4**  
Vinylating of imidazoles with vinyl bromides and chlorides<sup>a</sup>

Entry	Halides	Imidazoles	Product	Yield <sup>b</sup> (%)
1 2				51 <sup>c</sup> 89
3 4				45 <sup>c</sup> 82
5				79
6				84
7				80
8				78
9				20

<sup>a</sup> Reaction conditions: vinyl halides (1.0 mmol), imidazoles (1.0 mmol) CuO (2.0 mol), KOH (1.0 equiv), DMSO (2.0 mL) at 80 °C for 11 h under N<sub>2</sub>.<sup>b</sup> Isolated yield.<sup>c</sup> After 5 h.

of the double bond geometry. However, in this protocol the alkyl-substituted vinyl halides did not yield the desired products. The mild reaction conditions, high selectivity, operational simplicity, and recyclability of the metal catalyst should render this method attractive both from economic and industrial points of view as compared to the previous methods.

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**Table 5**  
Recycling of CuO Nanoparticles<sup>a</sup>

Recycles	Yield (%)	Catalyst recovery <sup>a</sup> (%)
1	98	98
2	96	95
3	92	91
4	92	91

<sup>a</sup> Reaction conditions: *trans*-β-iodostyrene (1.0 mmol), imidazoles (1.0 mmol) CuO (1.5 mol), KOH (1.0 equiv), DMSO (2.0 mL) under N<sub>2</sub>.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.022.

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10. The reaction taking place in the presence of DMSO and its absence in water may be explained by the formation of dimethyl ion (Ref. Hunter, D. H.; Cram, D. J. *J. Am. Chem. Soc.* **1966**, *88*, 5765).
11. **General procedure for the synthesis of vinyl imidazoles:** To a stirred solution of *trans*- $\beta$ -iodostyrene (1.0 mmol) and imidazole (1.0 mmol) in dry DMSO (2.0 mL) were added CuO nanoparticles (1.5 mol) followed by KOH (1.0 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was heated at 80 °C for 5 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool, and a 1:1 mixture of ethyl acetate/water (20 mL) was added, and CuO was removed by centrifuging for 1 h at 15,000 rpm. The combined organic extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent and volatiles were completely removed under vacuum to yield the crude product, which was further purified by column chromatography using petroleum ether and ethyl acetate as eluents to yield the expected product **3** (98% yield as yellow solid). The identity and purity of the product was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic analysis.
- Recycling of the catalyst:** After the reaction was complete, the reaction mixture was allowed to cool, and a 1:1 mixture of ethyl acetate/water (2.0 mL) was added, and CuO was removed by centrifugation. After each cycle, the catalyst was recovered by simple centrifugation, washed with deionized water and ethylacetate, and then dried in vacuo. The recovered nano CuO was used directly in the next cycle.
12. **Data for the representative examples of synthesized compounds:** (*E*)-4-Phenyl-1-styryl-1H-imidazole (Table 3, entry 2): mp 102–103 °C; IR (KBr):  $\nu$  3115, 3028, 2922, 1651 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 7.77 (d, 2H, *J* = 7.80 Hz), 7.72 (s, 1H), 7.50 (s, 1H), 7.38–7.22 (m, 9H), 6.73 (d, 1H, *J* = 14.63 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 142.9, 136.6, 134.2, 133.2, 128.7, 128.5, 127.8, 127.1, 126.0, 124.9, 122.3, 118.4, 111.3; mass (ESI): *m/z* 247 [M+1]. Anal. Calcd for (C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>): C, 82.90; H, 5.73; N, 11.37. Found: C, 82.83; H, 5.65; N, 11.29.
- (*E*)-1-(4-Methoxystyryl)-4-phenyl-1H-imidazole (Table 3, entry 8): mp 110–112 °C; IR (KBr):  $\nu$  3032, 2924, 1654 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 7.77–7.70 (m, 3H), 7.48 (s, 1H), 7.37–7.16 (m, 6H), 7.83 (d, 2H, *J* = 8.30 Hz), 6.67 (d, 1H, *J* = 14.35 Hz), 3.80 (s, 3H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 159.4, 133.4, 128.5, 127.3, 127.1, 126.7, 124.8, 120.7, 118.5, 114.2, 55.2; mass (ESI): *m/z* 277 [M+1]. Anal. Calcd for (C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O): C, 78.24; H, 5.84; N, 10.14. Found: C, 78.16; H, 5.76; N, 10.06.
- (*E*)-1-(3-Fluorostyryl)-1H-benzodimidazole (Table 3, entry 10): mp 130–132 °C; IR (KBr):  $\nu$  3090, 2924, 1656 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 8.19 (s, 1H), 7.87–7.81 (m, 1H), 7.64–7.50 (m, 2H), 7.37–7.29 (m, 3H), 7.23–7.12 (m, 2H), 7.04–6.98 (m, 1H), 6.92 (d, 1H, *J* = 14.35 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 161.4, 143.9, 140.6, 136.9, 130.4, 130.3, 123.9, 123.2, 120.7, 118.2, 114.9, 114.6, 112.7, 112.4, 110.2; mass (ESI): *m/z* 239 [M+1]. Anal. Calcd for (C<sub>15</sub>H<sub>11</sub>FN<sub>2</sub>): C, 75.62; H, 4.65; N, 11.76. Found: C, 75.56; H, 4.59; N, 11.68.
- (*E*)-1-(4-Methylstyryl)-1H-benzodimidazole (Table 3, entry 13): mp 111–113 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 8.32 (s, 1H), 7.94–7.62 (m, 1H), 7.47 (d, 1H, *J* = 14.35 Hz), 7.37–7.26 (m, 5H), 7.17–7.15 (m, 2H), 6.90 (d, 1H, *J* = 14.35 Hz), 2.38 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  = 143.9, 140.8, 138.0, 131.6, 129.5, 126.0, 123.7, 122.9, 120.5, 120.3, 120.1, 110.2, 21.7; mass (ESI): *m/z* 235 [M+1].