

## CuO Nanoparticles Supported on Silica: A Simple, Efficient, and Recyclable Catalyst for Hydroacylation Reactions of Aldehydes with Azodicarboxylate

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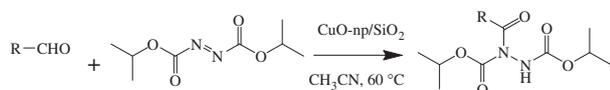
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We describe a green and efficient procedure for the hydroacylation of aldehydes with diisopropyl azodicarboxylate, using CuO nanoparticles supported on silica (CuO-np/SiO<sub>2</sub>) as a catalyst, in good to excellent yields. A wide range of aldehydes, including aromatic and aliphatic compounds, were considered. The catalyst is found to be truly heterogeneous in the reaction mixture and can be reused without loss of catalytic activity.

One of the most important reactions, which finds applications in the synthesis of many substances such as drugs, materials, and natural products,<sup>1</sup> is the formation of new carbon–nitrogen bonds from simple and easily available starting materials.<sup>2</sup> Over the last few decades, a very efficient reaction, which involves the use of azodicarboxylates as electrophiles for the formation of carbon–nitrogen bonds, has been successfully used.<sup>3</sup> The efficiency of the reaction is reported to be the result of the strong electron-withdrawing nature of azodicarboxylate acceptors possessing a vacant orbital.<sup>4</sup> Over the years, various reactions such as zwitterion intermediate reactions,<sup>5,6</sup> electrophilic  $\alpha$ -amination of carbonyl compounds,<sup>7,8</sup> C–H activation at the  $\alpha$ -positions of amines and ethers,<sup>9,10</sup> and ene-type reactions with olefins<sup>11–13</sup> in the presence of azodicarboxylates have been extensively studied. In addition, various other methods for hydroacylation reactions with aldehydes using a range of reagents and catalysts, for example, ionic liquids such as 1-*n*-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([BMIM][NTf<sub>2</sub>])<sup>14</sup> including water<sup>15</sup> without a catalyst, and transition-metal catalysts,<sup>16</sup> have been reported. All the above methods suffer from drawbacks and limitations such as choice of substrate, atom economy, reusability of the catalyst, and the reaction efficiency. Nanocatalysts having high surface area to volume ratios are expected to display unique electronic properties that may influence the reaction. To our knowledge, the reactions of aldehydes with azodicarboxylates have not yet been explored using nano copper oxide as a catalyst. Herein, we report a green cross-coupling reaction of a range of aldehydes with an azodicarboxylate, using a novel catalyst, namely CuO



**Scheme 1.** CuO-np/SiO<sub>2</sub>-catalyzed hydroacylation reaction of aldehydes and azodicarboxylate.

nanoparticles supported on silica<sup>17</sup> (Scheme 1). The factors affecting the reactions are also discussed.

Hydroacylation reactions between benzaldehyde and diisopropyl azodicarboxylate were studied, using CuO nanoparticles supported on silica as a catalyst, at a temperature of 60 °C, using different solvents. The catalyst requires no ligands and additives to accelerate the reaction, which is an added advantage in making the process clean. The pertinent data are presented in Table 3. The yield of the reaction varies in the range 60–95%, depending on the substrate and conditions used for the reaction. The CuO-np/SiO<sub>2</sub> catalyst was prepared as described in the literature.<sup>18</sup> The catalyst was characterized by powder X-ray diffraction, transmission electron microscopy, and atomic absorption spectroscopy (see the Supporting Information).<sup>19</sup>

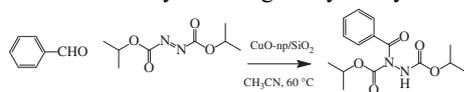
First, we studied the effect of the solvent on the hydroacylation reaction between benzaldehyde and diisopropyl azodicarboxylate. Remarkably, acetonitrile gave the hydroacylation product smoothly in good to excellent yield, whereas methanol, THF, toluene, dioxane, and dichloromethane gave slower reactions with moderate yields. The results are summarized in Table 1.

We screened various catalysts for the hydroacylation reaction in acetonitrile solvent at 60 °C; the results are summarized in Table 2. It is clear from the table that only CuO-np/SiO<sub>2</sub> provides good yields of the product compared to RuCl<sub>3</sub>, RhCl<sub>3</sub>, Cu(OAc)<sub>2</sub>, CuO, and CuO-np without the support provided a poor yield with the problem of catalyst recovery. We also studied the effect of different CuO-np loadings on the silica support for

**Table 1.** Effect of solvent on hydroacylation reaction catalyzed by CuO-np/SiO<sub>2</sub><sup>a</sup>

Entry	Solvent	Yield <sup>b</sup> /%
1	CH <sub>3</sub> CN	88, 57 <sup>c</sup>
2	THF	62
3	Toluene	56
4	Dioxane	69
5	Methanol	73

<sup>a</sup>Reaction conditions: diisopropyl azodicarboxylate (1 mmol), CuO-np/SiO<sub>2</sub> (10 mol %), benzaldehyde (1.2 mmol), solvent (5 mL), 60 °C, 24 h. <sup>b</sup>Isolated yields. <sup>c</sup>Reaction carried out at room temperature, 24 h.

**Table 2.** Effect of catalyst loading on hydroacylation reaction<sup>a</sup>

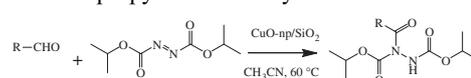
Entry	Catalyst	Loading /mol %	Yield <sup>b</sup> /%
1	RuCl <sub>3</sub>	10	47
2	RhCl <sub>3</sub>	10	39
3	Cu(OAc) <sub>2</sub>	10	58
4	CuO	10	26
5	CuO-np	10	57
6	Without catalyst	—	No reaction
7	CuO-np/SiO <sub>2</sub>	2	48
8	CuO-np/SiO <sub>2</sub>	5	62
9	CuO-np/SiO <sub>2</sub>	10	88

<sup>a</sup>Reaction conditions: diisopropyl azodicarboxylate (1 mmol), benzaldehyde (1.2 mmol), CuO-np/SiO<sub>2</sub> (10 mol %), CH<sub>3</sub>CN (5 mL), 60 °C, 24 h. <sup>b</sup>Isolated yields.

the hydroacylation reaction, and the data are presented in Table 2. The table shows that a 10 mol % copper(II) oxide nanoparticle loading on silica gives excellent results compared to 2 and 5 mol % copper loadings on silica, indicating the role of catalyst size in the reaction. However, needless to say, no product formation occurs in the absence of the catalyst under the same reaction conditions.

Electronic factors also play an important role in the reaction. In order to understand the electronic factors, the study was extended to aldehydes with different substituents. Table 3 presents the relevant data. Benzaldehydes with electron-donating groups, such as 4-methoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde, 4-methylbenzaldehyde, 4-hydroxybenzaldehyde, and 3-hydroxybenzaldehyde, provided excellent yields in short reaction times (Table 3, Entries 2–6) compared to benzaldehyde with electron-withdrawing groups, such as 4-bromobenzaldehyde, 4-chlorobenzaldehyde, 2,6-dichlorobenzaldehyde, and 4-nitrobenzaldehyde, which needed longer reaction times and gave moderate yields (Table 3, Entries 7–10). Thiophen-2-carbaldehyde provided an excellent yield (Table 3, Entry 11). Aliphatic aldehydes (Table 3, Entries 12 and 13) underwent smooth reactions with excellent yields, compared to benzaldehyde (Table 3, Entry 1). A dialdehyde provided a poor yield (Table 3, Entry 14), compared to the other aldehydes. It is clear from the table that aliphatic aldehydes give better yields than aromatic aldehydes, indicating the influence of the electronic properties of the substrates. It is also apparent from the table that electron-withdrawing groups decrease the overall yields of the reactions. These results make the process more attractive and interesting with respect to the economy and simplicity of the process.

The reusability of the silica-supported CuO nanoparticles catalyst was studied for the hydroacylation reaction of benzaldehyde with diisopropyl azodicarboxylate in acetonitrile solvent at 60 °C. CuO-np/SiO<sub>2</sub> was recovered quantitatively by simple filtration, and reused; it gave consistent activity even after the fifth cycle (Table 3, Entry 1). The absence of copper in the filtrate, measured by atomic absorption spectroscopy, confirmed that no leaching of copper occurred during the reaction. These results make the process more attractive and interesting with respect to the economy and simplicity of the process.

**Table 3.** CuO-np/SiO<sub>2</sub>-Catalyzed hydroacylation reaction of aldehyde and isopropyl azodicarboxylate<sup>a</sup>

Entry	Aldehyde	Product	Time /h	Yield <sup>b</sup> /%
1			24	85 83 <sup>c</sup>
2			24	90
3			26	92
4			18	87
5			26	89
6			28	88
7			24	79
8			24	82
9			36	78
10			24	60
11			12	95
12			15	93
13			18	90
14			30	63

<sup>a</sup>Reaction conditions: diisopropyl azodicarboxylate (1 mmol), benzaldehyde (1.2 mmol), CuO-np/SiO<sub>2</sub> (10 mol %), CH<sub>3</sub>CN (5 mL), 60 °C. <sup>b</sup>Isolated yields. <sup>c</sup>Isolated yield after fifth cycle.

In conclusion, a green, inexpensive, and efficient method for the hydroacylation of various aldehydes with diisopropyl azodicarboxylate, using a silica-supported nanocopper catalyst, in good to excellent yields is provided. The effects of solvent, catalyst loading, and substituents on the aldehyde are studied. The choice of aldehyde is paramount in the selectivity of the reaction. The protocol used is inexpensive and the CuO-np/SiO<sub>2</sub> catalyst is recyclable; no additional ligands and additives are required, so the method is simple, economical, and has practical advantages for the synthesis of biologically active heterocyclic compounds.

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- General experimental procedure for the CuO-np/SiO<sub>2</sub>-catalyzed hydroacylation reaction of aldehydes with azodicarboxylate:**  
Diisopropyl azodicarboxylate (1 mmol), aldehyde (1.2 mmol), and CuO-np/SiO<sub>2</sub> (10 mol%) were stirred in acetonitrile solvent (5 mL) at 60 °C. The progress of the reaction was monitored by TLC. After the appropriate time in Table 3 reaction mixture was diluted with 20 mL of acetonitrile and catalyst was separated by filtration, the solvent was evaporated and the residue purified by column chromatography on silica gel using hexane–ethyl acetate (80:20) as eluent to afford the pure product. All products were characterized by <sup>1</sup>H NMR and <sup>13</sup>C NMR.  
**Spectral data for selected compounds**  
**Spectral data for Hydroacylation product (Table 3, Entry 1), Yield: 85%;** <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.04–1.07 (d, 6H), 1.26 (d, 6H), 4.83 (m, 2H), 7.10 (s, 1H), 7.38–8.10 (m, 5H); <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>): δ 21.31, 21.91, 70.41, 72.15, 127.96, 130.13, 131.72, 133.37, 135.21, 152.8, 155.21, 170.7. Anal. Calcd for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>: C, 58.43; H, 6.54; N, 9.09%. Found: C, 58.21; H, 6.62; N, 9.13%.  
**Hydroacylation product (Table 3, Entry 2), Yield: 90%;** <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.11 (d, 6H), 1.29 (d, 6H), 3.84 (s, 3H), 4.86 (m, 2H), 5.28 (s, 1H), 6.85 (dd, 2H), 7.68–8.05 (dd, 2H); <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>): δ 21.58, 22.03, 56.32, 70.41, 72.03, 113.37, 121.1, 131.12, 132.34, 153.2, 155.31, 162.97. Anal. Calcd for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>: C, 56.80; H, 6.55; N, 8.28%. Found: C, 56.68; H, 6.61; N, 8.32%.
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- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.