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## Copper(II)-Catalyzed Oxidative N-Nitrosation of Secondary and Tertiary Amines with Nitromethane Under an Oxygen Atmosphere

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The combination of a catalytic amount of  $Cu(OTf)_2$  and less than a stoichiometric amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under an  $O_2$  atmosphere effectively promoted the *N*-nitrosation of both secondary aromatic/aliphatic amines and tertiary aromatic amines with nitromethane (CH<sub>3</sub>NO<sub>2</sub>) leading to the preparation of *N*-nitrosamine derivatives.

The facile preparation of N-nitrosamine derivatives has been extensively studied in organic and medicinal chemistry because a number of these derivatives are strong carcinogens, the structure of which are found in various biologically active substances and functional materials.1 The nitrosation of amines with nitrous acid that is generated from sodium nitrite and an acid represents a classic approach to the synthesis of Nnitrosamines.<sup>2</sup> In addition to this procedure, others have been reported using a nitroso source involving alkyl nitrites (RO- $N=O),^{3}$ (CI-N=O),<sup>4</sup> nitrosyl chloride nitrosonium tetrafluoroborate  $(NOBF_4)$ ,<sup>5</sup> thiol-N<sub>2</sub>O<sub>4</sub>,<sup>6</sup> nitrogen oxides  $(N_2O_3)$ or  $N_2O_4$ ),<sup>7</sup> oxyhyponitrite ( $N_2O_3^{2^-}$ ),<sup>8</sup> NO under  $O_2$  atmosphere, LiNH<sub>2</sub>-NO,<sup>11</sup> Fremy's salt,<sup>10</sup>  $[NO^{+}-18$ -crown-6-H $(NO_{3})_{2}]$ ,<sup>12</sup> NaNO<sub>2-</sub>SnCl<sub>4</sub>,<sup>13</sup> NO-AgNO<sub>3</sub>,<sup>14</sup> and bromonitromethane (BrCH<sub>2</sub>NO<sub>2</sub>).<sup>15</sup> Also during the last decade, a heterogeneous catalytic system has been widely developed using a combination of either sodium nitrate or nitrogen tetroxide and a catalyst support: NaNO<sub>2</sub>-SiO<sub>2</sub>-trichloroisocyanuric acid,<sup>16</sup> NaNO<sub>2</sub>-SiO<sub>2</sub>-OSO<sub>3</sub>H on SiO<sub>2</sub>,<sup>17</sup> NaNO<sub>2</sub>-Nafion-H on SiO<sub>2</sub>,<sup>18</sup> N<sub>2</sub>O<sub>4</sub> supported on PVP,  $^{19}$  N<sub>2</sub>O<sub>4</sub>-Chacoal,  $^{20}$  nitrite ionic liquid,  $^{21}$  and NaNO<sub>2</sub>-molybdate sulfuric acid.<sup>22</sup> In general, NaNO<sub>2</sub> has a high degree of toxicity and requires relatively strong acidic conditions, which are generally unsuitable for substrates bearing an acid-sensitive substituent. Quite recently, Hou et al. and Wan and co-workers, found that nitromethane (CH<sub>3</sub>NO<sub>2</sub>), which is economical and has been used as a common reaction

solvent in organic synthesis, functions as an alternative nitroso source in the presence of an oxidizing reagent, such as IBX (oiodoxybenzoic acid)/TBAF and кі/твнр (t-butvl hydroperoxide).<sup>23</sup> However, in both cases, the use of more than stoichiometric amounts (2-3 equiv per amine) of IBX/TBAF or the use of a relatively expensive TBHP requires completing the desired N-nitrosation. Therefore, there is ample room for the improvement of these procedures. Thus, we envisioned the development of a novel catalytic procedure for N-nitrosation of amines with both nitromethane and a more economical oxidizing agent in the presence of a metal catalyst. On the basis of oxidative Nef reaction conditions involving a base and an oxidizing agent,<sup>24</sup> we found interesting results. Under an O2 atmosphere, copper(II) triflate successfully catalyzed the N-nitrosation of secondary and tertiary amines with CH<sub>3</sub>NO<sub>2</sub> in the presence of a base. Herein, we report the preliminary results of this method. This is the first example of the copper(II)-catalyzed direct N-nitrosation of secondary and tertiary amines with CH<sub>3</sub>NO<sub>2</sub> under an O<sub>2</sub> atmosphere.<sup>25</sup>

Initially, we examined the nitrosation of N-methyl-ptoluidine in the presence of nitromethane and DBU with copper catalysts and several oxidizing reagents (Table 1). For example, when N-methyl-p-toluidine was treated with Cu(OTf)<sub>2</sub> (10 mol%) and a relatively strong oxidizing agent, tertbutyl hydroperoxide (TBHP) at 90 °C for 5 h, the desired nitrosation proceeded producing the nitrosation product 1a in a 38% yield (entry 1). Thus, when  $H_2O_2$  was then used, the yield was slightly improved to 41% (entry 2). It is noteworthy that the use of an abundant and economical oxidizing reagent, O<sub>2</sub>, gave **1a** in an excellent yield (entry 3). Next, we ran the reaction using several copper catalysts. Consequently, the use of CuBr<sub>2</sub>, Cu(OAc)<sub>2</sub> or a copper(I) catalyst reduced the catalytic effect for N-nitrosation (entries 4-7). Also, under either an ambient atmosphere or an inert gas atmosphere, both yields were substantially reduced to approximately 30% (entries 8 and 9). When both the copper catalyst and DBU had been reduced to 5 mol% and 0.5 equiv per the starting aniline,

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Electronic Supplementary Information (ESI) available: The experimental procedure, spectral data and NMR spectra chart. See DOI: 10.1039/x0xx00000x

CH,

CH<sub>3</sub>

CH3

CH<sub>3</sub>

6a: 91%

CH<sub>3</sub>

C٨

9a: 34%

NO

NO

CH<sub>3</sub>

NO

O<sub>2</sub>N

CH<sub>2</sub>CH<sub>3</sub>

NO

Cu(OTf)<sub>2</sub> (5 mol%)

CH<sub>3</sub>NO<sub>2</sub>, 90 °C, 20 h

2a: 63% (R = m-CH<sub>3</sub>)

**7a**: 85%

10a: 33%

 $CH_3$ 

`NO

CH<sub>3</sub>

NO

H<sub>2</sub>C

B

0

CH<sub>3</sub>

NC

DBU (0.5 equiv)

O2 atmosphere

3a: 77% (R = H)

CI

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Entry	[Cu]	[O] <sup>a</sup>	Conversion	Yield of <b>1a</b>
			(%) <sup>b</sup>	(%) <sup>b</sup>
1	Cu(OTf) <sub>2</sub>	TBHP	84	38
2	Cu(OTf)₂	$H_2O_2$	86	41
3	Cu(OTf)₂	O <sub>2</sub>	>99	91
4	CuBr <sub>2</sub>	O <sub>2</sub>	83	59
5	Cu(OAc)₂	O <sub>2</sub>	74	54
6	CuBr	O <sub>2</sub>	92	63
7	Cul	O <sub>2</sub>	76	60
8	Cu(OTf)₂	air	55	33
9	Cu(OTf) <sub>2</sub>	<sup>c</sup>	54	35
10 <sup>d</sup>	Cu(OTf)₂	O <sub>2</sub>	>99	89
11 <sup>e</sup>	Cu(OTf) <sub>2</sub>	O <sub>2</sub>	>99	90 (82)
12 <sup>f</sup>	Cu(OTf)₂	O <sub>2</sub>	>99	46
13 <sup>g</sup>	Cu(OTf) <sub>2</sub>	O <sub>2</sub>	>99	16 <sup>h</sup>
14		O <sub>2</sub>	24	7

<sup>*a*</sup> Unless otherwise noted, [O] denotes an oxidizing agent, O<sub>2</sub> denotes oxygen atmosphere. <sup>*b*</sup> NMR (Isolated) yield. <sup>*c*</sup> N<sub>2</sub> atmosphere. <sup>*d*</sup> Cu(OTf)<sub>2</sub> (5 mol%), DBU: (2 equiv). <sup>*e*</sup> Cu(OTf)<sub>2</sub> (5 mol%), DBU: (0.5 equiv). <sup>*f*</sup> Cu(OTf)<sub>2</sub> (5 mol%), DBU: (0.1 equiv), 7 h. <sup>*g*</sup> Cu(OTf)<sub>2</sub> (5 mol%), without DBU, 7 h. <sup>*h*</sup> N,4-dimethyl-N-(2-nitroethyl) benzenamine was obtained in a 11% NMR yield.

respectively, the *N*-nitrosation successively proceeded (entries 10 and 11). However, the use of 0.1 equiv of DBU led to an extreme decrease in the product yield, and without DBU the by-product was formed through a nitro-aldol reaction (entries 12 and 13). Without the copper catalyst, the desired *N*-nitrosation hardly occurred with the recovery of most of the starting amine (entry 14). In most cases with a copper(II) catalyst, the formation of a trace amount of the *N*-formylated *p*-toluidine derivative as a by-product was detected.

The scope and limitations using a variety of secondary aromatic amines were next examined under the optimal conditions, and the results are shown in Scheme 1. In all cases, a catalytic amount of copper(II) triflate in the presence of DBU promoted the reaction. Aniline derivatives bearing either an electron-donating group at the 3- or 4-position or no substituent, produced N-nitrosation products 2a-5a in moderate to good yields. In the case of the aniline having a dimethyl group, the nitrosation successfully proceeded to the product 6a in 91% yield. In addition, N-methylanilines with a relatively weak electron-withdrawing group, such as a chloro or bromo group, also gave the corresponding products 7a and 8a in excellent yields. Although the reaction of the substrate with a relatively strong electron-withdrawing group, such as an o-CN or a p-NO<sub>2</sub> group, afforded the N-nitrosation products 9a and 10a in a relatively low yields, the reaction of an aniline with an acetyl group produced the N-nitrosation derivative 11a in a practical yield. Also, the N-nitrosation of N-ethylaniline



Scheme 1 Scope of the N-nitrosation of secondary aromatic amines

gave the corresponding product **12a** in a good yield. Moreover,  $Cu(OTf)_2$  effectively promoted the *N*-nitrosation of the substrate with a pyridine ring without a drastic loss in catalyst activity, producing the corresponding product **13a** in 73% yield.

The suggested *N*-nitrosation process could also be applicable to aliphatic secondary amines (Scheme 2). For example, when the reaction of *N*-benzylmethylamine was carried out under our optimal conditions, the corresponding *N*nitrosation product **14a** was obtained in a relatively good yield.



Scheme 2 N-nitrosation of secondary aliphatic amines

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 $CH_3$ 

NO

CH3

 $CH_3$ 

NO

`NO

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4a: 85% (R = m-CH<sub>3</sub>O)

5a: 70% (R = p-CH<sub>3</sub>O)<sup>a</sup>

8a: 91%

11a: 63%<sup>t</sup>

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The reactions of a cyclic amine, such as tetrahydroisoquinoline and morpholine, also proceeded to give the *N*-nitroso products **15a** and **16a** in moderate yields. Also, although the yields of the nitrosation product were relatively low, this catalytic oxidizing system could be extended to substrates that have either a hydroxy group or an allyl moiety.

This procedure could also be applied to the nitrosation of a tertiary aromatic amine with an oxidative cleavage of the C-N bond. Initially, when an electron-rich aniline derivative such as either *N*,*N*-dimethyl-*p*-toluidine or *N*,*N*-dimethyl-*p*-anisidine was treated with the optimal conditions for 19 h, the corresponding nitrosamine derivatives **1a** and **5a** were obtained in 79% and 77% yields, respectively (Scheme 3). In contrast, the use of electron-poor anilines with an electron-withdrawing group, such as a bromo or a nitro group, under O<sub>2</sub> atmosphere led to a remarkable decrease in the yield and the recovery of the starting material. However, when the reaction was performed with 10 mol% of Cu(OTf)<sub>2</sub> and a relatively strong oxidizing agent, TBHP, under an N<sub>2</sub> atmosphere, the desired *N*-nitrosation managed to proceed and provided the nitrosamines **8a** and **10a**.



Scheme 3 N-Nitrosation of tertiary aromatic amines

To confirm the catalytic effect of the copper catalyst, several control experiments were performed (Scheme 4). Initially, when *N*-methyl-*p*-toluidine was treated with 1 equiv of a nitroalkane, 1-phenyl-2-nitroethane in acetonitrile, the expected nitroso compound **1a** was obtained in 69% yield. In a similar manner, when the reaction was carried out without the copper(II) catalyst, the yield of the nitroso compound was decreased to only 10% with the recovery of both the aniline (83% NMR yield) and the nitroalkane (40% NMR yield). From these results, it appeared that the copper(II) catalyst



<sup>o</sup> 1-Phenyl-2-nitroethane was not recovered. <sup>b</sup> N-Methyl-p-toluidine and 1-phenyl-2nitroethane were recovered in 83 and 40% yields.

Scheme 4 Control experiments for the nitrosation of a secondary aromatic amine

effectively promoted the decomposition of a nitroalkane compound under an  $O_2$  atmosphere.<sup>26,27</sup> Also, it was found that only 1 equiv of the nitroalkane for the aniline successfully functioned as a nitroso source in the nitrosation series.

On the basis of the results obtained above and the observation of changes in the color of the reaction solution from blue to brown during the initial preparatory step, we proposed a plausible mechanism for the copper-catalyzed Nnitrosation of secondary amines (Scheme 5).<sup>28</sup> We assumed that during the N-nitrosation series (first step), the generation of nitrous acid would be a key step. Nitromethane would be initially treated with DBU, followed by a single-electron oxidation with a copper(II) catalyst, producing the radical intermediate A. The intermediate A would then be coupled with molecular O<sub>2</sub>, and subsequently it would abstract a hydrogen atom from nitromethane to form the hydroperoxide intermediate B. The intermediate B would be reduced by the formed copper(I) catalyst to form formaldehyde and NO<sub>2</sub> radical species **C** along with the regeneration of a copper(II) catalyst and the generation of a base, a hydroxide ion. Finally, a NO<sub>2</sub> radical would abstract a hydrogen atom to produce nitrous acid. Subsequently, the reaction of a secondary amine with in situ generated nitrous acid gave an N-nitrosation product (second step). On the other hand, when a secondary amine was treated without DBU (see, entry 13 in Table 1), there was a tendency to increase the formation of a nitro-aldol product as a by-product. Consequently, in addition to its role as a base, DBU seemed to be essential in the present reaction in order to help to restrain the formation of the side products.<sup>29</sup> For tertiary aromatic amines, we assumed that after conversion to the corresponding secondary aromatic amines, nitrosation proceeded through a similar reaction mechanism.<sup>30,31,32</sup>



R = aryl or alkvl



Scheme 5 Plausible mechanism for the nitrosation of an aromatic secondary amine using a Cu(II)-DBU-O\_2 system

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In summary, we demonstrated the copper(II)-catalyzed *N*nitrosation of aromatic/aliphatic secondary amines with a less toxic nitromethane, a base, DBU, and an environmentally benign oxidizing agent,  $O_2$ . The important findings are that the addition of a catalytic amount of  $Cu(OTf)_2$  effectively promoted the in situ generation of nitrous acid, which led to the activation of the *N*-nitrosation series, and that unlike the conventional *N*-nitrosation of aliphatic amines under strong acidic conditions, this reaction proceeded under relatively mild basic conditions, and this catalytic system could be applied to the *N*-nitrosation of aromatic amines. Also, this oxidative catalytic system enabled the cleavage of the C-N bond of an aromatic tertiary amine, which promoted a subsequent *N*nitrosation.

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