Scalable synthesis of secondary and tertiary amines by heterogeneous Pt-Sn/\(\gamma\)-Al\(_2\)O\(_3\) catalyzed \(N\)-alkylation of amines with alcohols

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**Abstract**

Synthesis of secondary and tertiary amines has been efficiently realized from the \(N\)-alkylation of amines with alcohols by means of heterogeneous bimetallic Pt-Sn/\(\gamma\)-Al\(_2\)O\(_3\) catalyst (0.5 wt % Pt, molar ratio Pt:Sn = 1:3) through a borrowing hydrogen strategy. The Pt-Sn/\(\gamma\)-Al\(_2\)O\(_3\) catalyst has exhibited very high catalytic activity towards a wide range of amines and alcohols, and can be conveniently recycled without Pt metal leaching. The present protocol was applied for the synthesis of \(N\)-phenylbenzylamine in 96% isolated yield from aniline and benzyl alcohol on a 2.1 kg scale of the substrates, demonstrating its potential applicability for higher-order amine synthesis.

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1. Introduction

Amines are a class of important organic compounds and have been extensively utilized in organic synthesis and chemical industry.\(^1\) Amination using primary amines and organic halides has been applied as the major method to prepare secondary and tertiary amines, but this method often suffers from environmental problems, use of expensive starting materials, and low selectivity for the desired products.\(^2\) Alkylation of amines by means of alcohols as the alkylating agents is considered as a green and direct method to attain higher-order amines.\(^3\) In general, homogeneous transition metal complex-catalyzed direct \(N\)-alkylation of amines\(^4\) and ammonia\(^7\) with alcohols has been used to prepare amines through a borrowing hydrogen strategy, but the systems are usually inapplicable for scale-up production because of the problem of catalyst reusability and/or the indispensable use of large amounts of additives or co-catalysts. Heterogeneous transition metal catalysts can overcome some of the drawbacks of homogeneous catalysts, but they often have to suffer from harsh reaction conditions, low efficiencies, limited substrate scopes, use of large amount of toxic solvents and excessive amount of alcohols to obtain satisfactory yields.\(^6\) Thus, exploration of more general, operationally simple and versatile heterogeneous transition metal catalyst systems for the synthesis of amines has recently aroused considerable attention. It would be more applicable to adopt a green chemistry procedure such as a solvent-free reaction system with simple and readily available starting materials in view of economy and utility. However, to the best of our knowledge, only very limited work has been directed toward supported catalysts in this area.\(^7\) Pt-Sn/\(\gamma\)-Al\(_2\)O\(_3\) has been known as the effective catalyst for alkane dehydrogenation,\(^8\) reforming processes,\(^9\) and hydrogenation\(^10\) in petroleum industry. Pt@TiO\(_2\) can promote photoirradiation of o-arylenediamines in very dilute alcohol solution.\(^11\) Primary amines interacted with methanol over \(\gamma\)-Al\(_2\)O\(_3\) at >200 °C in the gas phase to yield an amine mixture.\(^12\) We recently reported that the heterogeneous bimetallic Pt-Sn/\(\gamma\)-Al\(_2\)O\(_3\) catalyst could be applied for the efficient synthesis of secondary and tertiary amines,\(^13\) and diamines\(^14\) from the reactions of amines with alcohols or diols. It was found that the Pt loadings\(^15\) and supports\(^16\) in the catalyst resulted in different catalytic performance in the synthesis of amines by \(N\)-alkylation of amines with alcohols through a borrowing hydrogen strategy. Keeping the excellent catalytic activity of the Pt-Sn/\(\gamma\)-Al\(_2\)O\(_3\) catalyst in mind, we reasonably envisioned that such a catalyst could be applicable to the greener construction of C–N bonds from amines and alcohols. Herein, we disclose scalable synthesis of secondary and tertiary amines from the \(N\)-alkylation of amines with alcohols by means of heteroge-
2. Results and discussion

The reactions of primary amines (1) with alcohols (2) to synthesize secondary amines were conducted under the conditions similar to those for the same reaction on a 1.0 mmol scale of substrates,12 but in the absence of a solvent. Thus, the reaction of aniline (1a) with benzyl alcohol (2a) in a 1:1 M ratio was performed at 145 °C on a 10 mmol scale of each substrate in a 15-mL sealed glass tube reactor with Pt-Sn/γ-Al2O3 (0.5 wt % Pt, molar ratio Pt:Sn = 1:3)13 as the catalyst (catalyst loading: 0.05 mol % Pt) under solvent-free conditions. Over a period of 8 h the desired product N-phenylbenzylamine (3a) was obtained in 95% isolated yield (Table 1, entry 1), demonstrating the potential application of the present heterogeneous catalyst for N-alkylation of amines by alcohols. Then, the scope of amines was explored by the direct N-alkylation reactions with benzyl alcohol (Table 1, entries 1–12). Variation of the methyl substituent at 2-, 3- and 4- positions on the aryl backbone of amines did not obviously affect formation of the target products 3b–3d (94–97%) (Table 1, entries 2–4). 3,5-Dimethylaniline (1e) also efficiently reacted with 2a to afford 3e (97%) (Table 1, entry 5), while 2,6-dimethylaniline (1f) exhibited a lower reactivity to 2a and had to be reacted using a higher catalyst loading, i.e., 0.075 mol % Pt, due to the increased steric hindrance, affording secondary amine 3f in a relatively low yield (82%) (Table 1, entry 6). The present N-benzylations reactions tolerated with a variety of electron-donating and withdrawing substituents such as ethoxy, chloro, and fluoro, forming the desired products 3g–3k in excellent yields (93–98%) (Table 1, entries 7–11). The reaction of 1-naphthylamine (1l) with benzyl alcohol also efficiently occurred, giving 3l in 93% yield over a period of 48 h (Table 1, entry 12). However, 2-aminopyridine (1m) did not react with 2a under the stated conditions due to its insolubility in 2a (Table 1, entry 13) although they could efficiently interact to form 3m in a solvent.13a

Aniline (1a) was also employed to react with various primary and secondary alcohols to prepare diverse types of secondary amines (Table 1, entries 14–19). 4-Chlorobenzyl alcohol (2b) reacted with aniline to form secondary amine 3n in 90% yield, exhibiting a lower reactivity than benzyl alcohol (2a) (Table 1, entry 14). Aliphatic alcohols such as 2-phenylethanol (2c) and n-heptanol (2d), also efficiently reacted with 1a, producing the desired products 3o–3p in 87–96% yields (Table 1, entries 15 and 16). Although both 2-hexanol (2e) and cyclohexanol (2g) could effectively react with 1a to form secondary amines 3q (97%) and 3s (85%), respectively, isopropanol (2f) only showed a moderate reactivity to afford 3r in 61% yield (Table 1, entries 17–19). Aliphatic primary amines, i.e., benzylamine (1n), cyclohexylamine (1o), and 2-(aminomethyl)pyridine (1p) were also used to react with benzyl alcohol, producing the desired products in moderate to excellent yields (52–97%) (Table 1, entries 20–22), revealing unfavorable electronic and steric effects from the amine substrates.

Next, synthesis of tertiary amines was tried by using the

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1.** Pt-Sn/γ-Al2O3 catalyzed direct N-alkylation of amines with alcohols through a borrowing hydrogen strategy.

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine (1)</th>
<th>Time (h)</th>
<th>Product (3)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>8</td>
<td>3a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
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<td>94</td>
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<td>3</td>
<td>1b</td>
<td>24</td>
<td>3b</td>
<td>97</td>
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<td>4</td>
<td>1c</td>
<td>24</td>
<td>3c</td>
<td>97</td>
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<td>5</td>
<td>1d</td>
<td>24</td>
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<td>97</td>
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<td>6</td>
<td>1e</td>
<td>48</td>
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<td>7</td>
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<td>48</td>
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<td>94</td>
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<td>8</td>
<td>1g</td>
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<td>95</td>
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<td>94</td>
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<td>10</td>
<td>1i</td>
<td>24</td>
<td>3i</td>
<td>93</td>
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<td>11</td>
<td>1j</td>
<td>24</td>
<td>3j</td>
<td>98</td>
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<td>12</td>
<td>1k</td>
<td>48</td>
<td>3k</td>
<td>93</td>
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</tr>
<tr>
<td>14</td>
<td>1m</td>
<td>36</td>
<td>3m</td>
<td>90</td>
</tr>
</tbody>
</table>

(continued on next page)
reaction of a primary amine, i.e., benzyl amine (1a), with two equivalents of an alcohol such as benzyl alcohol (2a) in the absence of a solvent under the typical conditions as shown in Table 1. Analysis of the reaction mixture revealed formation of a mixture of tribenzylamine (4a, major) and dibenzylamine (3t, minor). Modification of the reaction conditions by extending the reaction time or varying the temperature did not obviously improve the reaction efficiency, rendering the isolation process to be complicated and time-consuming. However, the same reaction underwent efficiently to form the desired tertiary amine product 4a in xylene as the solvent. In order to avoid the side reaction and simplify the isolation process, benzylamine was reacted with excessive amount of benzyl alcohol which acted as both the reactant and solvent during the reaction. To our delight, the reaction of benzylamine in 5 mL benzyl alcohol efficiently underwent to afford tribenzylamine (4a) in 95% yield within 8 h (Table 2, entry 1). Under the similar conditions methyl, chloro, and fluoro-substituted benzylamines (1q–1s) reacted with benzyl alcohol (2a) to afford the desired products 4b–4d in moderate to good yields (54–77%) (Table 2, entries 2–4), revealing a negative electronic impact on the reaction efficiency from the substituents. Aliphatic cyclohexylamine (1o) and (2-aminomethyl)pyridine (1p) also reacted with 2a to yield tertiary amines 4e (70%) and 4f (73%), respectively (Table 2, entries 5 and 6). Benzylamine reacted with substituted benzyl alcohol such as 4-methoxybenzyl alcohol (2h), forming 4g in 69% yield (Table 2, entry 7). Unexpectedly, benzylamine reacted with 1,4-butylene glycol (2i) to afford tertiary amine 4h in a moderate yield (61%) (Table 2, entry 8). Although most of the tested aliphatic primary amines (1 mmol) reacted with excessive amount of benzyl alcohol (5 mL) to form the desired tertiary amine products in moderate yields, the reaction of secondary amine dibenzylamine (3t) yielded tribenzylamine (4a) in 96% yield (Table 1, entry 9). Further screening the reaction conditions for secondary amines, it was found that the 1:1 M ratio reactions of aliphatic secondary amines (1t–1v and 3t) with benzyl alcohol could efficiently generate the desired tertiary amine products 4i–4k and 4a (83–97%) (Table 2, entries 10–13).

It should be noted that arylamines and heteroarylamines could not be utilized to synthesize tertiary amines although they can efficiently react with primary alcohols to afford the corresponding secondary amine products under the stated conditions (Table 1) or in the presence of a solvent. In this regard, control experiments were conducted to demonstrate the inactivity of arylamines to primary alcohols. Primary arylamine, that is, aniline 1a, was thus reacted with benzyl alcohol in the presence of the Pt-Sn/γ-Al2O3 catalyst (0.5 mol % Pt) over a period of 48 h, affording benzyllaniline 3a (90%) as the major product, and the desired product tertiary amine 4i (7%) as the minor product (Eqn (1)). Further reacting 3a with equimolar amount of benzyl alcohol under the stated condition as shown in Table 1 did not improve the transformation to the corresponding tertiary amine product 4i (9%) (Eqn (2)). Diphenylamine and benzamide did not react with benzyl alcohol either. These results suggest that a secondary arylamine could not be effectively transformed to the higher-order amines due to the weak nucleophilicity of its N–H bond under the stated conditions.

To explore the applicability of the present synthetic protocol, the scale-up reaction of aniline (1a) with benzyl alcohol (2a) was investigated under the solvent-free conditions (Table 3). It was found that the scale-up reaction could undergo more efficiently on a 3.5 M scale of each substrate (3.5 mol 1a and 3.5 mol 2a). Using a catalyst loading containing 0.015 mol % Pt the reaction reached >99% conversion for 1a with 98% selectivity for 3a. The secondary amine product was easily obtained in 95% isolated yield by distillation under reduced pressure (Table 3, entry 1). 1H NMR analysis of the final reaction mixture revealed formation of the desired secondary amine product 3a with about 98% purity as well as <2% imine intermediate 5 (Fig. 1). It is noteworthy that the by-product water was simultaneously removed by a water-trap to facilitate the reaction. After the reaction was finished, the reaction mixture was removed the solid catalyst by filtration.

The recovered bimetallic Pt-Sn/γ-Al2O3 catalyst did not lose any catalytic activity in the second-run reuse (Table 3, entry 2). Although it exhibited a lower catalytic activity in the third run reuse, it still promoted the reaction to completion by extending the reaction time from 5 h to 8 h (Table 3, entry 3). In the fourth run reuse the catalyst substantially lost catalytic activity and could not efficiently promote the reaction to form the desired product. To our delight on a 10.5 M scale of each substrate, that is, 1a (597.6 g) and 2a (1135.0 g), the reaction also efficiently underwent to afford N-phenylbenzylamine (3a) by using a much lower catalyst loading (0.0051 mol % Pt) within 12 h (Table 3, entry 5), reaching a TON of

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine (1)</th>
<th>Time (h)</th>
<th>Product (3)</th>
<th>Yield (%)</th>
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<td>16</td>
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<td>18</td>
<td>1a</td>
<td>48</td>
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<td>61</td>
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<td>19</td>
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<tr>
<td>1p</td>
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* a Conditions: 1 (10 mmol), 2 (10 mmol), Pt-Sn/γ-Al2O3 (195 mg, 0.05 mol % Pt), 145 °C, 0.1 MPa N2, in a sealed 15-mL Pyrex glass screw-cap tube.
* b Yield refers to the isolated product.
* c Using 0.075 mol % Pt.
After the reaction was finished in each run, the catalyst was removed by filtration, washed with THF and n-hexane, dried at 60 °C/2 mm Hg for 2 h, and then reused in the next run. N-alkylation of 1a with 2a under the same neat conditions. Analysis of the supernatant from the reaction mixture by ICP-AES technology revealed no Pt metal leaching into the liquid phase after the reaction (See the Supporting Information for details). Decrease of the catalytic activity of the Pt-Sn/γ-Al2O3 catalyst after used for two run reactions is attributed to the gradual aggregation of the Pt nanoparticles on the γ-Al2O3 support during the reaction, which reduces the available bare surface of Pt particles catalytically active for the borrowing hydrogen process. In addition, no Pt metal leaching was observed in the supernatant after each run reaction.

3. Conclusions

In summary, direct synthesis of secondary and tertiary amines from the N-alkylation of primary or secondary amines with alcohols has been successfully realized with heterogeneous bimetallic Pt-Sn/γ-Al2O3 catalyst through a borrowing hydrogen strategy. The catalyst can be readily recycled and has exhibited very high catalytic activity towards a wide array of amine and alcohol substrates. The present protocol provides a green and concise benign method to access higher-order amines.

4. Experimental section

4.1. General methods

1H and 13C{1H} NMR spectra were recorded on 400 and 100 MHz.

Table 2
Pt-Sn/γ-Al2O3 catalyzed alkylation of amines (1) with alcohols (2) to yield tertiary amines (3).a,b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine (1)</th>
<th>Time (h)</th>
<th>Product (3)</th>
<th>Yield (%)</th>
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<td>13</td>
<td>Ph-(\text{NH}_2)</td>
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Table 3
Scale-up reaction of aniline (1a) with benzyl alcohol (2a).

<table>
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<th>Run</th>
<th>Time (h)</th>
<th>Conversion of 1a (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
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<td>3a</td>
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<td>&gt;99</td>
<td>98 (95)</td>
</tr>
<tr>
<td>3b</td>
<td>5</td>
<td>&gt;99</td>
<td>98 &lt;2</td>
</tr>
<tr>
<td>3c</td>
<td>5</td>
<td>80</td>
<td>97 &lt;3</td>
</tr>
<tr>
<td>3d</td>
<td>5</td>
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<td>3e</td>
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<td>97 &lt;3</td>
</tr>
<tr>
<td>3f</td>
<td>70</td>
<td>94</td>
<td>96 &lt;3</td>
</tr>
</tbody>
</table>

Table 4
Scale-up reaction of aniline (1a) with benzyl alcohol (2a).

<table>
<thead>
<tr>
<th>Run</th>
<th>Time (h)</th>
<th>Conversion of 1a (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>5</td>
<td>99</td>
<td>97 (95)</td>
</tr>
<tr>
<td>3b</td>
<td>12</td>
<td>99</td>
<td>97 &lt;3</td>
</tr>
<tr>
<td>3c</td>
<td>5</td>
<td>97</td>
<td>96 &lt;3</td>
</tr>
</tbody>
</table>

a Condition A for entries 1–8: 1 (1 mmol), 2 (5 mL), Pt-Sn/γ-Al2O3 (98 mg, 0.25 mol % Pt), 145 °C, 0.1 MPa N2, in a sealed 15-mL Pyrex glass screw-cap tube.
b Condition B for entries 9–13: 1 (10 mmol), benzyl alcohol (2a, 10 mmol), Pt-Sn/γ-Al2O3 (195 mg, 0.05 mol % Pt), 145 °C, 0.1 MPa N2.
c Yield refers to the isolated product.
d Using 0.5 mol % Pt.
e Using 0.075 mol % Pt.

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FT-NMR spectrometer and all chemical shift values refer to $\delta_{TMS} = 0.00$ ppm or CDCl$_3$ ($\delta^{1H} = 7.26$ ppm; $\delta^{13C} = 77.16$ ppm). Analytical TLC plates (Sigma–Aldrich silica gel 60F$_{254}$) were viewed under UV light (254 nm). Chromatographic purifications were performed on SDZF silica gel 160. The known compounds were identified by comparison of their NMR spectra with the reported data or of their GC traces with those of authentic samples. All the amine products are known compounds and were characterized by NMR analysis with their spectroscopic features in good agreement with those reported in the literature (see ESI).

4.2. A typical procedure for the N-alkylation of primary amines (1) with alcohols (2) to yield secondary amines (3)

4.2.1. Synthesis of N-phenylbenzylamine (3a)

Under nitrogen atmosphere, to a 15-mL Pyrex glass screw-cap tube were added aniline (1a) (930 mg, 10 mmol), benzyl alcohol (2a) (1080 mg, 10 mmol), and the Pt-Sn/γ-Al$_2$O$_3$ catalyst (195 mg, 0.05 mol % Pt). The resultant mixture was stirred in the sealed tube at 145 °C for 8 h. After cooled to ambient temperature, the catalyst was removed by centrifugation and washed with Et$_2$O (2 × 5 mL). The combined supernatant was concentrated under reduced pressure and then subjected to purification by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 20:1, v/v), affording product 3a as a pale brown liquid (1740 mg, 95%).

4.3. A typical procedure for the N-alkylation of primary amines (1) with alcohols (2) to yield tertiary amines (4)

4.3.1. Synthesis of tribenzylamine (4a)

Under nitrogen atmosphere, to a 15-mL Pyrex glass screw-cap tube were added dibenzylamine (1n) (107 mg, 1 mmol), benzyl alcohol (2a) (5 mL), and the Pt-Sn/γ-Al$_2$O$_3$ catalyst (98 mg, 0.25 mol % Pt). The resultant mixture was stirred in the sealed tube at 145 °C for 8 h. After cooled to ambient temperature, the catalyst was removed by centrifugation and washed with Et$_2$O (2 × 5 mL). The combined supernatant was concentrated under reduced pressure and then subjected to purification by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 20:1, v/v), affording product 4a as a white solid (273 mg, 95%).

4.4. A typical procedure for the scale-up N-benzylation of aniline (1a) with benzyl alcohol (2a)

4.4.1. Synthesis of N-phenylbenzylamine (3a)

Under nitrogen atmosphere, to a four-necked 1000-mL glass flask equipped with a mechanical stirrer, thermometer, water trap connected to a condenser with an atmospheric nitrogen balloon, and a nitrogen input adaptor, were added aniline (1a) (328.8 g, 3.5 mol), benzyl alcohol (2a) (378.4 g, 3.5 mol), and the Pt-Sn/γ-Al$_2$O$_3$ catalyst (20.5 g, 0.015 mol % Pt). The resultant mixture was stirred at 160 °C for 5 h. During the reaction the formed water was simultaneously removed through the water trap. After the reaction was complete by GC monitoring, the reaction mixture was cooled to ambient temperature, and the solid catalyst was recovered by filtration. The filtrate was distilled at 126 °C/2 mm Hg to afford product N-phenylbenzylamine (3a) as a pale brown liquid (609.3 g, 95%). The collected solid was successively washed with THF (3 × 30 mL) and n-hexane (3 × 30 mL), dried at 60 °C/2 mm Hg for 2 h, and then reused in the next run reaction of 1a with 2a under the same conditions.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.11.029.

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