<table>
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<th><strong>Title</strong></th>
<th>Formal Intermolecular Hydroamination of Unbiased Olefins for Primary Amine Formation</th>
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<tr>
<td><strong>Author(s)</strong></td>
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Abstract: A Pd/Ir dual metal tandem catalyst system is found to be active in catalyzing the one pot two-step formal hydroamination of unbiased olefins such as 1-dodecene with an ammonia source, to give branched primary amines at high yields of > 85% using only 1 mol% Ir catalyst. This is the first example of a formal one pot intermolecular hydroamination of olefins to obtain primary amines.

Nitrogen-containing compounds such as amines, imines and enamines are important compounds for the pharmaceutical, agrochemical, bulk and specialty chemical industry. Primary amines in particular, are important synthetic tools for formation of various nitrogen-containing compounds. The olefin is an important chemical feedstock that can be easily obtained from crude oil or biomass. The ability to easily convert an olefin into a primary amine is of high industrial importance. Among various synthetic routes, hydroamination, the direct formation of a new C-N bond, is the most straightforward pathway for this conversion. However, intermolecular hydroamination has been plagued by various challenges and has yet to realize its industrial potential as a result. Formation of primary amines from intermolecular hydroamination is hence, even more difficult. Firstly, the reaction between ammonia and olefin to form an amine is entropically unfavorable and enthalpically neutral. Secondly, many organometallic catalysts are incompatible with the strongly basic ammonia. Lastly, the primary amine product is often very reactive and participates in self-coupling reactions to form secondary and tertiary amines. Hence, most reported examples in literature are multi-stepped in nature or involved the usage of protected amines to form secondary or tertiary amine products from olefins. Additional deprotection or hydrolysis steps are required to convert the secondary or tertiary amine to a primary amine. Given the broad utility of the primary amine, development of efficient methods for the synthesis of primary amines remains important.

One of the current methods to produce the primary amine from an olefin includes the hydroformylation/reductive amination procedure in one pot. However, this process is limited to lower olefins up to 1-pentene. Another method for amine production from olefin would be oxidation of olefin to alcohol followed by alkylation of the alcohol formed, with an amine. However, the formation of secondary amines using this process could not be avoided and also, this would be a multi-stepped process since the olefin would need to be oxidized to an alcohol first. Alternatively, one could first prepare a tertiary amine from an olefin through oxidation and reductive amination, followed by dehydrogenation and nucleophilic attack on the imine by ammonia to release the primary amine. This would again be a tedious multi-stepped process that involves several separate catalytic conversions, resulting in wastage of energy and reagents. Herein, we report a simple one pot two-step formal intermolecular hydroamination process to convert unbiased olefins such as 1-dodecene, into primary amines at high yields and selectivity, using a dual catalyst system (scheme 1).

![Scheme 1](image1)

Scheme 1. Formation of branched primary amine using Pd/RA catalyst system.

We first began our search for the right catalyst combination by screening a series of reductive amination (RA) catalysts for their compatibility with the reaction conditions for Wacker oxidation (Table 1). A one-pot one-step reaction was attempted but neither of the RA catalysts screened gave any amine yield. A trial experiment was conducted to explore the reason for the non-feasibility of a one-step reaction by subjecting the olefin (1) to Wacker oxidation conditions in the presence of ammonium formate. It was found that the olefin was not oxidized at all to give any ketone (3) or imine (4) and remained in the reaction totally unreacted (scheme 2). This is due to the formation of an inactive Pd complex immediately after the ammonia source was added to the reaction solution containing PdCl2(MeCN)2. As such, a one-pot two-step reaction had to be adopted instead so that the ammonia source does not deactivate the oxidation catalyst.

![Scheme 2](image2)

Scheme 2. Formation of oxidized product using Pd(II) catalyst and NH3(HCO2).

Although Shvo’s catalyst is known to be a good reductive amination catalyst, it tends to get deactivated by NH3 at low temperature by forming an inactive Ru-NH3 complex. Thus, no amine was formed with Shvo’s catalyst. With [RhCp*Cl2], the desired primary amine was formed in reasonable yields of 58 %

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Supporting information for this article is given via a link at the end of the document.
but a high catalyst loading of 10 mol% is required. Given the
high cost of [RhCp*Cl]₂, it is a less sustainable option to carry
out the transformation using this catalyst. We also attempted to
carry out the reaction with a chiral reductive amination catalyst
such as two of Noyori’s catalysts, Ru-DEPEN and Ru-BINAP but
low to negligible amine yields were obtained. With Xiao’s Ir-
OMe catalyst, it was found that a low catalyst loading of 2
mol% could be used to achieve an amine yield of 80% (Table 1).
Although Xiao has demonstrated the use of his RA catalyst on
several aliphatic ketones, the substrate scope remains limited
and the combination of the catalyst with olefin oxidation is
unexplored.

Table 1. Reductive amination catalyst screening for one-pot
formal hydroamination[a].

<table>
<thead>
<tr>
<th>RA Catalyst</th>
<th>Loading/%</th>
<th>2a yield/ %[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[RhCpCl]₂</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>[RhCpCl]₂</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>[RhCpCl]₂</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>[RhCpCl]₂</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>[Ir-OMe]</td>
<td>0.5</td>
<td>66</td>
</tr>
<tr>
<td>[Ir-OMe]</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>[Ir-OMe]</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>[Ir-OMe]</td>
<td>4</td>
<td>73</td>
</tr>
<tr>
<td>RuCl₂[(S)-(DM-BINAP)]</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Ru-DEPEN</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Shvo’s catalyst</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] 0.2 mmol 1-dodecene, 1 mol% PdCl₂(MeCN)₂, 1.5 eq. BQ, 5 eq. H₂O, 3 h
at 70 °C, MeOH/EtOH 1:1 0.075 M; 10 eq. NH₂(HCO₂), x mol% RA catalyst,
16.5 eq. H₂O/H₂EtN 5:2 complex, 4 Å MS, N₂ atmosphere, 70 °C, 8 h; [b] NMR
yield with mesitylene as internal standard.

Once the RA catalyst compatible with our Wacker oxidation
steps has been confirmed, we set out to optimize the reaction
conditions for the formal one-pot hydroamination of unbiased
olefins with 1-dodecene as a model substrate. The role of each
reagent in the reaction was also determined (Table 2). Clearly,
PdCl₂(MeCN)₂ is required as the oxidation catalyst and p-
benzoquinone (BQ) is required as a reoxidant to turnover the Pd
catalyst in Wacker oxidation cycle. It was also observed that the
benzoquinone (BQ) is required as a reoxidant to turnover the Pd
catalyst in the reaction was also determined (Table 2). Clearly,
olefins with 1
steps has been confi
NMR yield with mesitylene as internal standard.

1) 1 mol% PdCl₂(MeCN)₂,
1.5 eq. p-BQ, 5 eq. H₂O
MeOH/EtOH 1:1, 70 °C, 3 h
2) 1 mol% Ir-OMe,
10 eq. NH₂(HCO₂),
H₂O/H₂EtN 5:2 complex, 70 °C, 8 h

Scheme 3. Formation of amines using Pd/RA catalyst system.

A series of linear unbiased amines were screened and it was
found that the catalyst system is tolerant of a wide variety of
functional groups such as carboxylic acids, esters, ethers and
halides (scheme 3, Table 3). In particular, unsaturated carboxylic
acids such as 1-pentenoic acid (1e) and 1-hexenoic acid (1f) resulted in the formation of γ-lactam,
5-methyl-pyrolinidin-
2-one and δ-lactam, 5-methylpyrjedin-2-one, at 60 % and 76 %
isolated yield, respectively. Lactams are commonly found in
many important biologically active molecules. The ability to
synthesize them easily from unsaturated carboxylic acids would
be important for both the organic chemistry lab and
pharmaceutical industry. β-lactams can also be prepared using the
catalyst system albeit at lower yield due to incomplete
cyclization, resulting in a mixture of amino acid and β-lactam
obtained (scheme 4). Separation of the amino acid from the
lactam was difficult without causing significant hydrolysis of the
lactam. β-lactam could not be obtained from 1-butoxycarboxylic
acid using our catalyst system. Similarly, 5-hexen-1-ol, 1j, does not
result in the formation of the desired amino alcohol product,
despite our earlier experiments showing that 1j can be oxidized
to form 1, 5-hexadiol. A large mixture of unidentified products was obtained instead. 2c was found to undergo
cyclization to form a 6-membered N-heterocyclic ring, thereby
showing the stability of the product in our catalytic system.
Gram-scale synthesis of 2a was also attempted to show the
practical utility of the system. 2a was obtained in 79 % isolated yield (8 mmol 1a, 1.17 g 2a obtained).
Table 3. Catalytic formal hydroamination of terminal olefins[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>2-amine yield/ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>n.d.</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>n.d.</td>
</tr>
<tr>
<td>12</td>
<td>1l</td>
<td>90</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>83</td>
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<tr>
<td>14</td>
<td>1n</td>
<td>35</td>
</tr>
<tr>
<td>15</td>
<td>1o</td>
<td>94</td>
</tr>
<tr>
<td>16</td>
<td>1p</td>
<td>20</td>
</tr>
<tr>
<td>17</td>
<td>1q</td>
<td>81</td>
</tr>
</tbody>
</table>

Vinyl arene substrates were also tested with our catalytic system and it was found that a t-BuOH/MeOH solvent mixture would result in low amine product yields. The major isolated products were the corresponding ketals arising from reaction of ketone with methanol in an acidic environment caused by the Wacker oxidation step. However, the formation of the ketal could be suppressed by using only MeOH in the reaction. High 2-amine yields of 94% and 91% can be obtained from p-methylstyrrene and p-chlorostyrene respectively. α-Amines are highly valuable in medicinal and synthetic chemistry. Hence, the ability to prepare these important α-amines from olefins at high yield and selectivity, especially primary amines which can be further functionalized, would be a useful progress. Furthermore, the omission of protecting groups in the synthesis would make the process more atom-economical.

Scheme 4. Formation of lactams using Pd/RA catalyst system.

Secondary amines were also synthesized by replacing the amine source, ammonium formate, with a primary amine such as benzylamine or isopropylamine. The system displayed higher reactivity with primary amines and the product was isolated at 82% yield for 5a (Scheme 5).

Scheme 5. Formation of secondary amines using Pd/RA catalyst system. 5b yield is reported as NMR yield using mesitylene as internal standard, 0.6 mmol olefin.

In conclusion, we have presented here an operationally practical tandem catalyst system for formal intermolecular hydroamination of unbiased olefins to result in branched amines. A two-step operation is necessary to prevent catalyst deactivation due to presence of an ammonia source. Nevertheless, the one-pot conversion is operationally simple and inert atmospheres are not required. The wide substrate scope and the ability to prepare lactam rings of various sizes as well as secondary amines using different amine sources, are encouraging. Catalysts modification to ensure enantioselectivity in the conversion for the obtainment of chiral amines from the catalytic system, is ongoing in the lab.
Experimental Section

Experimental Details. To a 20 mL glass vial containing PdCl₂(MeCN)₂ (1.6 mg, 0.006 mmol) and p-benzoquinone (0.0973 g, 0.9 mmol), MeOH (3.6 mL) and t-BuOH (3.6 mL) were added, followed by H₂O (27 μL) and olefin (0.60 mmol). The mixture was stirred at 70 °C for 3 hours. HCOONH₄ (380 mg, 6 mmol), Ir-OMe (3.7 mg, 0.006 mmol) and formic acid/triethyl amine 5:2 complex (0.6 mL) were then added. The mixture was evaporated and NaHCO₃ was added. The aqueous layer was subjected to column chromatography to obtain pure isolated product.

Acknowledgements

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Keywords: hydroamination • primary amine • unbiased olefin • homogeneous catalysis • synthetic methods

(3) H. Klein, R. Jackstell, M. Kanti, A. Martin, M. Beller Chemical Engineering & Technologon 2007, 30, 741.
A Pd/Ir dual metal tandem catalyst system is found to be active in catalyzing the one pot two-step formal hydroamination of unbiased olefins such as 1-dodecene with an ammonia source, to give branched primary amines at high yields of up to 87% using only 1 mol% catalyst. Various lactams, α-amines as well as secondary amines can also be prepared using the catalytic system. This is the first example of a formal one pot intermolecular hydroamination of olefins to obtain primary amines.