Dehydrogenative Synthesis of Imines from Alcohols and Amines Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex

Maggi, Agnese; Madsen, Robert

Published in:
Organometallics

Link to article, DOI:
10.1021/om201095m

Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):
Dehydrogenative Synthesis of Imines from Alcohols and Amines Catalyzed by a Ruthenium N-Heterocyclic Carbene Complex

Agnese Maggi and Robert Madsen*
Department of Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

ABSTRACT: A new method for the direct synthesis of imines from alcohols and amines is described where hydrogen gas is liberated. The reaction is catalyzed by the ruthenium N-heterocyclic carbene complex [RuCl₂(iPr)(p-cymene)] in the presence of the ligand DABCO and molecular sieves. The imination can be applied to a variety of primary alcohols and amines and can be combined with a subsequent addition reaction. A deuterium labeling experiment indicates that the catalytically active species is a ruthenium dihydride. The reaction is believed to proceed by initial dehydrogenation of the alcohol to the aldehyde, which stays coordinated to ruthenium. Nucleophilic attack of the amine affords the hemiaminal, which is released from ruthenium and converted into the imine.

INTRODUCTION

The imine is an important functional group in organic chemistry and is often used for the synthesis of amines by various addition reactions.¹ Imines are usually prepared by condensation of an aldehyde or a ketone with a primary amine but can also be formed by oxidation of secondary amines,² oxidative condensation of primary amines,³ and the aza-Wittig reaction.⁴ In addition, imines can be prepared by coupling of alcohols and amines in the presence of an oxidant.⁵

Recently, new dehydrogenative reactions have been developed for the coupling of alcohols and amines where hydrogen gas is liberated and no stoichiometric additives are necessary. These procedures constitute more environmentally benign methods for oxidative couplings and produce a minimum of waste. Ruthenium pincer complexes have been shown to mediate the formation of amides⁶ and imines,⁷ depending on the structure of the ligand. An osmium pincer complex has been shown to catalyze the formation of imines,⁸ while the heterogeneous catalysts Ag/Al₂O₃⁹ and Pt/TiO₂¹⁰ mediate the formation of amides and imines, respectively. We have shown that ruthenium N-heterocyclic carbene complexes can catalyze the synthesis of amides from primary alcohols and amines with the extrusion of hydrogen gas.¹¹ Following our initial findings, several ruthenium N-heterocyclic carbene and related complexes have been shown to mediate the amidation.¹² Among these, the reaction is most efficiently performed with ruthenium complex 1 (Figure 1) in the presence of tricyclohexylphosphine (PCy₃) and potassium tert-butoxide.¹²c,d

During the study of the mechanism of this reaction, we observed that imines in some cases were formed to a significant degree¹²d and we speculated whether the conditions could be altered into a dehydrogenative imine synthesis. Herein, we describe a new ruthenium-catalyzed synthesis of imines from primary alcohols and amines where hydrogen gas is liberated (Scheme 1).

RESULTS AND DISCUSSION

For the initial studies equimolar amounts of benzyl alcohol and tert-octylamine were selected as test substrates (Table 1). It was quickly discovered that imine formation occurred in the absence of potassium tert-butoxide. The reaction was performed with 5% of complex 1 in refluxing toluene under a flow of argon. Molecular sieves were added to secure continuous removal of water during the reaction. Under these conditions a 40% yield of the imine was obtained after 24 h with 55% conversion of the alcohol (Table 1, entry 1). Only about 3% of the ester from self-condensation of the alcohol¹³ was observed as a byproduct, and no secondary amine or amide could be detected.

Imines are usually easy to reduce, and it is noteworthy that the C≡N bond is not saturated under the reaction conditions.

Received: November 8, 2011
were investigated as additives. With 5% of PCy$_3$ or 1,4-
diazabicyclo[2.2.2]octane (DABCO) the alcohol conversion
increased (Table 1, entries 2 and 3), while bidentate ligands as
well as PPh$_3$ and pyridine gave lower conversions (entries 4–
8). A further improvement could be achieved by increasing the
amount of ligand to 10% (entries 9 and 10), and since DABCO
gave the best result, this ligand was selected for general use.
With DABCO only a trace amount (∼2%) of the secondary
amine was detected and the moderate yield is presumably due to
in these reactions (entries 1–4). The methoxy group could also
be tolerated in the ortho position without affecting the yield of
the imine (entry 5). Notably, a small amount of anisole was
observed in entries 3 and 5, which presumably arises from
decarbonylation of the intermediate aldehyde. A methyl ester
was generated in a separate flask.

With the optimized catalyst system in place, our attention
then turned to other alcohols and amines in order to investigate
the scope of the imination. First, different alcohols were studied
in the reaction with tert-octylamine (Table 2). Para-substituted
benzylic alcohols with methoxy, methoxy, and fluoro substituents
gave the best result, this ligand was selected for general use.

The importance of the ruthenium complex was also
investigated. First, the isopropyl wingtips in 1 were replaced
by methyl groups and the reaction performed with the complex
[RuCl$_2$(IMe)(p-cymene)]$_2$ (2.5%), IPr·HCl (5%), and KOtBu (5%).

With DABCO only a trace amount (∼2%) of the secondary
amine was formed. With [RuCl$_2$(IMe)(p-cymene)]$_2$ (2.5%), IPr·HCl (5%),
and KOtBu (5%). 8% of the secondary amine was also formed.

"Determined by GC with nonane as internal standard. 9% of secondary amine was also formed. 4% with [RuCl$_2$(IMe)(p-
cymene)] (5%)."
amount of the secondary amine (entry 1). 1-Adamantylamine afforded the product in 70% yield together with 10% of the secondary amine (entry 2). Optically pure (R)-1-phenylethylamine and (R)-1-(1-naphthyl)ethylamine gave the corresponding imines without any sign of racemization (entries 3 and 4). The more hindered benzhydrylamine reacted very slowly and only gave 40% yield after 2 days (entry 5). Further steric hindrance inhibited the imination almost completely, as seen with tritylamine, where only a trace amount of the imine was observed together with benzyl benzoate from self-condensation of the alcohol (entry 6). These experiments indicate that the amine has to attack the ruthenium complex in order for the imination to proceed.15 Aniline reacted very sluggishly with benzyl alcohol and only gave the imine in low yield together with several byproducts (result not shown). Reacting benzyl alcohol with complex 1 in refluxing toluene in the absence of an amine gave about 10% of benzaldehyde after 2 h, as judged by GC-MS analysis, and this did not change upon prolonged treatment, where small amounts of benzyl benzoate were also observed.

The imination reaction provides access to a variety of imines which may be used directly in a subsequent addition reaction. This was illustrated with the enantiomerically pure imine from Table 3, entry 3, which has previously been reacted with a variety of nucleophiles.18 After the imine was formed from benzyl alcohol and (R)-1-phenylethylamine, the solvent was replaced with THF or Et₂O followed by addition of an allylating agent (Scheme 2). With allylzinc bromide the addition product was obtained in 61% overall yield from benzyl alcohol, but with almost no diastereoselectivity. With the more hindered B-allyl-9-BBN the product was isolated in 53% yield and with a diastereomeric ratio of 9:1.16

To obtain more information about the mechanism of the imination, two experiments with deuterium-labeled benzyl alcohol were performed. First, benzyl alcohol-\((\alpha,\alpha-d_2)\) was reacted with tert-octylamine under the standard conditions

### Table 2. Imination of Alcohols with tert-Octylamine

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>imine</th>
<th>amine conv. (%)³</th>
<th>imine yield (%)³</th>
<th>10% DABCO, 4 Å MS, toluene, Δ, 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>OMe</td>
<td>82</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>OH</td>
<td>90</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H3N</td>
<td>H3N</td>
<td>70</td>
<td>63³</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H3N</td>
<td>H3N</td>
<td>80</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>OMe</td>
<td>75</td>
<td>69³</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MeO2C</td>
<td>MeO2C</td>
<td>93</td>
<td>59³</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OH</td>
<td>OH</td>
<td>-</td>
<td>33³</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>OMe</td>
<td>77</td>
<td>48³</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>OH</td>
<td>OH</td>
<td>84</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

³Determined by GC with nonane as internal standard.

### Table 3. Imination of Amines with Benzyl Alcohol

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>imine</th>
<th>BnOH conv. (%)³</th>
<th>imine yield (%)³</th>
<th>10% DABCO, 4 Å MS, toluene, Δ, 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H3N</td>
<td>H3N</td>
<td>75</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NH2</td>
<td>NH2</td>
<td>82</td>
<td>70³</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H3N</td>
<td>H3N</td>
<td>77</td>
<td>63³</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H3N</td>
<td>H3N</td>
<td>70</td>
<td>52³</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NH2</td>
<td>NH2</td>
<td>73</td>
<td>40³</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NH2</td>
<td>NH2</td>
<td>-</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

³Determined by GC with nonane as internal standard. ⁴Isolated yield.

The imination reaction provides access to a variety of imines which may be used directly in a subsequent addition reaction. This was illustrated with the enantiomerically pure imine from Table 3, entry 3, which has previously been reacted with a variety of nucleophiles.18 After the imine was formed from benzyl alcohol and (R)-1-phenylethylamine, the solvent was replaced with THF or Et₂O followed by addition of an allylating agent (Scheme 2). With allylzinc bromide the addition product was obtained in 61% overall yield from benzyl alcohol, but with almost no diastereoselectivity. With the more hindered B-allyl-9-BBN the product was isolated in 53% yield and with a diastereomeric ratio of 9:1.16

To obtain more information about the mechanism of the imination, two experiments with deuterium-labeled benzyl alcohol were performed. First, benzyl alcohol-\(\alpha,\alpha-d_2\) was reacted with tert-octylamine under the standard conditions.
The initial rate was determined both with PhCH$_2$OH/tert-octyl-ND$_2$, which gave a kinetic isotope effect ($k_{D}/k_{H}$) of 1.1 ± 0.3. This negligible value indicates that the initial β-hydride elimination from the alcohol is not the rate-determining step in the imination mechanism.

The influence of the β-hydride elimination was further probed by measuring the primary kinetic isotope effect. The initial rate was determined both with PhCH$_2$OH/tert-octyl-ND$_2$ and with PhCD$_2$OD/tert-octyl-ND$_2$, which provided a kinetic isotope effect ($k_{D}/k_{H}$) of 1.1 ± 0.3. This negligible value indicates that β-hydride elimination from the alcohol is not the rate-determining step in the imination mechanism.

On the basis of these experiments and our previous studies on the amidation, we propose the imination mechanism in Scheme 3, where the amine attacks the coordinated aldehyde to afford the more acidic environment may affect the stability of complex 1. This is, so far, fairly similar to the mechanism proposed for the amidation with complex 1. The major difference, however, is the lack of a strong base in the imination, and the more acidic environment may affect the stability of complex 1.

**Experimental Section**

**General Information.** Toluene was distilled from sodium and benzophenone under an argon atmosphere. Column chromatography was performed on silica gel 60 (0.053–0.070 mm) saturated with Et$_3$N. NMR chemical shifts were measured with TMS or the residual solvent signal in CDCl$_3$ ($\delta_{H}$ 7.26 ppm, $\delta_{C}$ 77.0 ppm) as internal reference.

**General Procedure for Imination.** Ruthenium complex 1 (22.9 mg, 0.05 mmol), DABCO (11.2 mg, 0.01 mmol), and 4 Å molecular sieves (150 mg) were placed in an oven-dried Schlenk flask equipped with a cold finger. Vacuum was applied, and the flask was then filled with argon (repeated twice). Toluene (1 mL), alcohol (1 mmol), amine (1 mmol), and nonane (0.2 mmol as internal standard) were added.

**Organometallics**

Article

Scheme 3. Imination with Benzyl Alcohol-α,α-d$_2$

Scheme 4. Proposed Mechanism for Imination

6. Recently, Crabtree and Eisenstein performed a computational study on a similar hemiaminal bonded to a ruthenium(II) hydride in order to determine whether the amide or the imine would be formed. They showed that the amide is formed after hydrogen transfer to hydride, while imine formation requires hydrogen transfer to oxygen. Under the more acidic conditions of the imination, hydrogen transfer to oxygen may be more facile, e.g., through an outer-sphere proton transfer, which would afford complex 7 and then the imine after decarboxylation of the hemiaminal. In this way, the fate of the intermediate hemiaminal determines whether the amide or the imine is formed in the coupling. The scrambling observed in Scheme 3 can be explained by the observation that ruthenium dihydride complexes are able to scramble hydrogen and deuterium when exposed to hydrogen/deuterium gas. In combination with a reversible β-hydride elimination, this provides a route by which O–H or N–H hydrogens can be scrambled into the α positions of the alcohol.

In summary, we have presented a new method for the direct synthesis of imines from primary alcohols and amines in which water and hydrogen gas are formed as the only byproducts. The reaction is catalyzed by the ruthenium N-heterocyclic carbene complex 1, which is easy to handle and straightforward to prepare. A mechanism is proposed with a ruthenium dihydride species as the catalytically active component.
were added by syringe, and the mixture was refluxed with stirring under a flow of argon for 24 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The residue was purified by silica gel column chromatography (hexane/EtO 10/0 → 9/1 with 2% Et3N) to afford the imine.

- (4-Methylbenzylidene)-tert-octylamine (Table 2, Entry 2): 1H NMR (300 MHz, CDCl3) δ 8.21 (s, 1H), 7.76–7.70 (m, 2H), 7.10 (bt, 2H), 1.69 (s, 2H), 1.32 (s, 6H), 0.96 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 166.8, 153.5, 141.2, 129.3, 126.1, 121.4, 115.5, 106.9, 65.6, 55.4, 32.0, 31.8, 29.8; HRMS m/z calc'd for C19H31NO2 248.1970 [M + H]+, found 248.2010.

- (4-Fluorobenzylidene)-tert-octylamine (Table 2, Entry 4): 1H NMR (300 MHz, CDCl3) δ 8.21 (s, 1H), 7.76–7.70 (m, 2H), 7.10 (bt, 2H), 1.69 (s, 2H), 1.32 (s, 6H), 0.96 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 166.8, 153.5, 141.2, 129.3, 126.1, 121.4, 115.5, 106.9, 65.6, 55.4, 32.0, 31.8, 29.8; HRMS m/z calc'd for C19H31NO2 248.1970 [M + H]+, found 248.2010.

- (4-Bromoacetobenzylidene)-tert-octylamine (Table 2, Entry 5): 1H NMR (300 MHz, CDCl3) δ 8.67 (s, 1H), 7.39 (bt, 1H), 1.69 (s, 2H), 1.32 (s, 6H), 0.96 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 158.6, 150.4, 131.0, 127.0, 125.8, 120.8, 110.8, 61.3, 56.6, 55.4, 32.0, 31.8, 29.8; HRMS m/z calc'd for C19H31NO2 248.1970 [M + H]+, found 248.2010.

- (4-Chlorobenzylidene)-tert-octylamine (Table 2, Entry 6): 1H NMR (300 MHz, CDCl3) δ 8.27 (s, 1H), 8.07 (d, 2H, J = 8.1 Hz), 7.80 (d, 2H, J = 8.1 Hz), 3.93 (s, 3H), 1.70 (s, 2H), 1.33 (s, 6H), 0.95 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 166.8, 153.5, 141.2, 131.1, 129.7, 127.7, 61.5, 56.5, 52.2, 32.0, 31.7, 29.5; HRMS m/z calc'd for C19H31NO2 248.1970 [M + H]+, found 248.2010.

- (4-Nitrobenzylidene)-tert-octylamine (Table 2, Entry 8): 1H NMR (300 MHz, CDCl3) δ 8.30 (s, 1H), 8.26 (d, 2H, J = 8.7 Hz), 7.91 (d, 2H, J = 8.7 Hz), 1.71 (s, 2H), 1.34 (s, 6H), 0.94 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 152.3, 142.7, 128.5, 123.8, 61.9, 56.5, 32.0, 31.7, 29.5; HRMS m/z calc'd for C19H31NO2 263.1715 [M + H]+, found 263.1753.

**ASSOCIATED CONTENT**

**Supporting Information**

Text and figures giving experimental procedures, characterization data, and 1H and 13C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

**AUTHOR INFORMATION**

*E-mail: rm@kemi.dtu.dk.*

**ACKNOWLEDGMENTS**

We thank the Danish Council for Independent Research—Technology and Production Sciences for financial support.

**REFERENCES**