Catalytic hydrogenation of α,β-unsaturated carboxylic acid derivatives using copper(II)/N-heterocyclic carbene complexes

Birte M. Zimmermann, and Johannes F. Teichert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 115, 10623 Berlin (Germany, E-mail: johannes.teichert@chem.tu-berlin.de.

A simple and air-stable copper(II)/N-heterocyclic carbene complex enables the catalytic hydrogenation of hitherto unreactive enoates and enamides employing H₂ as terminal reducing agent. This atom economic transformation replaces commonly employed hydroxilanes and can also be carried out in an asymmetric fashion.

One of the main challenges of contemporary method development for synthetic chemistry is the development of atom economic and sustainable transformations. In this vein, catalytic hydrogenations are much desired reactions, as they serve to replace complex and waste-generating reducing agents such as borohydrides, aluminium hydrides or hydroxilanes. Catalytic reactions involving copper hydride intermediates serve to replace complex and waste-generating reducing agents such as borohydrides, aluminium hydrides or hydroxilanes. 

Catalytic hydrogenations are much desired reactions, as they serve to replace complex and waste-generating reducing agents such as borohydrides, aluminium hydrides or hydroxilanes. This atom economic transformation replaces commonly employed hydroxilanes and can also be carried out in an asymmetric fashion.

The copper-catalysed hydrogenation of enoates was optimised employing ethyl β-methyl cinnamate (1, Table 1). Using sodium tert-butanol as additive for the generation of the key Cu–O bond for H₂ activation, we investigated common copper(II)/NHC complexes 3-7 at 90 bar H₂ and 60 °C in THF (Table 1, entries 1–5). From these experiments, mesityl-derived complexes 3 and 6 emerged as most active, as judged by the conversion of 1 to 2. Notably, no other side-products were observed. We found that the amount of NaOtBu could be lowered to 30 mol% while maintaining full conversion, however, even smaller amounts of the additive (10 mol%) led to an almost complete halt of the reaction (Table 1, entries 6 and 7). Lowering the pressure to 50 bar at these limiting conditions led to diminished conversion of 32% (Table 1, entry 8). A subsequent solvent optimisation revealed 1,4-dioxane as optimal, with full conversion of 1 reached at lowered H₂ pressure of 50 bar (Table 1, entry 9). When comparing catalysts 3 and 6 at 10 bar H₂ pressure, imidazolium-based copper complex 6 turned out to be more active (Table 1, entries 10 vs. 12), even though no reactivity difference could be detected at higher temperature of 100 °C. The investigation of the substrate...
scope was therefore carried out with catalyst 6. Notably, lowering the \( \text{H}_2 \) pressure with catalyst 6 to 1 bar still led to a detectable conversion of 1 (32% conv. Table 1, entry 14).

Table 1. Cu-catalysed hydrogenation of enoates, optimisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 110 mol% NaOtBu, 90 bar ( \text{H}_2 ), THF, 60 °C</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>2</td>
<td>as entry 1</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>as entry 1</td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>as entry 1</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>5</td>
<td>as entry 1</td>
<td>41%</td>
</tr>
<tr>
<td>6</td>
<td>3 30 mol% NaOtBu, 90 bar ( \text{H}_2 ), THF, 60 °C</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>7</td>
<td>10 mol% NaOtBu, 90 bar ( \text{H}_2 ), THF, 60 °C</td>
<td>6%</td>
</tr>
<tr>
<td>8</td>
<td>30 mol% NaOtBu, 50 bar ( \text{H}_2 ), THF, 60 °C</td>
<td>32%</td>
</tr>
<tr>
<td>9</td>
<td>3 30 mol% NaOtBu, 50 bar ( \text{H}_2 ), 1,4-dioxane, 60 °C</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>10</td>
<td>3 30 mol% NaOtBu, 10 bar ( \text{H}_2 ), 1,4-dioxane, 60 °C</td>
<td>5%</td>
</tr>
<tr>
<td>11</td>
<td>3 30 mol% NaOtBu, 10 bar ( \text{H}_2 ), 1,4-dioxane, 100 °C</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>12</td>
<td>3 30 mol% NaOtBu, 10 bar ( \text{H}_2 ), 1,4-dioxane, 60 °C</td>
<td>79%</td>
</tr>
<tr>
<td>13</td>
<td>3 30 mol% NaOtBu, 10 bar ( \text{H}_2 ), 1,4-dioxane, 100 °C</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>14</td>
<td>3 30 mol% NaOtBu, 1 bar ( \text{H}_2 ), 1,4-dioxane, 100 °C</td>
<td>32%</td>
</tr>
</tbody>
</table>

With optimised reaction conditions in hand, we set out to investigate the substrate scope of the copper-catalysed conjugate reduction of \( \alpha,\beta \)-unsaturated carboxylic acid derivatives 8 (Scheme 2). We found that the catalytic hydrogenation could be applied to a variety of aryl or alkyl substituted enoates 8. Next to the successful generation of simple naphthyl derivative 9a, also the sterically more demanding tert-butyl ester 9b as well as diphenyl-substituted ester 9c could be furnished in good yields (68-84%). Both electron donating and withdrawing groups were tolerated as substituents of the cinnamic acid derivatives 9d-9h with similar results in terms of yield. Notably, no protodehalogenation was observed with bromide 9f or chloride 9g. Also, thiophene-derived 9i as possibly coordinating heterocycle could be successfully hydrogenated. The generation of cyclopropane-substituted 9j with almost quantitative yield (95%) gives an important indication that no carbon-based radical is involved in the overall process. Next to the successful formation of diester 9k, also 9l, bearing a methyl group in \( \alpha \)-position, which generally slows down the conjugate addition in other copper-catalysed processes,19 was turned over by the catalyst. Ester 9l was formed as a 41:59 mixture of diastereomers. Also, dialkyl-substituted enoates 9m-9o could be converted with similarly good results in terms of yield. We could demonstrate that even enamide 10, which generally is too electron-rich for reactivity in other copper-catalysed conjugate addition reactions,20 displays some reactivity with our catalyst (60% conv., 17% yield for 11). This result underscores the fact that the copper/NHC complexes employed in this transformation serve a key role for the generation of copper hydride intermediates with higher reactivity in comparison to the commonly used phosphine
complexes.\textsuperscript{5–9} The latter could not realize any conversion of carboxylic acid derivatives. Sorbic acid derivative 12 gave a mixture of 1,4- and 1,6-addition products, with unsaturated ester 13a (from 1,4-addition of the hydride nucleophile) as the major product (Scheme 3). The formation of 13b and 13c can be explained by prior 1,6-addition of the copper hydride, and, in the case of 13c, subsequent 1,4-addition.

Scheme 3. Conjugate reduction of an \(\alpha,\beta,\gamma,\delta\)-unsaturated ester.

\[
\begin{align*}
\text{Ph} - \text{CH} - \text{CO} - \text{OEt} & \quad \text{H} - \text{Cu} - \text{H} \\
\text{12} & \quad \text{Cu} - \text{Cl} \\
& \quad \text{NaOEtBu} \\
& \quad \text{1,4-dioxane, 100 °C, 16 h} \\
\end{align*}
\]

To gain insight in the mechanism of the present protocol, we carried out the conjugate reduction in the presence of deuterium gas (D\(_2\), Scheme 4). With the ethyl esters 8c and 8d, as expected for a hydride transfer reaction, the deuterium incorporation in the \(\beta\) position was high (\(\geq 90\%\) D), but also significant isotope labeling in the \(\alpha\) position was found, indicating an enolisation process with \(t\)-BuOD after the conjugate addition. Unexpectedly, also deuterium incorporation was observed in the ethyl ester (23–39\% D, D\(_{1}'\) and D\(_{2}'\)). Our current hypothesis is a sequence of transesterification with \(t\)-butanol to give a copper(I)–ethoxide complex which subsequent \(\beta\)-hydride elimination and reduction of the acetaldehyde thus generated by a copper deuteride, followed by another transesterification to give deuterated 9c and 9d.\textsuperscript{21}

Scheme 4. Cu-catalysed conjugate reduction with D\(_2\).

\[
\begin{align*}
\text{RC} - \text{CH} - \text{CO} - \text{OEt} & \quad \text{H} - \text{Cu} - \text{H} \\
\text{8c,d} & \quad \text{CuCl} \\
& \quad \text{10 mo% CuCl} \\
& \quad \text{10 bar D\(_2\)} \\
& \quad \text{1,4-dioxane, 100 °C, 48 h} \\
\end{align*}
\]

In line with these experiments, we propose a mechanism as outlined in Scheme 5. Primary activation of the copper chloride precatalyst by addition of NaOtBu leads to the corresponding copper \(t\)-butanolate complex A\textsuperscript{22} by ligand exchange. Compound A bears the key Cu–O–bond for heterolytic H\(_2\) activation,\textsuperscript{15–17} delivering copper hydride complex B\textsuperscript{22,23} and \(t\)-butanol. Conjugate addition of the copper hydride leads to copper enolate C\textsuperscript{24}, which could itself activate H\(_2\) by its intermediate Cu–O bond (C to B, giving 9 directly, dashed arrows) or react in a protodecupration with NaOtBu to give the desired product 9 while reforming the \(t\)-butanolate complex A. The strongly basic reaction conditions can then lead to additional enolisation of the ester via enolate 14, which accounts for the observed double deuterium incorporation in the \(\alpha\) position of the esters (Scheme 3).

Scheme 5. Proposed mechanism. (L = N-heterocyclic carbene ligand)

As an asymmetric variant of this reaction is highly attractive,\textsuperscript{19} we turned our attention to chiral NHC ligands. In preliminary experiments, we were able to demonstrate that indeed stereoinduction with chiral NHC ligands is possible, even though more drastic reaction conditions (100 bar H\(_2\), 48 h reaction time) had to be employed with chiral NHC precursors 15\textsuperscript{25} and 16\textsuperscript{26} (Scheme 5). The corresponding reduced ester 2 was obtained with an enantiomeric ratio of up to 82:18 with chiral NHC precursor 15, demonstrating the viability of an asymmetric reaction.

Scheme 6. Asymmetric conjugate reduction of cinnamate 1.

\[
\begin{align*}
\text{RC} - \text{CH} - \text{CO} - \text{OEt} & \quad \text{H} - \text{Cu} - \text{H} \\
\text{1} & \quad \text{CuCl} \\
& \quad \text{10 mo% CuCl} \\
& \quad \text{12 mol% 15 or 16} \\
& \quad \text{1.1 equiv NaOtBu} \\
& \quad \text{100 bar H\(_2\)} \\
& \quad \text{toluene, 60 °C, 48 h} \\
\end{align*}
\]

Conclusions

In summary, we have developed a simple and efficient copper-catalysed conjugate reduction of enoates and enamides with H\(_2\). Well-defined and easily accessible copper(I)-NHC complexes are employed as catalysts, giving the desired products which
had so far not been accessible with copper/phosphine complexes due to the lower reactivity of the substrates. This catalytic protocol serves as an atom economic alternative to replace the commonly used and waste-generating hydrosilanes as stoichiometric reducing agents with dihydrogen (H₂). Isotope labelling studies indicate a polar mechanism involving a copper hydride intermediate and the possibility of an asymmetric reaction has been demonstrated.

Conflicts of interest
There are no conflicts to declare.

Acknowledgements
This work was supported by the German Research Council (DFG, Emmy Noether Fellowship for J. F. T., TE1101/2-1), by the Fonds der Chemischen Industrie (Liebig-Stipendium for J. F. T.) and by the Daimler and Benz Foundation (postdoctoral fellowship for J. F. T.). We thank Sarah C. K. Kobolz for preliminary experiments. Prof. Dr. Martin Oestreich (TU Berlin) is kindly thanked for generous support.

Notes and references
1 For a review on green chemistry, see: P. Anastas and N. Eghbali, Chem. Soc. Rev., 2010, 39, 301–312.