Nickel-Catalyzed Synthesis of Enamides and Enecarbamates via Isomerization of Allylamides and Allylcarbamates

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Abstract: A single-component, air-stable nickel pre-catalyst can catalyze the isomerization of allylamides for the synthesis of enamides. The scope of the reaction encompasses various substituted allylamides and allylcarbamates as well as homoallylamides. The reaction can be performed on a multi-gram-scale without specialized glove-box equipment or Schlenk techniques.

Keywords: enamides; enecarbamates; homogeneous catalysis; isomerization; nickel catalysis

Enamides and enecarbamates are very useful synthetic intermediates for various transformations, such as cycloadditions, cross-coupling reactions or asymmetric C–C bond formations (Scheme 1).[1–4]

Furthermore, enamides and enecarbamates are valuable substrates for asymmetric hydrogenation reactions.[3,4] Besides these applications, the enamide motif is often found in natural products, for example, aspergilamides[5] and salicylhalamides[6].

Due to importance of these classes of compounds, several protocols for their preparation have been reported.[1–4] Classical procedures, such as the acylation of imines or the condensation of amides and carbonyl compounds require harsh reaction conditions and lead to the formation of considerable amounts of by-products.[7] An attractive alternative is the transition metal-catalyzed[8–11] or base-mediated[12] isomerization of readily available N-allylamides. Recently, Gooßen and co-workers developed a stereoselective synthesis of enamides based on a ruthenium-catalyzed direct addition of amides to terminal alkynes.[13–15]

For one of our current research projects, we were looking for an operationally simple, scalable and effi-
cient synthesis of aldehyde- and ketone-derived enamides and enecarbamates. From this point of view, the nickel(0)-catalyzed isomerization of N-allylamides reported by Lei\cite{16} looked very promising. However, the employed Ni(0) catalyst, Ni(PPh₃)₄, is very air sensitive and necessitates the use of specialized equipment for safe handling.\cite{17} In the last years, easily accessible, air-stable Ni(II)-aryl complexes have been used as efficient precatalysts for various cross-coupling reactions (Scheme 2).

We envisioned, that these easy-to-handle Ni(II) complexes could be useful precatalysts for the nickel(0)-catalyzed isomerization of N-allylamides.

To our delight, readily available Ni(II)-aryl complexes 1 and 2 catalyze the isomerization of allyl-AM 4a very efficiently even at room temperature (Table 1, entries 1 and 2).

The desired enamide could be obtained in 95% isolated yield and an $E:Z$-ratio of 77:23 and, respectively, 76:24. The Ni(II) precatalyst 3, bearing a bidentate phosphine ligand, displayed a significantly reduced activity (entry 3). Lowering the catalyst loading to 2 mol% did not affect the yield or $E:Z$-ratio (entry 4).

Strikingly, the use of specialized glove-box equipment or Schlenk techniques is not required for this nickel-catalyzed isomerization. The reaction can be carried out in commercially available MeOH without any pretreatment. Simple “argon sparging” of the catalyst-solvent mixture before addition of the starting material is sufficient for an effective isomerization. Performing the reaction at higher or lower temperatures did not affect the obtained $E:Z$-ratio (entry 5).

Performing the reaction in other, less polar aprotic solvents, such as THF or CH₂Cl₂ afforded the enamide in slightly lower yields (entries 6 and 7). When NiCl₂(PPh₃)₂, a stable nickel(II) complex, was used as catalyst precursor, the allylamine 4a was recovered almost quantitatively (entry 8).

With the optimized reaction conditions in hand, we explored the scope of our method. As shown in Scheme 3 various N-aryl and N-alkyl allylamides as well as cyclic allylamides are suitable substrates and the desired enamides 5b–k could be obtained in moderate to excellent yields.

The reaction of cinnamoylallylamine 4l proceeded smoothly to afford enamide 5l in 64% yield. Moreover, highly functionalized allylamides, such as valine

Table 1. Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Catalyst</th>
<th>Yield of 5a [a] (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>r.t./24 h</td>
<td>5 mol%  1</td>
<td>95% (77:23)</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>r.t./24 h</td>
<td>5 mol%  2</td>
<td>95% (76:24)</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>r.t./5 d</td>
<td>5 mol%  3</td>
<td>28% (46:54)</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>r.t./24 h</td>
<td>2 mol%  4</td>
<td>95% (75:25)</td>
</tr>
<tr>
<td>5</td>
<td>MeOH</td>
<td>50°C/24 h</td>
<td>2 mol%  5</td>
<td>95% (76:24)</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>r.t./24 h</td>
<td>2 mol%  6</td>
<td>81% (76:33)</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>r.t./24 h</td>
<td>2 mol%  7</td>
<td>87% (67:33)</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>r.t./24 h</td>
<td>5 mol%  8</td>
<td>0%</td>
</tr>
</tbody>
</table>

[a] Isolated yield after column chromatography. $E:Z$ ratio determined by NMR.

Scheme 3. Reaction scope for the Ni-catalyzed isomerization. Phth = phthaloyl.
allylamine 4m or the ibuprofen-derived allylamine 4n, were converted to the corresponding isomerization products 5m and 5n in 88% and 91% yields. Urea, imide and carbamate derivatives could be transformed efficiently into the N-protected enamines 5o–t in 48–95% yields. However, a higher catalyst loading, higher temperatures and prolonged reaction times were required for these substrates. It is worth mentioning that the isomerization of allylamine 4a was performed routinely on a 15-g scale. Although a slight decrease in the yield was observed, the desired enamide 5a was isolated in satisfactory yield of 82%.

This nickel-catalyzed isomerization is not limited to allylamides. Also homoallylamides 4u and 4v underwent the isomerization to the corresponding enamides 5u and 5v in 91% and 69% yield via a “long-distance” migration of the double bond (Scheme 4). However, prolonged reaction times are necessary for these “long-distance” isomerizations.

In summary, we have developed a practical synthesis of enamides starting from the corresponding, readily accessible N-allylamides. We have shown that single-component, air-stable Ni(II)-aryl complexes can catalyze this isomerization very efficiently. The scope of the reaction is broad and encompasses various substituted allylamides, -ureas, -imides and -carbamates as well as homoallylic substrates. The reaction can be performed on a multigram-scale in commercially available MeOH without specialized glove-box equipment or Schlenk techniques.

**Experimental Section**

**Typical Procedure for the Ni-Catalyzed Isomerization of Allylamides**

A 10-mL reaction tube was charged with \([\text{Ni}(\text{PPh}_3)_2(1\text{-naphthyl})\text{Br}] (5–10 \text{ mol%})\) and methanol (0.4 mL mmol \(^{-1}\) allylamine/-carbamate) and capped with a rubber septum. The resulting suspension was degassed by slowly bubbling argon through the mixture for 15 min with simultaneous sonication in an ultrasound bath. The N-allylamine or, respectively, -carbamate was added at room temperature under vigorous stirring. The reaction mixture was stirred at the specified temperature for the specified time, afterwards diluted with EtOAc+0.2 vol% NEt\(_3\) and filtered through a short plug of celite and silica gel. The plug was rinsed with additional EtOAc. The combined filtrates were concentrated under reduced pressure. Purification of the crude residue by column chromatography (n-hexane:EtOAc+0.2 vol% NEt\(_3\)) afforded the analytically pure product. For most enamides and enamcarbamates the E- and Z-isomers could be readily separated by column chromatography. In some cases partial purification of one isomer was possible. In other cases E- and Z-isomers could not be separated with simple column chromatography.

Detailed experimental procedures, NMR spectra, HR-MS data and IR analyses are available in the Supporting Information.

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**References**

[17] Handling of the sensitive nickel(0) complex inside a glove-box is necessary.
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