An Ammonia Equivalent for the Dimethyltitanocene-Catalyzed Intermolecular Hydroamination of Alkynes

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ABSTRACT

Commercially available α-aminodiphenylmethane 1 (benzhydrylamine) serves as a convenient ammonia equivalent in the dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes. The primary formed imines can be hydrogenated and cleaved directly to the corresponding primary amines by catalytic hydrogenation using Pd/C as catalyst.

The direct addition of ammonia or amines to carbon—carbon double and triple bonds, the so-called hydroamination of alkenes and alkynes, is of fundamental interest in organic chemistry. It represents the most atom economic synthesis of amines, imines, and enamines which are important building blocks for organic products, e.g., pharmaceuticals, detergents, technical additives, and dyes. However, at the moment no general hydroamination procedure for a wide variety of substrates is known.1,2

Recently we reported on the dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes. 3 While this procedure combined with a subsequent reduction of the initially formed imines is effective for the preparation of secondary amines, the direct use of ammonia, giving access to primary amines, has not been successful. Therefore, no simple means

for the preparation of primary amines using our hydroamination strategy has yet been found. Herein we report on a procedure that uses commercially available α-aminodiphenylmethane 1 (benzhydrylamine) as a convenient ammonia equivalent in the dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes.

Initial experiments to convert alkynes into primary amines using benzylamine as an ammonia equivalent in the hydroamination step followed by hydrogenation of the resulting imine have met with only limited success because benzylamine shows a very low reactivity in dimethyltitanocene-


catalyzed hydroamination reactions. This low reactivity which has generally been observed for primary \( n \)-alkylamines forced us to investigate primary \( s \)-alkylamines as ammonia equivalents. Among this class of compounds we found that \( \alpha \)-aminodiphenylmethane \( \text{I} \) (benzhydrylamine), which offers the possibility of a reductive cleavage of the carbon–nitrogen bond, serves as an ammonia equivalent in a convenient manner (Scheme 1).

**Scheme 1.** Formal Addition of Ammonia to Alkynes

\[
\begin{align*}
\text{Ph-NH}_3 & \quad \text{Ph-NH}_3 \\
\text{R}^1 \equiv \text{Aryl, Alkyl} & \quad \text{R}^1 \equiv \text{Aryl, Alkyl, H}
\end{align*}
\]

First we found that hydroamination reactions between \( \alpha \)-aminodiphenylmethane \( \text{I} \) (benzhydrylamine) and various alkynes \( \text{2} \) yielding the corresponding imines \( \text{3} \) can be realized efficiently in the presence of 3 mol \% of \( \text{Cp}_2 \text{TiMe}_2 \) at 110–120 °C in the absence of a solvent. The reactions are generally very clean but, however, relatively slow. For bisaryl alkynes and alkyl aryl alkynes, the reactions proceed to generally very clean but, however, relatively slow. For bisaryl alkynes, \( \text{3} \) serves as an ammonia equivalent in a convenient manner (Scheme 1).

Further investigations showed that the crude imines \( \text{3} \) can be directly reduced to the desired primary amines \( \text{4} \) by catalytic hydrogenation under 1 atm of \( \text{H}_2 \) at 25 °C using 1.5–5 mol \% of \( \text{Pd/C} \) as catalyst. Table 1 shows several examples for the described hydroamination–reduction strategy.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>product</th>
<th>yield(^{\text{a}}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph—Ph</td>
<td>( \text{2a} )</td>
<td>67(^{\text{b}} )</td>
</tr>
<tr>
<td>2</td>
<td>Ph—Me</td>
<td>( \text{2b} )</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>Ph—Et</td>
<td>( \text{2c} )</td>
<td>67(^{\text{b}} )</td>
</tr>
<tr>
<td>4</td>
<td>Ph—Pr</td>
<td>( \text{2d} )</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Et—Et</td>
<td>( \text{2e} )</td>
<td>59(^{\text{b}} )</td>
</tr>
<tr>
<td>6</td>
<td>Pr—Pr</td>
<td>( \text{2f} )</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>Ph—H</td>
<td>( \text{2g} )</td>
<td>41(^{\text{b}} )</td>
</tr>
</tbody>
</table>

\(^{\text{a}}\) Reaction conditions: (1) 1.0 equiv of amine, 1.2 equiv of alkyne, 3.0 mol \% of \( \text{Pd/C} \), 110 °C, 72 h; (2) 1 atm of \( \text{H}_2 \), 1.5 mol \% of \( \text{Pd/C} \), THF, 25 °C, 72 h. Reaction times have not been minimized. Yields represent isolated yields of pure compounds as judged by \( ^{1} \text{H NMR}, ^{13} \text{C NMR}, \) and TLC analysis. \(^{\text{b}}\) 5 mol \% of \( \text{Pd/C} \) was used for the reduction step. \(^{\text{c}}\) 3.0 equiv of alkyne was used for the hydroamination step. \(^{\text{d}}\) 20 h reaction time for the hydroamination step.


(5) General reaction procedure: A dry Schlenk tube equipped with a Teflon stopcock was charged under an argon atmosphere with \( \alpha \)-aminodiphenylmethane \( \text{I} \) (367 mg, 2.0 mmol), 1-phenyl-1-pentyne \( \text{2d} \) (346 mg, 2.4 mmol), and a solution of \( \text{Cp}_2 \text{TiMe}_2 \) in toluene (0.18 mL, 0.33 mol/L, 0.06 mmol, 3.0 mol \%). The mixture was heated to 110 °C for 72 h. The crude reaction mixture was then dissolved in THF (14 mL). \( \text{Pd/C} \) (64 mg, 3.2 mg \( \text{Pd} \), 0.03 mmol, 1.5 mol \%) was added and the mixture was stirred under 1 atm of \( \text{H}_2 \) at 25 °C for 72 h. Filtration, concentration, and purification by flash chromatography (\( \text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH} \), 10:1) afforded \( \text{4d} \) (230 mg, 1.41 mmol, 70\% as a colorless solid.


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take place during the hydroamination step, probably lowering the yield by converting the desired product into side products. One possible explanation for this observation which is in contrast to the behavior of all other alkynes used in this study is the fact that here the imine which is initially formed in the hydroamination step is an aldimine. This aldimine can easily undergo side reactions, e.g., aldol type reactions, under the reaction conditions leading to various amine products. Therefore, the obtained yield decreases if longer reaction times are employed.

In summary, we have demonstrated the utility of employing \( \alpha \)-aminodiphenylmethane \( 1 \) (benzhydrylamine) as a substitute for ammonia in the dimethyltitanocene-catalyzed hydroamination of alkynes. Using the presented hydroamination-reduction strategy, alkynes can be easily converted into primary amines. However, the obtained overall yield for the described reaction sequence strongly depends on the structure of the employed alkyne. While bisaryl alkynes and alkyl aryl alkynes react smoothly under the reaction conditions, bisalkyl alkynes and terminal alkynes give lower yields.

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**Supporting Information Available:** Characterization data for compounds 4a–4g. This material is available free of charge via the Internet at http://pubs.acs.org.

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