Nickel-catalyzed decarbonylative silylation, boronation and amination of arylamides via a deamidative reaction pathway

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Abstract A nickel catalyzed decarbonylative silylation, boronation and amination of amides has been developed. This new methodology allows the direct interconversion of amides to arylsilanes, arylboronates and arylamines and enables a facile route for carbon-heteroatom bond formations in a straightforward and mild fashion.

Key words nickel, amides, arylsilanes, arylboronates and arylamines

Nickel-catalyzed cross-coupling reactions have become promising alternatives to traditional noble metal mediated reactions mainly due to the low-cost of nickel catalysts and the environmental friendly nature of coupling partners. Over the last 10 years, nickel has been widely used for cross-coupling reactions, as well as for C-H functionalizations. Initially, cross-coupling reactions were used to construct biaryls from halides and organometallic reagents. However, organohalides can be toxic compounds and wastes production is observed. Yet, due to the outstanding ability of oxidative-addition of nickel, a wide range of reactions can be performed with halide-free substrates by activating stable C-X bonds, including C-S, C-Se and C-N bonds. Nevertheless, the types of reactions disclosed are still limited, and hence new reactivities and reaction types are desirable.

In recent years, various decarbonylative cross-coupling reactions via transition metal-catalysis have been described. As conventional electrophilic substrates, acyl chlorides, acid anhydrides and esters are normally selected and used in decarbonylative reactions. In contrast, the amide C-N bond cleavage is more challenging and requires particular attention. Amides exist abundantly in nature, e.g. in proteins and peptides and are widely used in artificial compounds like drugs and polymers. From the perspective of synthesis, amides would be ideal starting materials for their conversion to further functional groups. However, the C-N bonds are highly stable and difficult to insert and cleave with transition metals. Therefore, direct methods for the transfer of amide moieties to other functional groups would be very advantageous and are highly demanded.

Given our recent developments in the field of Ni-catalysis and in particular decarbonylative cross-coupling reactions with esters, we decided to expand our newly developed protocols to valuable amide substrates.

Over the past few decades, organosilicon and organoboron compounds proved to provide a good platform for further functional group interconversion to access complex molecular scaffolds. Furthermore, their application in the synthesis of natural products and drug molecules is widely acknowledged. In addition to organosilicon and organoboron derivatives, amines are further valuable intermediates in organic synthesis. Conventionally, organosilicon and organoboron compounds are synthesized from sensitive Grignard reagents or organolithium reagents. Recently, transition-metal catalyzed silyl/boryl substitution of aryl halides and arene C-H silylation/borylation have been achieved. However, poor functional group tolerance, the utilization of expensive substrates, or site selectivity might cause limitations of the above methods. Herein, we report a practical method to achieve the silylation, borylation and amination of amides in an easy manner via C-N bond cleavage.
Recently, we and the Shi group have described the nickel/copper catalyzed decarboxylative silylation reaction of esters by applying silyboranes as coupling partners. In addition, Martin group described the nickel/copper catalyzed silylation of pivalates with silyboranes as coupling partners. Building up on these results, we started our investigation for the decarboxylative silylation of amides by examining various amides 1a-6a in reaction with silylborane 7 (Table 1). Firstly, we evaluated N-Boc, N-Benzyl and N-Boc, N-Phenyl imides 1a and 2a, however only low yields of the desired arylsilane product 8a were observed (entries 1 and 2). Replacing the Boc protecting group with methyl and trifluoroacetyl groups (3a, 4a) resulted in considerably lower yields (entries 3 and 4). Next, we turned our attention to sterically distorted amides 5a and 6a and were pleased to see that derivative 6a provided the desired product in good yield (entry 6). To further enhance the yield, we examined different reaction conditions. Use of 30 mol % of LiCl as additive under the standard conditions did not improve the yield (entry 7). The effect of concentration was also evaluated, however no positive effect was observed upon increasing or decreasing the concentration (entries 8 and 9 vs 6). The yield slightly decreased when changing the solvent to 1,4-dioxane, which has a similar solubility and boiling point as toluene (entry 10).

Next, we turned our attention to the loading of Ni(COD)₂. When the catalyst amount was reduced from 10 to 5 mol %, a lower yield was obtained (entry 11). Finally, different bases were tested (entries 12-14), however, better yields were not achieved. Furthermore, no product was observed in the absence of CuF₂ (entry 15).

To evaluate the applicability and utility of the optimized protocol, different amide substrates were employed to determine the scope of the Ni-catalyzed deaminative silylation reaction. As illustrated in Scheme 2, different amide substrates could be converted into the corresponding aryltriethysilanes 8a in moderate to high yields. For example, napthyl (6a) and a wide range of phenyl (6b-j) and heterocyclic (6k-m) derived amides could be efficiently converted into the corresponding arylsilanes 8a-m by employing silyborane compound 7. The protocol shows a good functional group tolerance and groups such as tert-buty1 (8c), methyl ester (8d), methoxy (8e), methyl (8h), fluorde (8i), benzofuran (8k), benzoephene (8l) and quinoline (8m) are tolerated. Para- and ortho-substitutions are also tolerated, as shown by the formation of aryl silanes 8b and 8g, respectively. Notably, a high yield (95%) was obtained for the dioxole and m-methoxy derivatives 8f and 8j.

With a slightly modified protocol conversion of the amides into the corresponding arylboronates 10 was also accomplished. Glutarimide substrates 6 can be easily prepared in a one-step procedure from the appropriate acyl chlorides and are therefore useful starting materials for the synthesis of arylsilanes as well as arylboronates. For the C-B bond forming protocol, representative substrates 6a-f were selected to undergo reaction using bispinacolato diboron as coupling nucleophile and the products 10a-f were obtained in acceptable yields (Scheme 3).

### Table 1: Optimization of arylsilane synthesis through decarboxylative silylation of amides

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a-6a</th>
<th>Ni(COD)₂ (mol %)</th>
<th>Base</th>
<th>Solvent (conc. M)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.2)</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.2)</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.2)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>4a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.2)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.2)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>6a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.2)</td>
<td>83 (79)</td>
</tr>
<tr>
<td>7a</td>
<td>6a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.4)</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>6a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.4)</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>6a</td>
<td>10</td>
<td>KF</td>
<td>Toluene (0.13)</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>6a</td>
<td>10</td>
<td>KF</td>
<td>Dioxane (0.2)</td>
<td>61</td>
</tr>
<tr>
<td>11</td>
<td>6a</td>
<td>5</td>
<td>KF</td>
<td>Toluene (0.2)</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>6a</td>
<td>10</td>
<td>CsF</td>
<td>Toluene (0.2)</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>6a</td>
<td>10</td>
<td>CsF</td>
<td>Toluene (0.2)</td>
<td>36</td>
</tr>
<tr>
<td>14</td>
<td>6a</td>
<td>10</td>
<td>KPO₄</td>
<td>Toluene (0.2)</td>
<td>41</td>
</tr>
<tr>
<td>15</td>
<td>6a</td>
<td>10</td>
<td>KPO₄</td>
<td>Toluene (0.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a-6a (0.20 mmol), 7 (96.6 mg, 0.40 mmol), Ni(COD)₂ (5.5 mg, 10 mol %), P₃Bu₃ (20 μL, 40 mol %), CuF₂ (6.1 mg, 30 mol %), base (3.0 equiv.) in solvent (1 mL, 0.2 M) at 160 °C for 36 h. Yields were determined by 1H-NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene.

* Yield of isolated product.

* 30 mol % LiCl was used as additive.

* Without CuF₂.

* Boc = tert-buty1 carbonyl, COD = 1,5-cyclooctadiene.
Based on the results in Schemes 3 and 4, we subsequently turned our interest to the use of imine nucleophiles to examine the decarboxylative amination of amides (Scheme 4). Based on our previous protocol, we selected benzophenone imine 11 as amine source with dpff as supporting ligand, K$_3$PO$_4$ as base, LiCl as additive, Ni(COD)$_2$ as catalyst in 0.2 M toluene at 170 °C for 24 hours under Ar. As show in Scheme 4, naphthyl arylamines, which are important building blocks in synthetic chemistry, were prepared with good yields and high stereospecificity.

In summary, we have developed Ni-catalyzed decarboxylative silylation, borylation and amination reactions of amides. Under the optimized conditions, various arylsilanes, arylboranes and arylamines, which are important building blocks in synthetic chemistry, were prepared with good yields and high stereospecificity. The here described cross coupling stands out due to the ready accessibility of substrates, mild reaction conditions and simple reaction handling allowing a stereo-selective product formation. Further mechanistic studies and other related transformations are currently underway in our laboratories.

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Click here to insert sources of funding, grant numbers, etc. Do not repeat the same in the acknowledgment.

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**Supporting Information**
YES (this text will be updated with links prior to publication)

**Primary Data**
Is there Primary Data to be associated with this manuscript? Click here, then the arrow, and choose YES or NO.

**References and Notes**


Recently, a protocol for the decarbonylative borylation of amides was established by Shi and co-workers, see reference 12c. With a catalytic system consisting of nickel and an N-heterocyclic carbene ligand, the N-Boc-N-Me derived amides were converted into the corresponding borylation products in moderate to high yields. Interestingly, distorted cyclic imides were completely unsuccessful.


