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Heterogeneous Nickel-Catalyzed Cross-Coupling between Aryl Chlorides and Alkyllithiums Using a Polystyrene-Cross-Linking Bisphosphine Ligand

Yuki Yamazaki, Nozomi Arima, Tomohiro Iwai,* and Masaya Sawamura*

Abstract: A polystyrene-cross-linking bisphosphine ligand PS-DPPBz was used for Ni-catalyzed cross-coupling with organolithiums. A bench-stable precatalyst [NiCl₂(PS-DPPBz)] enabled efficient coupling reactions between aryl chlorides and alkyllithiums. The heterogeneous Ni system showed good reusability.

The development of an efficient, green and simple synthetic process for transition metal-catalyzed cross-coupling reactions is important not only for industrial applications but also for fundamental chemistry.[1,2] Since the pioneering work of Murahashi and co-workers[2] and the later improvement by Feringa and co-workers[3] and the later improvement by Feringa et al.[3] organic chloroform has recently emerged as an intense area for pursuing environmentally benign organic synthesis.[3,4] However, due to the intrinsic high reactivity of organolithiums, prior dilution and/or slow addition protocols are required for efficient catalysis, as described by Hornillos and Feringa.[8d] Moreover, only a few catalyst systems allow efficient reaction of alkyllithiums having β-hydrogen atoms.[8d,e]

Recently, we developed a polystyrene-fourfold-cross-linking bisphosphine ligand PS-DPPBz (structure shown in Table 1).[10] This ligand allowed spatial isolation of the bisphosphine unit in the polystyrene matrix, resulting in formation of a highly active mononuclear monochelated metal-bisphosphine species. We demonstrated its utility in the Ni-catalyzed amination of aryl chlorides and C–H/C–O cross-coupling between 1,3-azoles and aryl pivalates. Herein, we report heterogeneous Ni catalysis for the cross-coupling of aryl chlorides and alkyllithiums with PS-DPPBz. This cross-coupling reaction required neither prior dilution nor slow addition of the alkyllithium. Excellent catalyst reusability was a favorable feature of this heterogeneous system.

Table 1. Ligand effects in the Ni-catalyzed cross-coupling reaction between 1a and 2a[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time [h]</th>
<th>Conv. 1a [%]</th>
<th>Yield 3a [%]</th>
<th>Yield 4a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PS-DPPBz</td>
<td>6</td>
<td>98</td>
<td>93</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>PS-DPPBz</td>
<td>0.5</td>
<td>19</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>DPPBz</td>
<td>6</td>
<td>21</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>4-Pr-DPPBz</td>
<td>6</td>
<td>70</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>SciOPP</td>
<td>6</td>
<td>29</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>DETPE</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PCy₃ (3 mol%)</td>
<td>6</td>
<td>25</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>IPr (3 mol%)</td>
<td>6</td>
<td>35</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>none</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>[NiCl₂(PS-DPPBz)]</td>
<td>6</td>
<td>&gt;99</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>[NiCl₂(PS-DPPBz)]</td>
<td>0.5</td>
<td>&gt;99</td>
<td>96</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>[NiCl₂(PS-DPPBz)]</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>[NiCl₂(PS-DPPBz)]</td>
<td>5</td>
<td>66</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>+ DPPBz (2 mol%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ 4-Pr-DPPBz (2 mol%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Conditions: 1a (0.25 mmol), 2a (1.55 M in hexane, 0.375 mmol), [Ni(cod)]₂ (1 mol%), ligand (1.5 mol%), hexane (0.5 M based on 1a), 25 °C. [b] Determined by GC spectroscopy. [c] Determined by 1H NMR spectroscopy. [d] [NiCl₂(PS-DPPBz)] (1 mol% Ni) was used as catalyst.

Initially, we investigated ligand effects for the Ni-catalyzed cross-coupling of aryl chlorides, which are readily accessible and cheaper than the corresponding bromides and iodides, with alkyllithiums.[11] Specifically, with 1 mol% of a Ni catalyst prepared in situ from [Ni(cod)]₂ and PS-DPPBz (Ni:L 1:1.5), the reaction between 2-chloronaphthalene (1a, 0.25 mmol) and n-butyllithium (2a, 1.55 M in hexane, 1.5 eq) proceeded smoothly without prior dilution or slow addition of the alkyllithium at 25 °C in hexane (0.5 M based on 1a) over 6 h, giving 2-butylnaphthalene (3a) in 93% yield.

Supporting information for this article is given via a link at the end of the document.

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NMR yield (Table 1, entry 1), along with a small amount of a protodehalogenated product (4a, 5%). In contrast, DPPBz, which is the parent soluble ligand of PS-DPPBz, induced much lower activity (13%, entry 3). A DPPBz derivative, 4-iPr-DPPBz,[12] which has iPr groups at the para positions of the four P-Ph groups as a model for the polystyrene chain, gave a moderate yield (65%, entry 4), while the yield was reduced with SciOPP, the 3,5-di-tBu-substituted derivative of DPPBz (24%, entry 5).[13] These results indicated the polymer effect is crucial, and that para-substituents on the P-Ph groups of DPPBz-type ligands are effective for increasing the catalytic activity. Other soluble ligands such as DETPE, PCy3 and IPr, which had been employed as effective ligands for Ni-catalyzed cross-coupling with organolithiums,[8] were also much less effective than PS-DPPBz (entries 6–8). No reaction occurred in the absence of an added ligand (entry 9).

Next, we examined the use of a bench-stable Ni(II) salt as a Ni source instead of the air-sensitive Ni(0) complex [Ni(cod)2]. A polymer-bound Ni(II) precatalyst [NiCl2(PS-DPPBz)] (Ni: 0.12 mmol/g),[14] which was prepared from NiCl2·6H2O and PS-DPPBz in MeOH/THF (Scheme 1), showed much higher activity than the [Ni(cod)2]/PS-DPPBz system (93% vs. 97% for 6 h, Table 1, entries 1 and 10; 14% vs. 96% for 0.5 h; entries 2 and 11). Notably, complete substrate consumption was observed within 0.5 h (entry 11). Addition of a soluble DPPBz derivative, DPPBz or 4-iPr-DPPBz (2 mol%), to the [NiCl2(PS-DPPBz)] system led to a decrease in the yield (entries 12 and 13), offering support for the importance of the controlled bisphosphine monochelation to the Ni center.[15]

### Scheme 1. Synthesis of [NiCl2(PS-DPPBz)].

We next examined other aryl electrophiles in the reactions with 2a and the [NiCl2(PS-DPPBz)] catalyst system (in hexane at 25 °C, Scheme 2). The coupling reaction of 2-bromonaphthalene occurred smoothly to give 3a in 85% yield. 1-Fluoronaphthalene also participated in the reaction, affording 1-butylnaphthalene (3b) in 61% yield, while the corresponding iodide was not suitable due to rapid Li/I exchange (2%). Although aryl triflates were applicable substrates in the Pd-catalyzed cross-coupling with organolithiums,[3e] 2-naphthyl trifluoromethanesulfonate did not provide 3a but formed 2-naphthol (~20% conv. by GC analysis) instead. The corresponding methyl ether was also inactive.[16]

### Scheme 2. Screening of aryl electrophiles.

The scope of aryl chlorides in the catalysis with the [NiCl2(PS-DPPBz)] system was investigated using 2a as a representative organolithium reagent (Scheme 3). The reaction of 1-chloronaphthalene with 2a occurred at 25 °C, giving 3b in high yield. The more π-extended 2-chloroanthracene was a suitable substrate (3c). A commercially available 1-bromopyrene gave 3d in good yield.

Compared to polyaromatic aryl chlorides, monocyclic substrates showed lower reactivities. Specifically, the reaction of 4-chlorobiphenyl gave 3e in moderate yield. The reaction of 4-t-butylchlorobenzene with 2 mol% Ni loading at 40 °C for 24 h afforded 3f in only 8% NMR yield. Introduction of a CF3 group instead of the tBu group increased the yield to 55% (3g). This trend suggests that C–Cl oxidative addition of aryl chlorides to Ni(0) may be a rate-determining step.[17]

A methoxy group, which is often employed as a directing group in ortho-lithiation,[18] attached on the naphthalene ring was tolerated (3h). Silyl ether (3i), acetal (3j) and amine (3k) groups remained untouched. A hydroxy-tethered aryl chloride (3l) was a suitable substrate for the C–Cl cross-coupling reaction with 3 equiv of 2a. With 2 mol% Ni catalyst at 40 °C for 24 h, 2-chlorobenzofuran was converted to the corresponding coupling product 3m in an acceptable yield.

### Scheme 3. Scope of aryl chlorides. Conditions: 1 (0.25 mmol), 2a (1.55 M in hexane, 0.375 mmol), [NiCl2(PS-DPPBz)] (1 mol%), hexane (0.5 M based on 1) at 25 °C for 5 h. Yields of isolated products are shown. In some cases, small amounts of protodehalogenated byproducts of 1 were formed.
The applicability of commercially available alkyllithiums is summarized in Table 2. n-Hexyllithium reacted with 1a, giving 3n in 96% yield (entry 1). The reaction with methyl lithium proceeded smoothly at 40 °C to afford 3o in 83% yield (entry 2). (Trimethylsilyl)methyl lithium also participated in the coupling reaction (3p, entry 3).[19] The reaction of s-Butyllithium gave the corresponding coupling product (3q, entry 3) in high yield (86%), while 2-n-butylnaphthalene (3a) was also produced in 11%, suggesting isomerization of a putative alkyl-Ni(II) intermediate through β-hydride elimination (entry 4).

Table 2. Scope of organolithiums[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>State of RLi Conditions</th>
<th>Products (3)</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nHex</td>
<td>2.3 M in hexane 25 °C, 5 h</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>1.11 M in Et2O 40 °C, 24 h</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>3[c]</td>
<td>Me3SiCH2</td>
<td>1.0 M in pentane 25 °C, 24 h</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>s-Bu</td>
<td>1.05 M in cyclohexane-hexane 25 °C, 5 h</td>
<td>86[d]</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>1.52 M in pentane 25 °C, 5 h</td>
<td>22[e,f]</td>
<td></td>
</tr>
</tbody>
</table>

[a] Conditions: 1a (0.25 mmol), 2 (0.375 mmol), [NiCl2(PS-DPPBz)] (1 mol%), hexane (0.5 M based on 1a), 25 °C, 6 h. [b] Isolated yields. [c] 2 equiv of Me3SiCH2Li. [d] The isolated product contains 11% of 3a. [e] Determined by 1H NMR spectroscopy. [f] 2-Isobutylnaphthalene (6%, an isomerization product) and 2,2'-binaphthalene (26%, a homocoupling product, based on 1a) were also detected in the crude product.

The heterogeneous [Ni-(PS-DPPBz)] catalyst was examined for reusability. After the reaction between 1a and 2a with [NiCl2(PS-DPPBz)] (1 mol% Ni in hexane, 25 °C, 0.5 h), the polymer-bound Ni catalyst was separated in a glove box and reused at least six times with high yields retained (>95%, Scheme 4).

A catalyst turnover number (TON) as high as 1880 was achieved in a larger scale reaction with 20 mmol of 1a and 2.6 M 2a in hexane without an additional solvent at 40 °C over 24 h (0.05 mol% Ni, 94% yield of 3a, NMR) (Scheme 5). To our knowledge, this is the highest TON achieved to date for cross-coupling of organolithiums using Ni catalysts.

Scheme 5. The reaction of 1a and 2a with low catalyst loading (S/C = 2000).

In summary, a polystyrene-cross-linking bisphosphine PS-DPPBz enabled the efficient Ni-catalyzed cross-coupling of aryl chlorides with alkyl lithiums. The bench-stable polymer-bound Ni(II) precatalyst [NiCl2(PS-DPPBz)] showed improved performance over previously reported Ni systems. The utility of the heterogeneous Ni catalyst was demonstrated in catalyst reuse and on a larger scale reaction. Further applications of the polystyrene-cross-linking bisphosphine as a ligand are currently being investigated in our laboratory.

Experimental Section

General Procedure for Ni-catalyzed Cross-Coupling between Aryl Chlorides and Alkyllithiums (Table, 1, entry 11).

In a nitrogen-filled glove box, [NiCl2(PS-DPPBz)] (0.12 mmol/g, 20.8 mg, 0.0025 mmol, 1.0 mol%), 2-chloronaphthalene (1a, 40.6 mg, 0.25 mmol) and hexane (0.255 mL) were successively placed in a 10-mL glass tube containing a magnetic stirring bar. The tube was sealed with a screw cap and removed from the glove box. nBuLi (2a, 1.55 M in hexane, 0.245 mL, 0.375 mmol, 1.5 eq) was added by a syringe at once. The reaction mixture was stirred at 25 °C for 0.5 h. After quenching with MeOH, the mixture was filtered with a silica gel pad (eluting with Et2O). The solvent was removed under reduced pressure. Internal standard (p-dimethoxybenzene) was added to the residue. The yield of the coupling product 3a was determined by 1H NMR (96%). The crude material was then purified by silica gel chromatography with hexane for isolation (44.9 mg, 96% yield, contaminated with a trace amount of naphthalene (4a)).

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Keywords: nickel • cross-coupling • organolithium • bisphosphine • heterogeneous catalyst


[14] The Ni loading value of [NiCl2(PS-DPPBz)] had deviations depending on determination methods. Elemental analysis of Cl or P for [NiCl2(PS-DPPBz)] indicated that the Ni loading to the polystyrene resin was estimated to be 0.093 or 0.094 mmol/g, respectively, based on the Ni to Cl or P stoichiometry of 1:2. These values were underestimated as compared to the value of the DPPBz moiety of PS-DPPBz calculated by elemental analysis of P (0.12 mmol/g, see ref 10). Thus, this calculated value (0.12 mmol/g) was used as the Ni loading in this study, assuming that the ratio of Ni to the DPPBz moiety was equal. See Supporting Information for characterization details.


[19] Rueping et al. reported the Ni-catalyzed cross-coupling reactions of Me2SiCH2Li via C–O or C–F bond cleavage. See refs 8a,b,f.

[20] The [NiCl2(PS-DPPBz)] catalyst system was applicable to the reactions of aryllithiums. Specifically, the reaction between 1a and PhLi (1.09 M in cyclohexane/Et2O, 1.5 eq) with 1 mol% of [NiCl2(PS-DPPBz)] in hexane (0.5 M) at 40 °C for 24 h without slow addition produced the corresponding biaryl compound (2-phenylanthalene, 3a) in 48% NMR yield (68% conv. of 1a), which was comparable to that with the Feringa’s catalyst [NiCl2(IPr)(PPh3)] (ref 8d) under otherwise the same conditions (69% conv., 53% yield). The reaction using 2-thienyllithium (1.0 M in THF/hexane, 1 mol% Ni, 25 °C, 5 h) gave 2-(2-naphthyl)thiophene (3) in 32% isolated yield.
A polystyrene-cross-linking bisphosphate ligand PS-DPPBz was used for Ni-catalyzed cross-coupling with organolithiums. A bench-stable precatalyst [NiCl$_2$(PS-DPPBz)] enabled efficient coupling reactions between aryl chlorides and alkyllithiums. The heterogeneous Ni system showed good reusability.

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