



## Coupling reactions with haloaromatic amines and alcohols for a practical synthetic route to 2-substituted aminophenyl and hydroxyphenyl pyridines

Seung-Hoi Kim, Reuben D. Rieke\*

Rieke Metals, Inc., 1001 Kingbird Rd., Lincoln, NE 68521, USA

### ARTICLE INFO

#### Article history:

Received 4 September 2009

Revised 24 September 2009

Accepted 25 September 2009

Available online 1 October 2009

### ABSTRACT

A practical synthetic route to 2-substituted aminophenyl and hydroxyphenyl pyridines has been developed. It has been accomplished by the cross-coupling reactions of readily available 2-pyridylzinc bromides with haloaromatic amines and alcohols under mild conditions.

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Recent developments in the preparation methods of 2-pyridyl derivatives show the significance of their uses especially in natural product synthesis, pharmaceutical, and material chemistry.<sup>1</sup> To this end, the transition metal-catalyzed cross-coupling reactions of the corresponding 2-pyridylmetallic reagents have been intensively used in spite of some difficulties such as instability and formation of by-products.<sup>2,3</sup>

In order to avoid these difficulties of using 2-pyridylmetallic reagents, new synthetic methodologies utilizing the direct arylation of pyridines have been developed.<sup>4</sup>

In our continuing study on the application of organozinc reagents, we found that a stable 2-pyridylzinc bromide was easily prepared by the direct insertion of highly active zinc into 2-bromopyridine and the subsequent coupling reactions of the resulting organozinc reagent with several different types of electrophiles afforded the desired products in good manner. All the coupling reactions were easily carried out under very mild conditions.<sup>5</sup>

Including our study, most of the electrophiles used in aforementioned transition metal-catalyzed cross-coupling reactions of 2-pyridylmetallics contain relatively non-reactive functional groups toward organometallics, such as ester, ketone, nitrile, halogen, and ether.

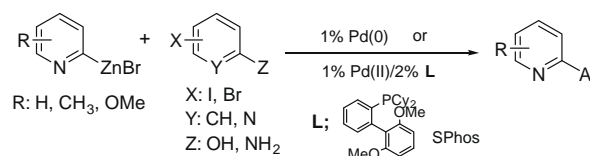
For the preparation of a variety of 2-pyridyl derivatives, highly functionalized electrophiles are necessary as the coupling partner in the reactions. Here, we have performed the cross-coupling reactions of 2-pyridylzinc bromides with haloaromatic compounds containing relatively acidic protons. To this end, haloaromatic amines, phenols, and alcohols are reasonable candidates as coupling reactants. By utilizing this strategy, 2-substituted aminophenyl and hydroxyphenyl pyridines have been successfully prepared under mild conditions. To our best knowledge, it is the first general example of the transition metal-catalyzed cross-coupling reactions

of 2-pyridylmetallic reagents providing pyridyl amines and pyridyl phenols (Scheme 1).<sup>6</sup>

Since Pd(II)-catalysts along with an appropriate ligand have been used in the coupling reactions of organozinc reagents with haloaromatic amines and alcohols,<sup>7a</sup> it seemed reasonable to try these conditions in our study. The coupling reactions worked well with 2-pyridylzinc bromide (**1a**) and the results are summarized in Table 1.

The reaction of **1a** with 4-iodoaniline in the presence of 1 mol % Pd(OAc)<sub>2</sub> and 2 mol % SPhos gave rise to the cross-coupling product, **2a**, in 90% isolated yield (Table 1, entry 1). Two more reactions, methyl substituted 2-pyridylzinc bromide (**1c**) with 4-iodoaniline and **1a** with 4-bromoaniline resulted in relatively low yields (Table 1, entries 2 and 3). However, a significantly improved yield was obtained by the simple change of reaction temperature (Table 1, entry 4). An elevated reaction temperature also worked well for the reaction of **1c** with 3-iodoaniline leading **2c** in 85% isolated yield (Table 1, entry 5). As described in the previous report,<sup>7a</sup> we also found that the presence of an extra ligand (SPhos) was critical for the completion of the coupling reaction.

At this point, even though the similar conditions with the previous work<sup>7a</sup> were used, it should be emphasized that a more practical procedure, especially for the large scale synthesis, has been demonstrated in our study. For example, the organozinc solution was added into the flask containing Pd(II)-catalyst, ligand (SPhos) and electrophile at a steady-stream rate at rt. A very slow addition

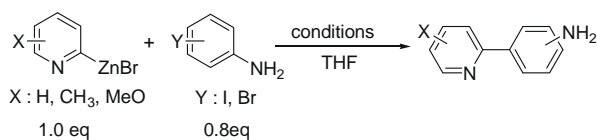


**Scheme 1.** Coupling reactions with haloaromatic amines and alcohols.

\* Corresponding author.

E-mail address: [sales@riekemetals.com](mailto:sales@riekemetals.com) (R.D. Rieke).

**Table 1**  
Coupling reaction with haloanilines



Entry	X	Y	Conditions <sup>a</sup>	Product	Yield <sup>b</sup> (%)
1	H( <b>1a</b> )	4-I	<b>A</b>		90
2	4-CH <sub>3</sub> ( <b>1c</b> )	4-I	<b>A</b>		50
3	H( <b>1a</b> )	4-Br	<b>A</b>	<b>2a</b>	50
4	H( <b>1a</b> )	4-Br	<b>B</b>	<b>2a</b>	89
5	4-CH <sub>3</sub> ( <b>1c</b> )	3-I	<b>B</b>		85
6	H( <b>1a</b> )	4-I	<b>C</b>	<b>2a</b>	89
7	H( <b>1a</b> )	3-I	<b>C</b>		64
8	H( <b>1a</b> )	2-I	<b>C</b>		74
9	3-CH <sub>3</sub> ( <b>1b</b> )	4-I	<b>D</b>		68
10	6-OMe( <b>1d</b> )	4-Br	<b>D</b>		Trace <sup>c</sup>

<sup>a</sup> **A**: 1% Pd(OAc)<sub>2</sub>/2% SPhos/rt/24 h; **B**: 1% Pd(OAc)<sub>2</sub>/2% SPhos/reflux/24 h; **C**: 1% Pd[P(Ph)<sub>3</sub>]<sub>4</sub>/rt/24 h; **D**: 1% Pd[P(Ph)<sub>3</sub>]<sub>4</sub>/reflux/24 h.

<sup>b</sup> Isolated yield (based on aniline).

<sup>c</sup> By GC-MS.

of organozinc reagent into the reaction flask was crucial in order to obtain high yields.<sup>8</sup>

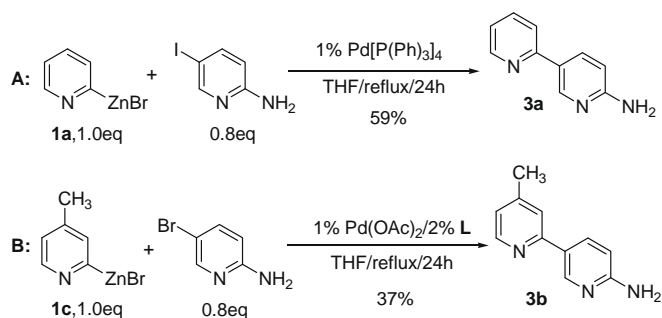
As mentioned above, the extra ligand (SPhos) was necessary when using the Pd(II)-catalysts for the coupling reactions in our study as well as others. From an economic point of view as well as ease of work-up, a ligand-free reaction conditions would be highly beneficial. Thus, with the preliminary results (Table 1, entries 1–5) in hand, we have investigated the SPhos-free Pd-catalyzed coupling reactions of 2-pyridylzinc bromides with haloanilines. They were performed by employing a Pd(0)-catalyst and the results are summarized in Table 1. Significantly, the Pd(0)-catalyzed coupling reactions were not affected by the presence of acidic protons (NH<sub>2</sub>).<sup>9</sup>

The reaction of **1a** with 4-iodoaniline in the presence of 1 mol % Pd[P(Ph)<sub>3</sub>]<sub>4</sub> provided 2-(4-aminophenyl)pyridine (**2a**) with a compatible result (Table 1, 89% isolated yield, entry 6). 3-Iodoaniline and 2-iodoaniline were also coupled with **1a** under the same conditions (condition **C**, Table 1) affording the aminophenyl pyridines (**2d** and **2e**) in 64% and 74% isolated yields, respectively (Table 1, entries 7 and 8). Another successful coupling reaction (Table 1, en-

try 9) was achieved from a sterically hindered 3-methyl-2-pyridylzinc bromide (**1b**), resulting in 68% isolated yield with the formation of **2f**. Unfortunately, no satisfactory coupling reaction occurred with 4-bromoaniline using the Pd(0)-catalyst (Table 1, entry 10).

Interestingly, unsymmetrical amino-bipyridines were produced from the coupling reactions of 2-pyridylzinc bromides with halogenated aminopyridines under the conditions used above.<sup>10</sup> As shown in Scheme 2, 2-amino-5-iodopyridine reacted with **1a** to afford 2,3-bipyridine (**3a**) in 59% isolated yield in the presence of Pd[P(Ph)<sub>3</sub>]<sub>4</sub> (1 mol %) catalyst. However, in the case of 2-amino-5-bromo-pyridine, the Pd(II)-catalyst was more useful for the coupling reaction and the reaction proceeded smoothly to give 2,3-bipyridine (**3b**) in 37% yield (B, Scheme 2). It is of interest that the bipyridyl amines can be used as intermediates for the synthesis of highly functionalized molecules after transformation of the amino group to a halogen.<sup>11</sup>

With the results obtained from the coupling reactions with haloaromatic amines, it can be concluded that Pd(0)-catalyzed reaction of 2-pyridylzinc bromides works effectively with iodoaro-



Scheme 2. Preparation of aminopyridine.

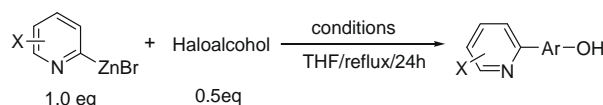
matic amines and also the relatively more reactive bromoaromatic amines.

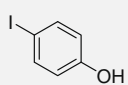
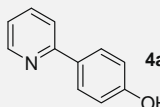
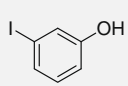
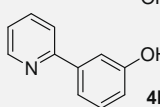
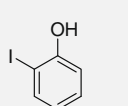
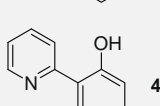
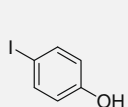
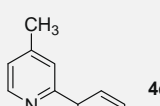
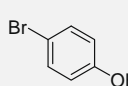
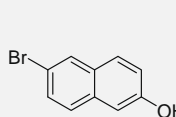
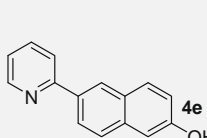
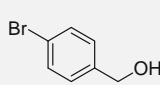
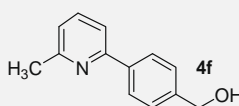
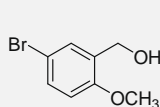
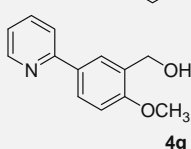
Another interesting reaction of 2-pyridylzinc bromides would be the coupling reaction with phenols or alcohols, which also have

an acidic proton. Encouraged by the results described above, the coupling reactions with iodophenols were carried out in the presence of Pd(0)-catalyst.

As shown in Table 2, 4-iodophenol and 3-iodophenol were coupled with **1a** affording the corresponding hydroxyphenyl pyridine products (**4a** and **4b**) in excellent yields (Table 2, entries 1 and 2). A slightly disappointing result (25%) was obtained from 2-iodophenol (Table 2, entry 3). The reason is not clear, but it is presumably because the coupling was next to the hydroxy group. A similar outcome has also been reported in another study.<sup>12</sup> In the case of bromophenolic alcohols, no coupling reaction took place with the Pd(0)-catalyst. Instead, the Pd(II)-catalyst was more efficient for the coupling reaction. 4-Bromophenol and 6-bromo-2-naphthol were nicely coupled with **1a** resulting in the coupling products (**4a** and **4e**) in 86% and 92% (Table 2, entries 5 and 6). Unlike the reactions with bromophenols, it is of interest that the coupling products (**4f** and **4g**) of **1d** and **1a** were efficiently achieved from the Pd(0)-catalyzed reactions with 4-bromobenzyl alcohol and 3-bromo-5-methoxybenzyl alcohol (Table 2, entries 7 and 8), respectively.

**Table 2**  
Coupling reaction with haloaromatic alcohols

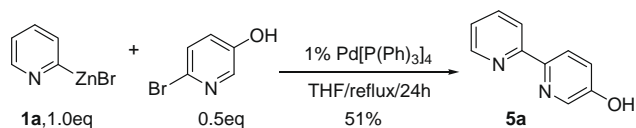


Entry	X	Alcohol	Conditions <sup>a</sup>	Product	Yield <sup>b</sup> (%)
1	H( <b>1a</b> )		<b>I</b>		95
2	H( <b>1a</b> )		<b>I</b>		80
3	H( <b>1a</b> )		<b>I</b>		25
4	4-CH <sub>3</sub> ( <b>1b</b> )		<b>I</b>		54
5	H( <b>1a</b> )		<b>I</b> <b>II</b>	<b>4a</b>	0 <sup>c</sup> 86
6	H( <b>1a</b> )		<b>II</b>		92
7	6-CH <sub>3</sub> ( <b>1d</b> )		<b>I</b>		60
8	H( <b>1a</b> )		<b>I</b>		65

<sup>a</sup> **I**: 1% Pd[P(Ph)<sub>3</sub>]<sub>4</sub>; **II**: 1% Pd(OAc)<sub>2</sub>/2% SPhos.

<sup>b</sup> Isolated yield (based on alcohol).

<sup>c</sup> No coupling observed by GC.



**Scheme 3.** Preparation of hydroxyl 2,2'-bipyridine.

Treatment of 2-pyridylzinc bromide with a halopyridine bearing a hydroxyl group provided another functionalized bipyridine. Interestingly, the relatively reactive bromopyridyl alcohol, 2-bromo-5-hydroxypyridine, was coupled with **1a** using Pd(0)-catalyst. As a result, the corresponding hydroxyl 2,2'-bipyridine (**5a**) was obtained in 51% isolated yield (Scheme 3). The hydroxyl group on 2,2'-bipyridine can also be converted to halogen to make halobipyridines by using several different methods.<sup>13</sup>

In conclusion, a practical synthetic procedure for the preparation of 2-substituted aminophenyl and hydroxyphenyl pyridines has been demonstrated utilizing readily available 2-pyridylzinc bromides with haloaromatic amines, phenols, and alcohols. Reactions have been carried out in the presence of either a Pd(0)-catalyst or a Pd(II)-catalyst under mild conditions. Further applications of 2-pyridylzinc bromides are currently under way.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.160.

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- Slow cannulation (over 90 min) of organozinc (2.4 mmol) via syringe pump was required, see: Ref. 12.
- pK<sub>a</sub> Values; range between 15 and 20 for phenols, 20 and 30 for anilines, source from <http://www.chem.wisc.edu/areas/reich/pkatable/index.htm>.
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