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2-Pyridyl and 3-pyridylzinc bromides: direct preparation and coupling reaction

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ABSTRACT

A facile synthetic approach to the direct preparation of 2-pyridyl and 3-pyridylzinc bromides has been demonstrated using Rieke zinc with 2-bromopyridine and 3-bromopyridine, respectively. A variety of different electrophiles have been coupled with the resulting organozinc reagents to give the corresponding cross-coupling products in moderate to good yields.

1. Introduction

Heterocyclic compounds, which contain a pyridine ring are frequently found in natural products. Accordingly, they are of special interest in pharmaceutical, agrochemical, and medicinal chemistry.[1] Also, a number of pyridine derivatives have been used in material chemistry.[2] Bipyridine groups are found to be a key element in antibiotics such as caerulomycins and collismycins. Another example is pyridylpyrimidines, which are used as fungicides as well as tyrosine kinase inhibitors.[3] In addition, pyridine-containing oligomers are frequently found in liquid crystals.[4]

As described above, the pyridine moiety has played a very significant role in a wide range of organic compounds. Consequently, new practical synthetic approaches for introducing a pyridine ring into complex organic molecule are of high value. To this end, preparation of pyridyl derivatives are mostly performed by transition metal-catalyzed cross-coupling reactions of pyridylmetallic reagents. However, the preparation of electron-deficient pyridinyl organometallic reagents has been a challenging subject mainly because of some difficulties such as instability and formation of by-products.

Most of the 2-pyridyl derivatives have been prepared using the Suzuki,[5] Stille,[6] Grignard,[7] and Negishi[8] coupling reactions in the presence of a transition metal catalyst. Among these, the Suzuki coupling reaction is the most intensively studied and a very extensive work has been developed.[9] Recently, several outstanding studies on the direct arylation of pyridine have been reported to avoid these inevitable difficulties. For examples, Rh(I)[10] and Au(I)[11]-catalyzed arylation of pyridines, Pd-catalyzed arylation of pyridine *N*-oxide with unactivated arenes[12] and haloarenes[13] have been developed. Also, the direct arylation of pyridine *N*-oxide by Grignard reagents was reported.[14]

Even though there are many examples of the preparation of 2-pyridylmetallic halides from the reaction of halopyridines, a limited number of studies have been reported on the preparation of 3-pyridylmetallic halides. 3-Pyridylmagnesium,[15] 3-pyridylzinc,[16] 3–pyridylindium[17] halides, and Suzuki reagents[18] are the most widely used reagents for the preparation of pyridine-containing compounds. Lithiation of 3-halopyridine followed by transmetallation with appropriate metals (Mg, Zn, In) afforded the corresponding 3-pyridylmetallic halides. However, this route has limitations such as cryogenic conditions, several side reactions and limited functional group tolerance.[19] Very few studies have been reported on the direct synthesis of 3-pyridylmetallic halide reagents. Most of these reports included the treatment of 3-iodo or 3-bromopyridine with highly active metals.[20] Also, the subsequent coupling reactions were carried out with limited electrophiles.

Interestingly, in our continuing study on the preparation and application of organozinc reagents, we found that 2-pyridylzinc bromide and 3-pyridylzinc bromide were easily prepared by treatment of 2-bromopyridine and 3-bromopyridine with active zinc under mild conditions, respectively. Significantly, the resulting organozinc reagents were found to react with a variety of different electrophiles with/without transition metal catalysts affording the coupling products in good yields.

2. Results and discussion

In general, the preparation of 2-pyridyl organometallics is mostly performed by lithiation of 2-halopyridine at cryogenic conditions followed by transmetallation with an appropriate metal halide. As mentioned above, this procedure causes some limitations on the use of the 2-pyridyl organometallics. In our study, readily available 2-bromopyridine was treated at rt with active zinc prepared by the Rieke Method.[21] The oxidative addition of the active zinc to carbon–bromine bond was completed in an hour at refluxing temperature to give rise to the corresponding 2-pyridylzinc bromide (**P1**).

In order to investigate the reactivity of the 2-pyridylzinc bromide, it was treated with benzoyl chlorides. As summarized in Table 1, the coupling ketone products were obtained in moderate yields. It should

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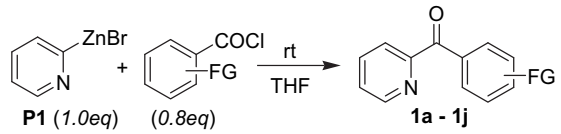
Table 1
Coupling reaction of 2-pyridylzinc bromide (**P1**) with benzoyl chlorides[a]



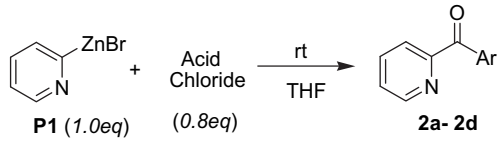
Entry	FG	Product	Yield[b](%)
1	2-F	2-F (**1a**)	65
2	3-F	3-F (**1b**)	52
3	2-Br	2-Br (**1c**)	45
4	4-Br	4-Br (**1d**)	47
5	4-I	4-I (**1e**)	36
6	3-CN	3-CN (**1f**)	54
7	4-CN	4-CN (**1g**)	50
8	4-Me	4-Me (**1h**)	64
9	3,4-$(OMe)_2$	3,4-$(OMe)_2$ (**1i**)	40
10	4-NO_2	4-NO_2 (**1j**)	47

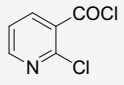
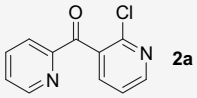
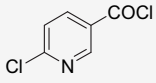
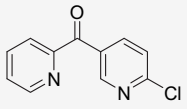
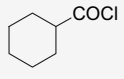
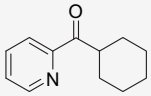
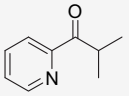
[a] No catalyst was used.
[b] Isolated yield(based on electrophile).

be emphasized that the coupling reaction with acid chlorides described in Table 1 was carried out in the absence of any transition metal catalyst under mild conditions. Generally, a copper catalyst is widely used for the coupling reactions of organozinc reagents.[22] Halobenzoyl chlorides were easily coupled with 2-pyridylzinc bromide (**P1**) at rt to give the corresponding ketones (**1a**, **1b**, **1c**, **1d**, and **1e**, Table 1) in moderate yields. Both benzoyl chlorides containing an electron-withdrawing group (CN and NO_2) and an electron-donating group (Me and MeO) also successfully afforded the corresponding ketones (**1f**, **1g**, **1h**, and **1i**, Table 1). Even with nitrobenzoyl chloride, ketone (**1j**, Table 1) was obtained in moderate yield. According to GC–MS analysis of the reaction mixture, a major by-product was the coupling product obtained from the reaction of acid chloride with THF.

More results obtained from the catalyst-free coupling reactions are shown in Table 2. Treatment of **P1** with chloronicotinoyl chlorides (entries 1 and 2, Table 2) at rt for 3 h provided the corresponding ketones (**2a**, and **2b**) in 62% and 53%, respectively. Alkyl carbonyl chlorides were also coupled with 2-pyridylzinc bromide resulting in the formation of the ketones (**2c** and **2d**, Table 2) in 42% and 63% yields.

Table 2
Coupling reaction of **P1** with acid chlorides[a]



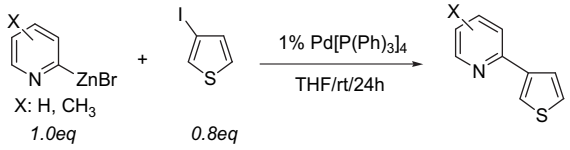
Entry	Acid chloride	Product	Yield[b](%)
1		 **2a**	62
2		 **2b**	53
3		 **2c**	42
4		 **2d**	63

[a] No catalyst used.
[b] Isolated yield(based on electrophile).

With these results in hand, we also explored the Pd-catalyzed C–C bond forming reaction of P**1**. Even though 2-pyridylaryl derivatives were successfully prepared via the aforementioned direct arylation methods, relatively harsh conditions (excess amount of reactant, high temperature, protection/deprotection step and addition of additives) were required.

Prior to the Pd-catalyzed coupling reaction with a variety of aryl halides, a preliminary test was performed using Pd(0)-catalyst to find out any effect of substitutents on the C–C bond forming reactions. Several different types of 2-pyridylzinc bromides (**P1**–**P6**, Table 3) were coupled with 3-iodothiophene in the presence of 1 mol % of $Pd(PPh_3)_4$ in THF at rt and the results are summarized in Table 1. In general, good yields (entries 1, 3, and 4, Table 3) were obtained from using 2-pyridylzinc bromide (**P1**), 4-methyl-2-pyridylzinc bromide (**P3**), and 5-methyl-2-pyridylzinc bromide (**P4**). Reactions with 3-methyl-2-pyridylzinc bromide (**P2**), 6-methyl-2-pyridylzinc bromide (**P5**), and 6-methoxy-2-pyridylzinc bromide (**P6**) resulted in moderate yields (entries 2, 5, and 6, Table 3).

Table 3
Study of substitutent effect

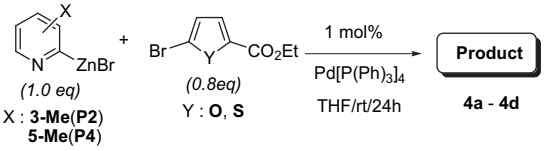


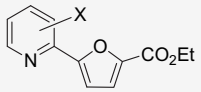
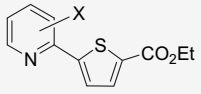
Entry	X	Product, X	Yield[a](%)
1	H(**P1**)	H (**3a**)	85
2	3-CH_3(**P2**)	3-CH_3 (**3b**)	58
3	4-CH_3(**P3**)	4-CH_3 (**3c**)	77
4	5-CH_3(**P4**)	5-CH_3 (**3d**)	79
5	6-CH_3(**P5**)	6-CH_3 (**3e**)	57
6	6-OCH_3(**P6**)	6-OCH_3 (**3f**)	54

[a] Isolated yield (based on 3-iodothiophene).

An additional study was carried out to investigate the steric effect on cross-coupling reaction using 2-pyridylzinc bromides (**P2** and **P4**). As shown in Table 4, the steric hindrance (76% vs 89%, 51% vs 84% isolated yield) was clearly observed from the coupling reactions with 5-bromofuran-2-carboxylic acid ethyl ester and 5-bromothiophen-2-carboxylic acid ethyl ester (entries 1 vs 2 and 3 vs 4, Table 4), respectively. The results clearly demonstrate that the steric bulk around the reaction site reduces the coupling ability of the corresponding organozinc reagents.

Table 4
Steric effect on cross-coupling reaction

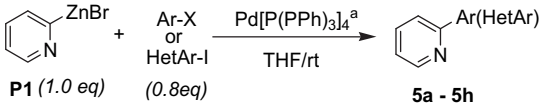


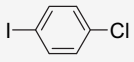
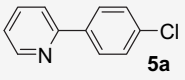
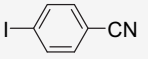
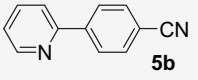
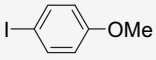
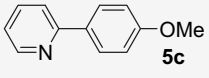
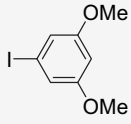
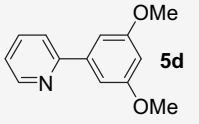
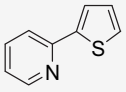
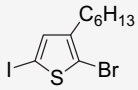
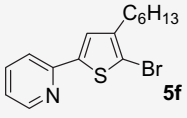
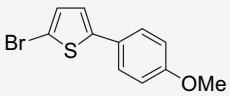
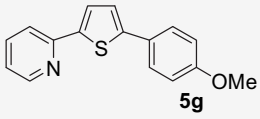
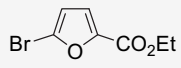
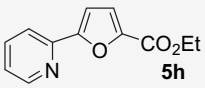
Entry	RZnBr	Y	Product	Yield(%)[a]
1	**P2**	O		X; 3-Me(**4a**) 76
2	**P4**			X; 5-Me(**4b**) 89
3	**P2**	S		X; 3-Me(**4c**) 51
4	**P4**			X; 5-Me(**4d**) 84

[a] Isolated (based on electrophile).

With the preliminary results, we expanded this methodology to the coupling reactions with a variety of haloaromatic compounds. The results are described in Table 5. Interestingly, the mild conditions worked well to complete the coupling reactions of 2-pyridylzinc bromide (**P1**). As shown in Table 5, several different types of functionalized aryl halides and heteroaryl halides were coupled with **P1** in the presence of 1 mol % of $Pd[P(Ph)_3]_4$ at rt in THF. Functionalized iodobenzenes were first treated with 2-pyridylzinc bromide and the coupling products (**5a**–**5d**) were obtained in good to excellent yields (entries 1–4, Table 5). Mono-substituted thiophene was also easily coupled with 2-pyridylzinc bromide to give rise to 2-(2′-pyridyl)thiophene (**5e**) in 68%. Di- and tri-substituted thiophenes (entries 6 and 7, Table 5) were also good coupling partners to give interesting thiophene derivatives (**5f** and **5g**) in high yields. The coupling reaction with a furane derivative resulted in the formation of **5h** in an excellent yield (entry 8, Table 5).

Table 5
Pd-catalyzed coupling of **P1** with arylhalide

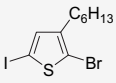
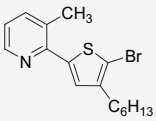
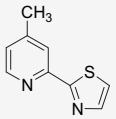
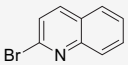
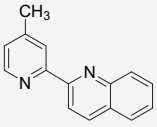
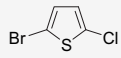
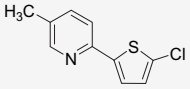
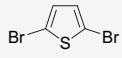
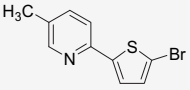
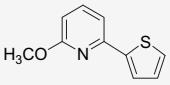
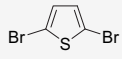
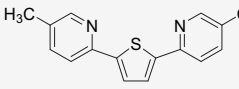
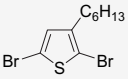
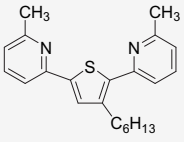


Entry	Electrophile	Time	Product	Yield[b] (%)
1		24 h	 **5a**	81
2		24 h	 **5b**	88
3		24 h	 **5c**	68
4		4 h	 **5d**	90
5		24 h	 **5e**	68
6		24 h	 **5f**	89
7		24 h	 **5g**	80
8		3 h	 **5h**	91

[a] Performed with 1 mol %
[b] Isolated yield(based on electrophile).

More interesting materials were prepared by the coupling reaction of various 2-pyridylzinc bromides with halo heterocyclic derivatives and the results are summarized in Table 6. A selective C–C bond forming reaction occurred in the reactions with 2-bromo-3-hexyl-5-iodothiophene and 2-bromo-5-chlorothiophene giving **6a** and **6d** in 41% and 64% isolated yield, respectively (entries 1 and 4, Table 6). A slightly longer reaction time was required to complete the coupling reaction with 2-bromothiazole and 2-bromoquinoline with 4-methyl-2-pyridylzinc bromide (**P3**) (entries 2 and 3, Table 6).

Table 6
Coupling reactions of **P2**–**P6** with heteroaryl halides

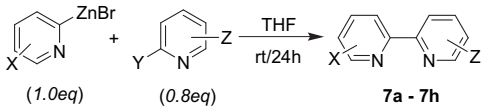
Entry	RZnBr	Electrophile[a]	Conditions[b]	Product	Yield[c] (%)
1	**P2**		**A**	 **6a**	41
2	**P3**		**B**	 **6b**	60
3	**P3**		**B**	 **6c**	40
4	**P4**		**A**	 **6d**	64
5	**P4**		**A**	 **6e**	51
6	**P6**		**A**	 **6f**	47
7[d]	**P4**		**C**	 **6g**	68
8[d]	**P5**		**C**	 **6h**	23

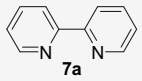
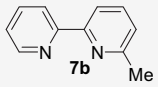
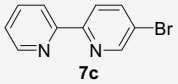
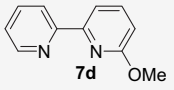
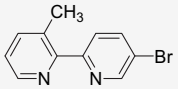
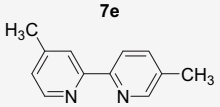
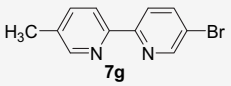
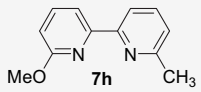
[a] 0.8 equiv of electrophile used otherwise mentioned.
[b] **A**: $Pd[P(Ph)_3]_4$/rt/24 h **B**: $Pd[P(Ph)_3]_4$/rt/72 h **C**: $Pd[P(Ph)_3]_2Cl_2$/reflux/24 h.
[c] Isolated yield (based on electrophile).
[d] 2.2 equiv of organozinc used.

Moderate yields (60% and 40%) were obtained from these reactions. Significantly, another selective C–C bond forming reaction was achieved from the coupling reaction with symmetrically disubstituted thiophene, 2,5-dibromothiophene (entry 5, Table 6), affording **6e**, which could be used for further application. Even though slightly different reaction conditions (Pd-II catalyst and refluxing temperature) were applied to carry out the coupling reactions with dibromothiophenes, symmetrically disubstituted thiophene derivatives (**6g** and **6h**) were easily prepared by its twofold reaction (entries 7 and 8, Table 6). These types of linear oligomers are important materials for optoelectronic device applications.[23]

As described in many previous reports, bipyridine units are very important futures for many natural products as well as many molecules used in material chemistry.[24] Significantly, this structural future can be readily prepared utilizing 2-pyridylzinc bromides. As described in Table 7, not only symmetrical 2,2′-bipyridine (**7a**) but several different types of unsymmetrical 2,2′-bipyridines (**7b**–**7h**) were prepared in moderate yields. Again, the coupling reaction was completed in the presence of 1 mol % $Pd[P(Ph)_3]_4$ in THF at rt and, in general, 3-methyl-2-pyridylzinc bromide (**P2**) and 6-methoxy-2-pyridylzinc bromide (**P6**) produced 2,2′-bipyridines,

Table 7
Preparation of 2,2′-bipyridines[a]



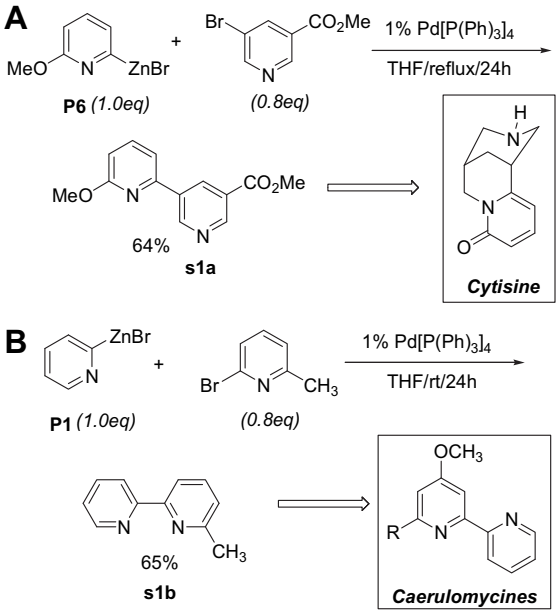
Entry	X	Y	Z	Product	Yield[b] (%)
1	H(**P1**)	I	H	 **7a**	60
2	H(**P1**)	Br	6-Me	 **7b**	65
3	H(**P1**)	I	5-Br	 **7c**	72
4	H(**P1**)	Br	6-OMe	 **7d**	53
5	3-Me(**P2**)	I	5-Br	 **7e**	30
6[c]	4-Me(**P3**)	Br	5-Me	 **7f**	75
7	5-Me(**P4**)	I	5-Br	 **7g**	63
8[c]	6-OMe(**P6**)	Br	6-Me	 **7h**	26

[a] Performed in the presence of 1 mol % of $Pd[P(Ph)_3]_4$.
[b] Isolated yield (based on electrophile).
[c] Carried out for 72 h at rt.

7e and **7h**, in low yields (entries 5 and 8, Table 7). It should be emphasized that the preparation of bipyridines using readily available 2-pyridylzinc bromides (**P1**–**P6**) could be a very practical approach because considerable effort has been directed toward the preparation of unsymmetrical 2,2′-bipyridines.

As aforementioned, some of natural products have bipyridine unit in their structure. Therefore, we also tried to make an intermediate, which could be utilized for the preparation of the natural product. Scheme 1 shows two examples. 2,3-Bipyridine (**s1a**) was prepared by the coupling reaction of **P6** with 5-bromonicotinic acid methyl ester in the presence of $Pd(PPh_3)_4$ in THF at refluxing temperature affording the coupling product in 64% isolated yield (route **A**, Scheme 1). Under the similar conditions, 2,2′-bipyridine (**s1b**) was achieved in moderate yield (65%) by Pd(0)-catalyzed cross-coupling reaction of **P1** (route **B**, Scheme 1). As depicted in Scheme 1, further manipulation of **s1a** and **s1b** would result in the formation of the natural products.

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. Therefore, we have performed



Scheme 1. Preparation of intermediates.

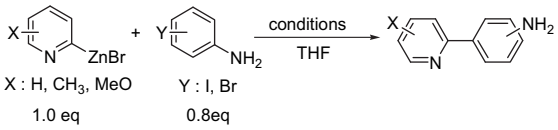
the cross-coupling reactions of 2-pyridylzinc bromides with haloaromatic compounds containing relatively acidic protons. To this end, haloaromatic amines, phenols, and alcohols are reasonable candidates as coupling reactants. By utilizing this strategy, 2-substituted aminophenyl and hydroxyphenyl pyridines have been successfully prepared under mild conditions.

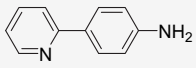
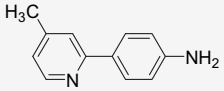
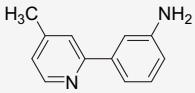
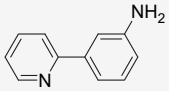
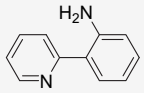
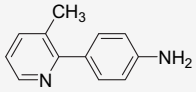
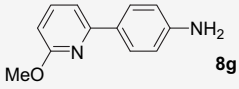
Since Pd(II)-catalysts along with an appropriate ligand have been used in the coupling reactions of organozinc reagents with haloaromatic amines and alcohols,[25] it seemed reasonable to try these conditions in our study. The coupling reactions worked well with 2-pyridylzinc bromide (**1a**) and the results are summarized in Table 8. The reaction of **P1** with 4-iodoaniline in the presence of 1 mol % $Pd(OAc)_2$ and 2 mol % SPhos gave rise to the cross-coupling product, **8a**, in 90% isolated yield (entry 1, Table 8). Two more reactions, methyl substituted 2-pyridylzinc bromide (**P3**) with 4-iodoaniline and **P1** with 4-bromoaniline resulted in relatively low yields (entries 2 and 3, Table 8). However, a significantly improved yield was obtained by the simple change of reaction temperature (entry 4, Table 8). An elevated reaction temperature also worked well for the reaction of **P3** with 3-iodoaniline leading **8c** in 85% isolated yield (entry 5, Table 8). As described in the previous report,[25a] 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 similar conditions with the previous work[25a] 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. However, in the previous report, a very slow addition of organozinc reagent into the reaction flask was crucial in order to obtain high yields.[26]

As mentioned above, the extra ligand (SPhos) was necessary when using the Pd(II)-catalysts for the coupling reactions in our study and others. From an economic point of view as well as ease of work-up, a ligand-free reaction condition would be highly beneficial. Thus, with the preliminary results (entries 1–5, Table 8) in hand, we have investigated the SPhos-free Pd-catalyzed coupling reactions of 2-pyridylzinc bromides with haloanilines. The reactions were performed by employing a Pd(0)-catalyst and the results are summarized in Table 8 (entries 6–10). Significantly, the Pd(0)-catalyzed coupling reactions were not affected by the presence of acidic protons (NH_2).[27]

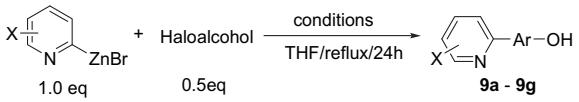
Table 8
Coupling reaction with haloaromatic amines

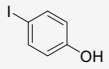
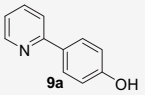
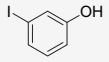
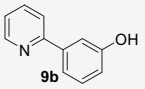
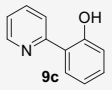
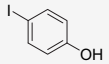
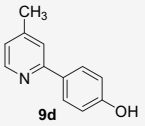
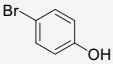
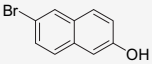
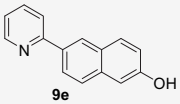
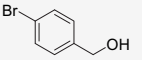
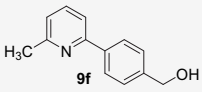
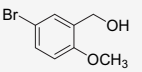
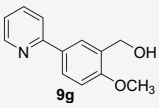


Entry	X	Y	Conditions[a]	Product	Yield[b] (%)
1	H(**P1**)	4-I	**A**	 **8a**	90
2	4-CH_3(**P3**)	4-I	**A**	 **8b**	50
3	H(**P1**)	4-Br	**A**	**8a**	50
4	H(**P1**)	4-Br	**B**	**8a**	89
5	4-CH_3(**P3**)	3-I	**B**	 **8c**	85
6	H(**P1**)	4-I	**C**	**8a**	89
7	H(**P1**)	3-I	**C**	 **8d**	64
8	H(**P1**)	2-I	**C**	 **8e**	74
9	3-CH_3(**P2**)	4-I	**D**	 **8f**	68
10	6-OMe(**P6**)	4-Br	**D**	 **8g**	Trace[c]

[a] **A**: 1% $Pd(OAc)_2$/2% SPhos/rt/24 h **B**: 1% $Pd(OAc)_2$/2% SPhos/reflux/24 h **C**: 1% $Pd[P(Ph)_3]_4$/rt/24 h **D**: 1% $Pd[P(Ph)_3]_4$/reflux/24 h.
[b] Isolated yield (based on aniline).
[c] By GC–MS.

Table 9
Coupling reaction with haloaromatic alcohols



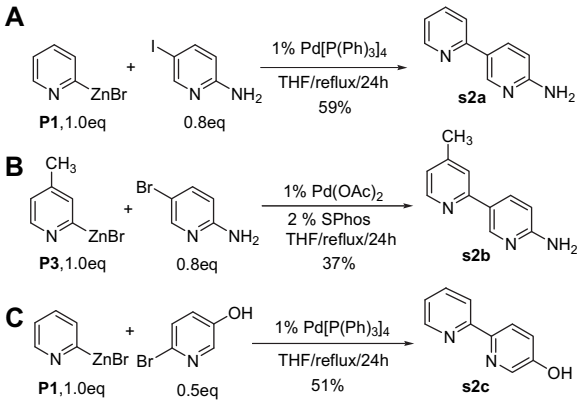
Entry	X	Alcohol	Conditions[a]	Product	Yield[b] (%)
1	H(**P1**)		**A**	 **9a**	95
2	H(**P1**)		**A**	 **9b**	80
3	H(**P1**)		**A**	 **9c**	25
4	4-CH_3(**P3**)		**A**	 **9d**	54
5	H(**P1**)		**A** **B**	**9a**	0[c] 86
6	H(**P1**)		**B**	 **9e**	92
7	6-CH_3(**P5**)		**A**	 **9f**	60
8	H(**P1**)		**A**	 **9g**	65

[a] **A**: 1% $Pd[P(Ph)_3]_4$ **B**: 1% $Pd(OAc)_2$/2% SPhos.
[b] Isolated yield (based on alcohol).
[c] No coupling observed by GC.

The reaction of **P1** with 4-iodoaniline in the presence of 1 mol % $Pd[P(Ph)_3]_4$ provided 2-(4-aminophenyl)pyridine (**8a**) with similar results (89% isolated yield, entry 6, Table 8). 3-Iodoaniline and 2-iodoaniline were also coupled with **P1** under the same conditions (condition **C**, Table 8) affording the aminophenyl pyridines (**8d** and **8e**) in 64% and 74% isolated yields, respectively (entries 7 and 8, Table 8). Another successful coupling reaction (entry 9, Table 8) was achieved from a sterically hindered 3-methyl-2-pyridylzinc bromide (**P2**), resulting in 68% isolated yield with the formation of **8f**. Unfortunately, no satisfactory coupling reaction occurred with 4-bromoaniline using the Pd(0)-catalyst (entry 10, Table 8). 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 iodoaromatic 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 9, 4-iodophenol and 3-iodophenol were coupled with **P1** affording the corresponding hydroxyphenyl pyridine products (**9a** and **9b**) in excellent yields (entries 1 and 2, Table 9). A slightly disappointing result (25%) was obtained from 2-iodophenol (entry 3, Table 9). 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.[26] 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 **P1** resulting in the coupling products (**9a** and **9e**) in 86% and 92% (entries 5 and 6, Table 9). Unlike the reactions with bromophenols, it is of interest that the coupling products (**9f** and **9g**) of **P5** and **P1** were efficiently achieved from the Pd(0)-catalyzed reactions with 4-bromobenzyl alcohol and 3-bromo-5-methoxybenzyl alcohol (entries 7 and 8, Table 9), respectively.

Interestingly, unsymmetrical amino-bipyridines were produced from the coupling reactions of 2-pyridylzinc bromides with halogenated aminopyridines under the conditions used above. As shown in Scheme 2, 2-amino-5-iodopyridine reacted with **P1** to afford 2,3-bipyridine (**s2a**) in 59% isolated yield in the presence of 1 mol % of $Pd[P(Ph)_3]_4$ catalyst (route **A**, Scheme 2). However, in the case of 2-amino-5-bromo-pyridine, the Pd(II)-catalyst was more efficient for the coupling reaction and the reaction proceeded smoothly to give 2,3-bipyridine (**s2b**) in 37% yield (route **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.[28]



Scheme 2. Preparation of amino and hydroxyl bipyridines.

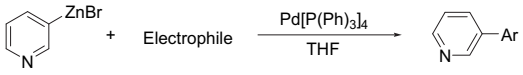
Treatment of 2-pyridylzinc bromide (**P1**) with a halopyridine bearing a hydroxyl group provided another functionalized bipyridine. Interestingly, the relatively reactive bromopyridyl alcohol, 2-bromo-5-hydroxypyridine, was coupled with **P1** using Pd(0)-catalyst. As a result, the corresponding hydroxyl 2,2′-bipyridine (**s2c**) was obtained in 51% isolated yield (route **C**, Scheme 2). The hydroxyl group on 2,2′-bipyridine can also be converted to halogen to make halobipyridines by using several different methods.[29]

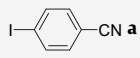
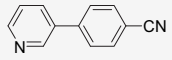
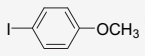
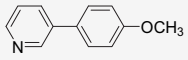
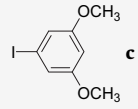
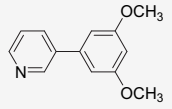
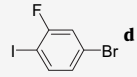
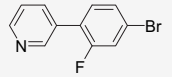
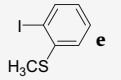
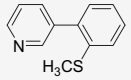
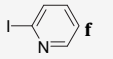
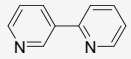
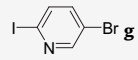
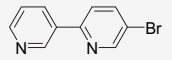
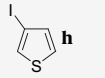
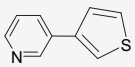
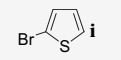
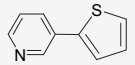
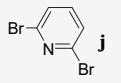
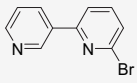
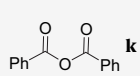
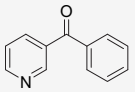
As mentioned earlier, direct preparation of 3-pyridylzinc reagents has been another challenging subject in organometallic chemistry. In our continuing study of heterocyclic organozinc reagents,[30] it has been found that Rieke zinc in the presence of certain additives exhibits a very high reactivity to 3-bromopyridine. The corresponding 3-pyridylzinc bromide was easily prepared by the direct insertion of active zinc to 3-bromopyridine and the resulting 3-pyridylzinc bromide was successfully applied to the cross-coupling reaction with a variety of electrophiles under mild conditions.

The first attempt to synthesize 3-pyriylzinc bromide from the direct reaction of active zinc and 3-bromopyridine in THF at rt and refluxing temperature resulted in low conversion (70%) to the organozinc reagent. Almost the same result was obtained from an extended reaction time (reflux/24 h). However, a dramatic improvement in the oxidative addition of active zinc has been achieved by adding 10–20 mol % of lithium chloride to the reaction mixture. Even though the role of lithium chloride has not been totally explained, more than 99% conversion of 3-bromopyridine to 3-pyridylzinc bromide was obtained in 2 h at refluxing temperature in THF. As was pointed out in 1989,[21] the rate limiting step in the oxidative addition is electron transfer. Accordingly, this process will be accelerated by the presence of alkali salts, which are generated in the reduction process of forming the active metals or additional salts can be added to the reaction mixture.[22b]

In order to confirm the formation of 3-pyridylzinc bromide, the resulting organozinc reagent was first treated with iodine affording 90% 3-iodopyridine and 3% pyridine. Next, the resulting 3-pyridylzinc bromide (**P7**) was added to a variety of different electrophiles to give the corresponding coupling products in moderate to good yields. The results are summarized in Table 10. Palladium catalyzed cross-coupling reactions with aryl iodides (**a**–**c**, Table 10) were completed in 1 h at rt to give 3-pyridylbenzene derivatives (**10a**, **10b**, and **10c**) in good yields (entries 1–3, Table 10). A longer reaction time was required with aryl iodides (**d** and **e**), bearing a substitutent in the 2-position (entries 4 and 5, Table 10). This is probably due to steric hindrance. With this result in hand, heteroaryl iodides (**f**–**h**) were also coupled with 3-pyridylzinc bromide affording the heteroaryls (**10f**–**10h**) in good yields. Coupling reactions with heteroaryl bromides (**i** and **j**) needed also a longer reaction time and afforded the coupling product (**10i** and **10j**, Table 10) in 86% and 29% isolated yields, respectively. As shown in entries

Table 10
Pd-catalyzed coupling Reactions of 3-pyridylzinc bromide (**P7**)



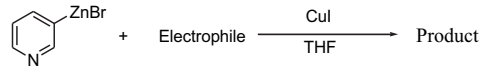
Entry	Electrophile[a]	Conditions[b]	Product	Yield[c] (%)
1	 **a**	rt/1 h	 **10a**	65
2	 **b**	rt/1 h	 **10b**	81
3	 **c**	rt/1 h	 **10c**	63
4	 **d**	rt/24 h	 **10d**	63
5	 **e**	rt/24 h	 **10e**	32
6	 **f**	rt/1 h	 **10f**	71
7	 **g**	rt/1 h	 **10g**	62
8	 **h**	rt/1 h	 **10h**	71
9	 **i**	rt/48 h	 **10i**	86
10	 **j**	rt/48 h	 **10j**	29
11	 **k**	rt/12 h	 **10k**	38

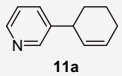
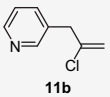
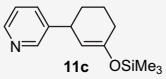
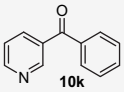
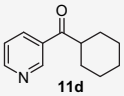
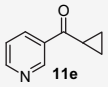
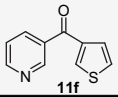
[a] 0.8 equiv of electrophile used.
[b] 1 mol % of $Pd[P(Ph)_3]_4$ used.
[c] Isolated yield(based on electrophile).

4 and 7 in Table 10, the carbon–iodine bond was selectively reacted in coupling reactions with the organozinc reagent (**P7**) for carbon–carbon bond formation under the conditions used here. Even though a low yield was obtained from 2,6-dibromopyridine (**j**), the coupling product (**10j**) bearing a bromine atom can serve as a valuable intermediate for the preparation of a variety of materials. Interestingly, it was also possible to obtain an aromatic ketone (**10k**) in moderate yield from the reaction of **P7** with benzoic acid anhydride in the presence of palladium (0) catalyst.

To expand the application of 3-pyridylzinc bromide, several other copper-catalyzed coupling reactions were also investigated and the results are summarized in Table 11. S_N2'-type reactions have been tried with allyl halides affording the resulting products (**11a** and **11b**, Table 11) in moderate to good yields. In the presence of TMSCl, silyl enol ether (**11c**, Table 2) was obtained from the conjugate addition intermediate. Like other general organozinc

Table 11
Copper-catalyzed coupling reaction of **P7**



Entry	Electrophile[a]	Conditions[b]	Product	Yield[c] (%)
1		0 °C/10 min	 **11a**	71
2		0 °C/10 min	 **11b**	50
3		TMSCl/0 °C∼rt	 **11c**	48
4		0 °C∼rt/12 h	 **10k**	50
5		0 °C∼rt/12 h	 **11d**	69
6		0 °C∼rt/12 h	 **11e**	38
7		0 °C∼rt/12 h	 **11f**	50

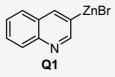
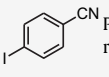
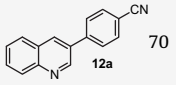
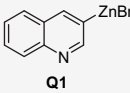
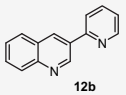
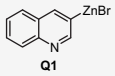
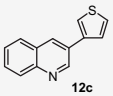
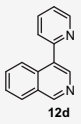
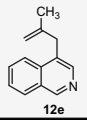
[a] 0.8eq of electrophile used.
[b] 10 mol % CuI used.
[c] Isolated yield(based on electrophile).

reagents, 3-pyridylzinc bromide (**P7**) was successfully used for the copper-catalyzed synthesis of ketone compounds. As shown in Table 11, 10 mol % of CuI promoted the coupling reaction with **P7** to give the ketones (**10k**, **11d**–**11f**, Table 11) in moderate yields under the conditions described in Table 11.

This study was expanded to several analogues of 3-bromopyridine. As described in Table 12, 3-bromoquinoline and 3-bromoisoquinoline were treated with active zinc along with 20 mol % of lithium chloride. It was found that the oxidative addition of active zinc was completed in 2 h at refluxing temperature to give the corresponding organozinc reagents (**Q1** and **Q2**). The subsequent coupling reactions of **Q1** were performed with aryl iodide (entry 1, Table 12) and heteroaryl iodides (entries 2 and 3, Table 12) in the presence of palladium catalyst affording the corresponding products (**12a**–**12c**) in moderate to good isolated yields. Entries 4 and 5 in Table 12 showed the results of the coupling reactions of **Q2** with heteroaryl iodide and allyl chloride. From these reactions, more new heteroaryl compounds (**12d**–**12e**, Table 12) were obtained in moderate yields.

Since we obtained successful results from the coupling reaction of 2-pyridylzinc bromides with aromatic haloamines and alcohols, we also demonstrated the same strategy for the coupling reaction of the 3-pyridylzinc bromides. It was found that the readily available 3-pyridylzinc bromide was easily coupled with haloaromatic compounds bearing relatively acidic protons under mild conditions affording the corresponding cross-coupling products in the moderate to excellent yields. Of primary interest, we report the general procedure for the transition metal-catalyzed cross-coupling reactions of 3-pyridylzinc bromides with haloanilines and halophenols providing 3-(aminophenyl)pyridines and 3-(hydroxyphenyl) pyridines. The results also include the preparation of quinoline and isoquinoline derivatives as well as other pyridine derivatives.

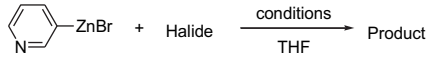
Table 12
Preparation of quinoline and isoquinoline derivatives via heteroarylzinc reagent

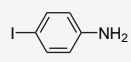
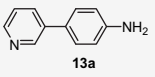
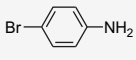
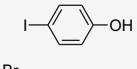
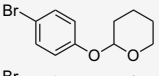
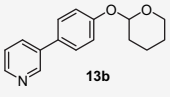
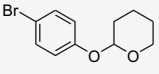
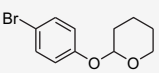
Entry	Organozinc	Electrophile[a]	Conditions[b]	Product	Yield[c] (%)
1	 **Q1**		$Pd[P(Ph)_3]_4$ rt/1 h	 **12a**	70
2	 **Q1**		$Pd[P(Ph)_3]_4$ rt/1 h	 **12b**	65
3	 **Q1**		$Pd[P(Ph)_3]_4$ rt/1 h	 **12c**	53
4	 **Q2**		$Pd[P(Ph)_3]_4$ rt/1 h	 **12d**	37
5	 **Q2**		CuI[d] 0 °C∼rt/1 h	 **12e**	35

[a] 0.8 equiv of electrophile used.
[b] 1 mol % Pd-catalyst used.
[c] Isolated yield(based on electrophile).
[d] 10 mol % used.

The first approach included the reaction of 3-pyridylzinc bromide (**P7**) with 4-iodoaniline in the presence of 1% of $Pd(OAc)_2$ along with 2% of SPhos in THF (enty1, Table 13). The coupling reaction was completed at rt in 30 min affording 4-pyridin-3-yl-phenylamine (**13a**) in 80% isolated yield. Even though a little longer reaction time was required, the coupling product (**13a**) was also obtained in good yield from the reaction with 4-bromoaniline under the same conditions (entry 2, Table 13). Interestingly, trace amounts of the coupling product was detected by GC from the reaction with 4-iodophenol using the same conditions (entry 3, Table

Table 13
Preliminary test for the coupling reaction of **P7**



Entry	Halide[a]	Conditions	Product	Yield[b] (%)
1		1% $Pd(OAc)_2$ 2% SPhos rt/30 min	 **13a**	80
2		1% $Pd(OAc)_2$ 2% SPhos rt/3 days	**13a**	80
3		1% $Pd(OAc)_2$ 2% SPhos rt/24 h	**13a**	Trace[c]
4		1% $Pd(OAc)_2$ 2% SPhos rt/24 h	 **13b**	44
5		1% $Pd(OAc)_2$ rt/3 days	**13b**	Trace[c]
6		$Pd(PPh_3)_4$ rt/24 h	**13b**	0[c]

[a] 0.8 equiv of amine, 0.5 equiv of alcohol used.
[b] Isolated (based on halide).
[c] Monitored by GC.

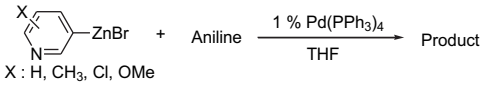
13). A protected bromophenol gave rise to the coupling product (**13b**) in moderate yield under the same conditions (entry 4, Table 13). The critical role of an extra ligand (SPhos) for the completion of the coupling reaction was also noticed. Trace amounts of product formation was detected in the absence of SPhos (entry 5, Table 13). It was also found that a Pd(0)-catalyst was not effective for the coupling with a protected bromophenol (entry 6, Table 13).

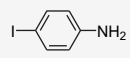
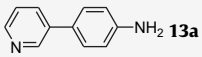
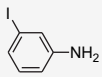
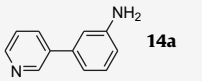
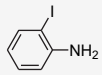
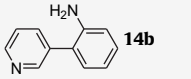
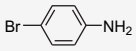
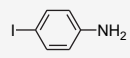
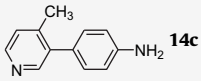
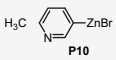
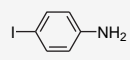
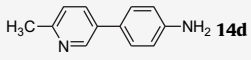
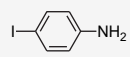
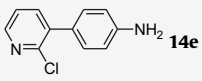
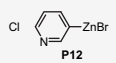
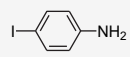
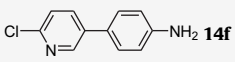
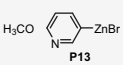
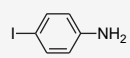
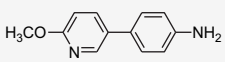
Even though the conditions used in the preliminary tests worked well, an extra ligand(SPhos)-free reaction condition would be more interesting. Thus, once again, the SPhos-free Pd-catalyzed coupling reactions of 3-pyridylzinc bromides with haloanilines were carried out. This was accomplished by using 1 mol% of $Pd(PPh_3)_4$ without any extra additives and the corresponding coupling products were obtained in moderate to excellent yields. The results are summarized in Table 14. As observed in the coupling reaction of 2-pyridylzinc bromide (**P1**) with haloaromatic amine, no significant effect of the presence of acidic protons was observed from the study of **P7**.

The coupling reactions were easily accomplished by the addition of 3-pyridylzinc bromide into the mixture of haloaniline and Pd(0)-catalyst in THF. The organozinc solution was added into the reaction flask in one portion via a syringe at rt. The lack of a large heat of reaction should be a useful feature for large scale synthesis.

The reaction of **P7** with 4-iodoaniline in the presence of 1 mol% $Pd(PPh_3)_4$ provided 4-pyridin-3-yl-phenylamine (**13a**) in 86% isolated yield (entry 1, Table 14). 3-Iodoaniline and 2-iodoaniline were also coupled with **P7** under the same conditions (at rt for 1.0 h) affording the aminophenyl pyridines (**14a** and **14b**) in 85% and 61% isolated yield, respectively (entries 2 and 3, Table 14). However, even at an elevated temperature, a low yield of **13a** was obtained from the coupling reaction using 4-bromoaniline (entry 4, Table 14). With the results obtained from the simple 3-pyridylzinc bromide, we also expanded this reaction conditions to the wide range of functionalized 3-pyridylzinc reagents. All of these 3-pyridylzinc bromides were easily prepared under the same conditions used for the preparation of **P7**. For the sterically hindered 4-methyl-3-pyridylzinc bromide (**P8**), a slightly severe condition (refluxing for 6 h) was required to complete the coupling, resulting in the formation of **14c** in 48% isolated yield (entry 5, Table 14). However, the reaction with 2-methyl-5-pyridylzinc bromide (**P10**) provided the coupling product (**14d**) in a good yield (entry 6, Table 14). Interestingly, excellent results were achieved from the coupling reactions using chlorine substituted 3-pyridylzinc reagents. As shown in Table 14, a 92% isolated yield of **14e** and **14f** was obtained from both reactions of 2-chloro-3-pyridylzinc bromide (**P11**) and 2-chloro-5-pyridylzinc bromide (**P12**) after 3 h stirring at rt (entries 7 and 8, Table 14). Unfortunately, no satisfactory coupling reaction occurred with 2-methoxy-5-pyridylzinc bromide (**P13**) using the Pd(0)-catalyst (entry 9, Table 14). Similar results were also obtained from the reaction with iodophenol (entry 10, Table 8). From the

Table 14
Preparation of aminophenylpyridines



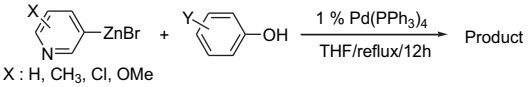
Entry	RZnX	Aniline	Conditions	Product	Yield[a] (%)
1	 **P7**		rt/1 h	 **13a**	86
2	P7		rt/1 h	 **14a**	85
3	P7		rt/1 h	 **14b**	61
4	P7		Reflux/24 h	**13a**	15
5	 **P8**		Reflux/6 h	 **14c**	48
6	 **P10**		rt/1 h	 **14d**	85
7	 **P11**		rt/3 h	 **14e**	92
8	 **P12**		rt/3 h	 **14f**	92
9	 **P13**		Reflux/24 h		0[b]

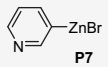
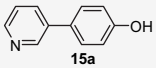
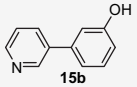
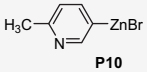
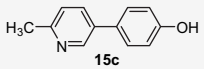
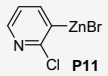
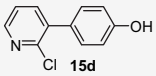
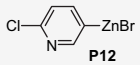
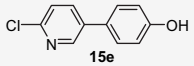
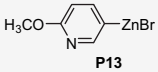
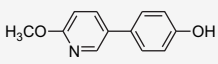
[a] Isolated yield (based on amine).
[b] No reaction. Starting materials were recovered (confirmed by GC and GC–MS).

results described above, it can be concluded that Pd(0)-catalyzed coupling reactions of 3-pyridylzinc bromides work effectively with iodoanilines under mild conditions.

Another interesting reaction of 3-pyridylzinc bromide would be the coupling reaction with phenols, which also have an even more acidic proton.[27] Encouraged by the results achieved from the reaction with haloanilines, the coupling reactions with iodophenols were carried out using Pd(0)-catalyst. As shown in Table 15, 2.0 equiv of organozinc reagent were reacted with halophenols at refluxing temperature in the presence of 1 mol % of $Pd(PPh_3)_4$ in THF. In the case of **P7**, even though the coupling reaction with iodophenol worked fairly at rt, increasing the reaction temperature worked more effectively to complete the coupling reaction. Therefore, all of the coupling reactions with halophenols in this study were conducted at refluxing temperature for 12 h. 4-Iodophenol was coupled with **P7** affording the corresponding 3-(4-hydroxyphenyl) pyridine (**15a**) in excellent yields (entry 1, Table 15). A slightly disappointing result (49%) was obtained from 3-iodophenol (entry 2, Table 15). Unlike the reaction with 4-bromoaniline, treatment of **P7** with 4-bromophenol gave rise to the product **15a** in moderate yield (entry 3, Table 15). More coupling reactions of methyl and chlorine substituted 3-pyridylzinc bromides (**P10**, **P11**, and **P12**) were also performed with 4-iodophenol. The reactions occurred successfully to result in good yields (81%, entry 4, Table 15) to moderate yields (61% and 60%, entries 5 and 6, Table 15, respectively). Again, no coupling product was obtained from 2-methoxy-5-pyridylzinc bromide (**P13**).

Table 15
Preparation of hydroxyphenylpyridines

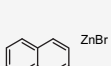
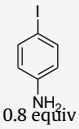
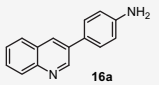
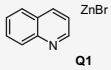
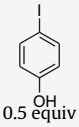
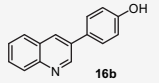
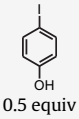
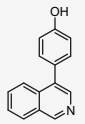
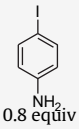


Entry	RZnX	Y	Product	Yield[a] (%)
1	 **P7**	4-I	 **15a**	90
2	**P7**	3-I	 **15b**	49
3	**P7**	4-Br	**15a**	40
4	 **P10**	4-I	 **15c**	81
5	 **P11**	4-I	 **15d**	61
6	 **P12**	4-I	 **15e**	60
7	 **P13**	4-I		0[b]

[a] Isolated yield (based on alcohol).
[b] Carried out at refluxing temperature for 24 h. No reaction. Starting materials were recovered (confirmed by GC and GC–MS).

Since the coupling reactions of 3-pyridylzinc bromides provided very positive results of preparing highly functionalized pyridine derivatives, this study was applied to several analogues of 3-bromopyridine. The results are described in Table 16. Quinolinylzinc bromide (**Q1**) and isoquinolinylzinc bromide (**Q2**) were prepared

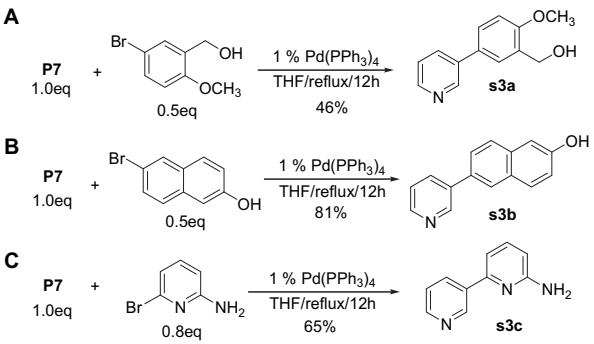
Table 16
Preparation of quinoline and isoquinoline derivatives

Entry	RZnX	Halide	Conditions	Product	Yield[a] (%)
1	 **Q1** 1.0 equiv	 0.8 equiv	1% $Pd(PPh_3)_4$ THF/rt/3.0 h	 **16a**	89
2	 **Q1** 1.0 equiv	 0.5 equiv	1% $Pd(PPh_3)_4$ THF/rt/12 h	 **16b**	64
3	 **Q2** 1.0 equiv	 0.5 equiv	1% $Pd(PPh_3)_4$ THF/rt/3 h	 **16c**	90
4	 **Q2** 1.0 equiv	 0.8 equiv	1% $Pd(PPh_3)_4$ THF/reflux/24 h	—	0[b]

[a] Isolated yield (based on halide).
[b] No reaction. Starting materials were recovered (confirmed by GC and GC–MS).

easily by using the previously mentioned procedure. Subsequent coupling reactions of 3-quinolinylzinc bromide with 4-iodoaniline and 4-iodophenol afforded the corresponding products (**16a** and **16b**, Table 16) in 89% and 64% isolated yield, respectively. The coupling reaction of 4-isoquinolinylzinc bromide (**Q2**) with 4-iodophenol was carried out at rt for 3 h to give the product (**16c**) in excellent yield (entry 3, Table 16). Unfortunately, coupling of 5-pyrimidinylzinc bromide showed no product at all (entry 4, Table 16).

Further application of this practical synthetic approach has been performed by the coupling reaction with different types of alcohols. 2-Methoxy-5-bromobenzyl alcohol and 6-bromo-2-naphthol were nicely coupled with **P7** under the reaction conditions given in Scheme 3 resulting in the coupling products (**s3a** and **s3b**) in 48% and 81% yield, respectively (routes **A** and **B**, Scheme 3). Interestingly, unsymmetrical amino-bipyridines were produced from the coupling reactions of **P7** with 2-amino-6-bromopyridine (route **C**, Scheme 3). It was accomplished by the reaction of **P7** with 2-amino-6-bromopyridine in the presence of 1 mol % of $Pd(PPh_3)_4$ in THF at refluxing temperature for 12 h affording 2,3-bipyridine (**s3c**) in 65% isolated yield. It is of interest that the resulting product (**s3c**) can be utilized for further applications after transformation of the amino group to a halogen.[28]



Scheme 3.

3. Conclusions

We have demonstrated a practical synthetic route for the preparation of 2-pyridyl and 3-pyridyl derivatives. It has been accomplished by utilizing a simple coupling reaction of readily available 2-pyridylzinc bromides and 3-pyridylzinc bromides, which were prepared via the direct insertion of active zinc to the corresponding bromopyridines. The subsequent coupling reactions with a variety of different electrophiles have been performed under mild conditions affording the coupling products.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvent and vacuum line was employed for all manipulations of air-sensitive compounds. Commercially available reagents were used without further purification. Active zinc was prepared by literature procedure.[21] Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded on 300 MHz, 400 MHz and/or 500 MHz in $CDCl_3$ and ^{13}C NMR spectra was recorded on 75 MHz, 100 MHz and/or 125 MHz in $CDCl_3$, THF-d_8 or DMSO-d_6 using TMS as internal standard.

4.2. Preparation of 2-pyridylzinc bromide (P1)

A 250 mL RBF was charged with active zinc(9.81 g, 150 mmol) in 100 mL of THF. 2-Bromopyridine (15.8 g, 100 mmol) was then added into the flask via a cannula while being stirred at rt. After the addition was completed, the resulting mixture was allowed to stir at refluxing temperature. The oxidative addition was monitored by GC analysis of the reaction mixture. After being settled down overnight, the supernatant was transferred into a 500 mL bottle and then diluted with fresh THF to 200 mL.

4.3. Preparation of 3-pyridylzinc bromide (P7)

An oven-dried 100 mL round-bottomed flask was charged with 3.3 g of active zinc (50 mmol) in 30 mL of THF and 0.2 g of lithium chloride (20 mol %) under the positive pressure of argon gas. 3.9 g of 3-Bromopyridine (25 mmol) was added into the solution of active zinc at rt. The resulting mixture was then stirred at refluxing temperature for 2 h. Cooled down to rt and settled down overnight. Then the supernatant was used for the subsequent coupling reactions.

4.4. General procedure for copper-free coupling reactions

In a 50 mL round-bottomed flask, isobutyryl chloride (1.27 g, 12 mmol) and 10 mL of THF were placed. Next, 20 mL of 0.5 M solution of 2-pyridylzinc bromide (**P1**) in THF (10 mmol) was added into the reaction flask via a syringe. The resulting mixture was stirred at rt for 4 h. The reaction was monitored by GC analysis. Quenched with saturated NH_4Cl solution, then extracted with ether (30 mL×3). Combined organics were washed with saturated $NaHCO_3$ solution and brine, then dried over anhydrous $MgSO_4$. A vacuum distillation gave 0.94 g of 2-methyl-1-pyridin-2-yl-propan-1-one (**2d**) as colorless oil in 63% isolated yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.64 (d, 1H, J=5 Hz), 8.01 (d, 1H, J=5 Hz), 7.81 (t, 1H, J=5 Hz), 7.42 (dd, 1H, J=5 Hz), 4.08 (q, 1H, J=5 Hz), 1.18 (d, 6H, J=5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.81, 153.01, 148.99, 137.03, 127.00, 122.55, 34.32, 18.78; GC–MS (EI, rel ratio): 149 (M^+, 31), 106 (36), 79 (100), 51 (44).

4.5. Pd-catalyzed coupling reaction with 4-iodoanisol (10b)

In a 50 mL round-bottomed flask, Pd[P(Ph)$_3$]$_4$ (0.10 g, 1 mol %) was placed. Next, 20 mL of 0.5 M solution of 3-pyridylzinc bromide (**P7**) in THF was added into the flask at rt. 4-Iodoanisol (1.80 g, 8 mmol) dissolved in 10 mL of THF was added via a syringe. The resulting mixture was stirred at rt for 1.0 h. Quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (30 mL×3). Combined organics were washed with saturated $NaHCO_3$ solution and brine, then dried over anhydrous $MgSO_4$. A flash column chromatography (20% EtOAc/80% Heptane) gave 1.20 g of **10b** as a light yellow solid in 81% isolated. Mp=56–58 °C; IR (thin film) 2972, 1605, 1516, 1248, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.84 (s, 1H), 8.56 (m, 1H), 7.85 (m, 1H), 7.55 (d, 2H, J=10 Hz), 7.36 (m, 1H), 7.04 (d, 2H, J=10 Hz), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.75, 148.03, 147.91, 136.25, 133.86, 130.27, 128.24, 123.51, 114.55, 55.39; HRMS (EI) calculated for $C_{12}H_{11}NO$ 185.0841, found 185.0844.

4.6. Preparation of bipyridines

In a 50 mL round-bottomed flask, Pd[P(Ph)$_3$]$_4$ (0.10 g, 1 mol %) and 5-bromo-2-iodoaniline (2.26 g, 8 mmol) were placed. Next, 20 mL of 3-pyridylzinc bromide (**P7**) (0.5 M in THF, 10 mmol) was added via a syringe. The resulting mixture was allowed to stir at rt for 1 h. Quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (30 mL×3). Combined organics were washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$. Flash chromatography on silica gel (20% EtOAc/80% Heptane) gave 1.17 g of 5-bromo-2,3′-bipyridine (**10g**) as a beige solid in 62% isolated yield. Mp=75–76 °C; IR (thin film) 3039, 2931, 1578, 1465, 1415, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.18 (s, 1H), 8.78 (s, 1H), 8.67 (d, 1H, J=20 Hz), 8.30 (d, 1H, J=20 Hz), 7.92 (d, 1H, J=20 Hz), 7.66 (d, 1H, J=30 Hz), 7.42 (d, 1H, J=25 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.23, 151.18, 150.30, 148.05, 139.57, 134.16, 133.76, 123.66, 121.60, 120.22; HRMS (EI) calculated for $C_{10}H_7BrN_2$ 235.9772, found 235.9777.

4.7. Pd-catalyzed coupling reactions with haloanilines

In a 50 mL round-bottomed flask, Pd[P(Ph)$_3$]$_4$ (0.10 g, 1 mol %) and 4-iodoaniline (1.75 g, 8 mmol) were placed. Next, 20 mL of 3-pyridylzinc bromide (**P7**) (0.5 M in THF, 10 mmol) was added via a syringe. The resulting mixture was stirred at rt for 1 h. Quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (30 mL×3). Combined organics were washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$. Flash chromatography on silica gel (30% EtOAc/70% Heptane) gave 1.17 g of 3-(4-aminophenyl)pyridine (**13a**) as a beige solid in 86% isolated yield. Mp=114–116 °C; IR (thin film) 3405, 3307, 3171, 1640, 1601, 1281 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.81 (s, 1H), 8.51 (d, 1H, J=5 Hz), 7.81 (m, 1H), 7.41 (d, 2H, J=5 Hz), 7.32 (m, 1H), 6.79 (d, 2H, J=5 Hz), 3.81 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.90, 147.60, 146.81, 136.74, 133.64, 128.23, 128.03, 123.65, 115.69; HRMS (EI) calculated for $C_{11}H_{10}N_2$ 170.0844, found 170.0843.

4.8. Pd-catalyzed coupling reactions with halophenols

In a 50 mL round-bottomed flask, Pd[P(Ph)$_3$]$_4$ (0.10 g, 1 mol %) and 4-iodophenol (1.10 g, 5 mmol) were placed. Next, 20 mL of 2-pyridylzinc bromide (**P1**) (0.5 M in THF, 10 mmol) was added via a syringe. The resulting mixture was heated to reflux for 24 h while being stirred. Cooled down to rt and quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (30 mL×3). Combined organics were washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$. Flash

chromatography on silica gel (10% EtOAc/90% Heptane) gave 0.80 g of 4-pyridin-3-yl-phenol (**9a**) as a white solid in 95% isolated yield. Mp=159–160 °C; IR (thin film) 3358 (br), 2975, 2893, 1593, 1467, 1270, 1182 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6, 500 MHz): δ 9.09 (s, 1H), 8.52 (d, 1H, J=5 Hz), 7.75 (d, 2H, J=10 Hz), 7.60 (m, 2H), 7.05 (m, 1H), 6.83 (d, 2H, J=10 Hz); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 125 MHz): δ 158.43, 157.32, 149.26, 136.66, 130.52, 128.11, 121.12, 119.63, 115.80; HRMS (EI) calculated for $C_{11}H_9NO$ 171.0684, found 171.0691.

4.9. Copper-catalyzed S_N2 addition reactions

In a 100 mL round-bottomed flask, CuI (0.50 g, 10 mol %) and LiCl (0.20 g, 20 mol %) were placed. Next, 50 mL of 3-pyridylzinc bromide (**P7**) (0.5 M in THF, 25 mmol) was added via a syringe. Cooled down to 0 °C using an ice-bath. 4.0 g (25 mmol) of 3-Bromocyclohexene was added via a syringe while being stirred in the ice-bath. After being stirred at 0 °C, quenched with saturated NH_4Cl solution, then extracted with ethyl ether (30 mL×3). Combined organics were washed with 7% NH_4OH solution and brine, then dried over anhydrous $MgSO_4$. Flash chromatography on silica gel (50% Ether/50% Pentane) gave 2.50 g of 3-cyclohex-2-enyl-pyridine (**11a**) as a yellow oil in 71% isolated yield. IR (thin film) 3020, 2928, 1670, 1573, 1422, 713 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.48 (s, 1H), 8.44 (m, 1H), 7.51 (m, 1H), 7.22 (m, 1H), 5.94 (m, 1H), 5.66 (q, 1H, J=20 Hz), 3.42 (m, 1H), 2.09 (m, 2H), 2.02 (m, 1H), 1.72 (m, 1H), 1.64 (m, 1H), 1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.60, 147.49, 141.67, 135.08, 129.38, 128.72, 123.25, 39.30, 32.35, 24.85, 20.85; HRMS (EI) calculated for $C_{11}H_{13}N$ 159.1048, found 159.1050.

4.10. Pd-catalyzed bimolecular coupling reactions

In a 50 mL round-bottomed flask, bis(triphenylphosphine)-palladium (II) dichloride, $Pd[P(Ph)_3]_2Cl_2$ (0.50 g) was placed. Next, 25 mL of 5-methyl-2-pyridylzinc bromide (**P4**) (0.5 M in THF, 12.5 mmol) was added via a syringe. 1.21 g (5.0 mmol) of 2,5-Dibromothiophene was added into the flask. The resulting mixture was heated to reflux for 24 h while being stirred. Cooled down to rt and quenched with saturated NH_4Cl solution, then extracted with ethyl acetate (30 mL×3). Combined organics were washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous Na_2SO_4. Flash chromatography on silica gel (10% EtOAc/90% Heptane) gave 0.90 g of 2,5-di(5-methylpyridin-2-yl)thiophene (**6g**) as a yellow solid in 68% isolated yield. Mp=dec at 170 °C; IR (thin film) 2975, 2928, 1596, 1470, 1378, 1292, 808 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.43 (m, 2H), 7.58 (m, 4H), 7.51 (m, 2H), 2.27 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.99, 145.48, 137.19, 131.66, 129.97, 125.01, 118.55, 18.32; HRMS (EI) calculated for $C_{16}H_{14}N_2S$ 266.0878, found 266.0879.

4.11. Preparation of quinolinylzinc reagents and subsequent coupling reactions

Preparation of quinolinylzinc bromide: A 250 mL round-bottomed flask was charged with active zinc (2.70 g, 41 mmol) in 30 mL of THF and lithium chloride (0.23 g, 20 mol %) under an argon atmosphere. 5.70 g (27.5 mmol) of 3-Bromoquinoline (or 3-bromoisoquinoline) was added into the solution of active zinc at rt. The resulting mixture was then stirred at refluxing temperature for 2 h. Cooled down to rt and settled overnight. Then the supernatant was used for the subsequent coupling reactions.

Coupling reaction: In a 50 mL round-bottomed flask, CuI (0.19 g, 10 mol %) and LiCl (0.08 g, 20 mol %) were placed. Next, 20 mL of 3-isoquionolinyl bromide (**Q2**) (0.5 M in THF, 10 mmol) was added via a syringe. Cooled down to 0 °C using an ice-bath. 0.80 g (9 mmol) of 3-chloro-2-methylpropene was added via a syringe while being stirred in the ice-bath. After being stirred at ambient temperature for 1.0 h, quenched with saturated NH_4Cl solution. Then, extracted with ethyl acetate (30 mL×3). Combined organics were washed with 7% NH_4OH solution and brine, then dried over anhydrous $MgSO_4$. Flash chromatography on silica gel (20% EtOAc/80% Heptane) gave 0.57 g of 4-(2-methyl-allyl)-isoquinoline (**12e**) as a beige solid in 35% isolated yield. Mp=59–61 °C; IR (thin film) 2967, 2933, 2362, 1620, 1582, 1445, 1390, 1231, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.16 (s, 1H), 8.39 (s, 1H), 7.97 (dd, 2H, J=5 Hz), 7.69 (t, 1H, J=5 Hz), 7.59 (t, 1H, J=5 Hz), 4.88 (s, 1H), 4.63 (s, 1H), 3.72 (s, 2H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.89, 143.96, 143.91, 135.36, 130.32, 128.99, 128.78, 128.32, 127.04, 123.65, 112.88; HRMS (EI) calculated for $C_{13}H_{13}N$ 183.1048, found 183.1054.

Supplementary data

Copies of ^1H, ^{13}C NMR data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.02.061.

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